A continuous manufacturing model for the production of granules by roller compaction

Rute Sofia Fonseca Cordeiro Dias

Dissertation to obtain the Master of Science Degree in Pharmaceutical Engineering

Work supervised by:
Professor João Almeida Lopes (Supervisor)
Professor Ossi Korhonen (Co-Supervisor)

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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
Abstract

Continuous manufacturing is an encouraging and a sustaining innovation in pharmaceutical manufacturing, build upon quality-by-design principles, with a huge potential to improve agility, flexibility and robustness to the manufacturing process. In this field, the Roller Compaction (RC) process plays an important role since it enables continuous dry granulation of powders. Here, the powder is densified by two counter-rotating rolls that produce a ribbon. Then, the ribbon is milled into granules, adequate for tableting or capsule filling. RC overcomes granulation problems with thermolabile moisture or solvents sensitive compounds.

In this work, an experimental design was performed in order to identify the critical process parameters (CPP) and evaluate their impact on the critical quality attributes (QCA) of granules produced by RC. The roller compactor used was the Hosokawa Bepex Pharmapaktor® L200/30P, with a Flake Crusher FC 200. The RC process was monitored by a near infrared (NIR) system and a direct imaging analyzer for granules’s size (Eyecon).

For the DoE the CPP’s proposed and their respective range were: compression force (15-35 kN), roller speed (3-8 rpm) and mill speed (50-250 rpm). The produced granules were characterized according to their particle size, as well as their bulk and tapped density—granules’ CQA’s.

All process variables were kept constant 2 minutes after the process onset. The compression force fluctuated throughout the process run time. The compression force was the variable that most affected the granules’ CQA’s: the size and the density of the granules are directly proportional to the compression force.

The Eyecon’s measurements exhibited significant deviations when compared with the gold standard method, thus it was not an accurate method for monitoring the granules’ size.

Two approaches were followed for the prediction of granules’ physical properties. The first model, that used partial least squares to predict the granules’ size, was built upon near infrared data. It returned a high RMSEP (50.54 μm) and a poor coefficient of determination for the prediction set (0.19), so it was not acceptable for the prediction of the granules’ size. The second approach considered process parameters data to predict the bulk density, tapped density and size of the granules. One partial least squares model was built to predict
each response. The coefficient of determination for the prediction set was high for the three models (0.93 for granules’ size, 0.95 for tapped density and 0.96 for bulk density) demonstrating a good prediction ability.

Key words: Continuous Manufacturing; Critical Process Parameters; Near-infrared Spectroscopy; Partial Least Squares; Roller Compaction.
Resumo

A produção contínua no contexto da indústria farmacêutica surge da contínua demanda pela produção de medicamentos de alta qualidade combinada com formas mais eficazes de avaliação da qualidade. Ao contrário da produção em “lote”, na produção contínua as matérias-primas entram e saem continuamente ao longo do ciclo de produção. Com efeito, as vantagens da adoção do processo em contínuo são diversas e podem resumir-se em três áreas fundamentais: controlo de qualidade e desenvolvimento do produto/processo, custos e área de produção.

O projeto de produção em contínuo pode ser apoiado nos princípios definidos pelo “quality-by-design”, desde o início do desenvolvimento do produto até à sua entrada no mercado. Portanto, a qualidade é erigida por desenho e não apenas avaliada no produto final. Para isso, realizam-se delineamentos experimentais para perceber de que forma os parâmetros críticos do processo (CPP’s) influenciam as respostas do processo. As tecnologias analíticas de process são ferramentas fundamentais de monitorização que fornecem dados do produto e do processo em tempo real. Estes dados alimentam os modelos multivariados, os quais não só fornecem informações para a compreensão do processo como também estão na base da construção dos modelos de controlo. Os controlos estão aptos a detetar anomalias no processo e a ajustar os CPP’s de forma a garantir que os atributos críticos de qualidade (CQA’s) do produto cumprem as especificações.

Por outro lado, no processo contínuo, os equipamentos são de menores dimensões, já que operam em contínuo. Por conseguinte, a área de produção requer igualmente menores dimensões, pelo reduzido tamanho dos equipamentos, pela ausência de salas de quarentena e de operações intermediárias. Deste modo se depreende uma significativa redução de custos pela redução de recursos humanos, pela redução de gastos com equipamentos de grande escala, pelo menor consumo energético, pela redução de desperdícios com produtos fora de especificação e pela redução no tempo de chegada de novos produtos ao mercado.

A granulação é uma operação unitária com vista à obtenção de grânulos, aplicados tanto na sua forma intermediária para a produção de comprimidos, quanto na sua forma farmacêutica final. A granulação a seco operada num compactador de rolos é, em si, um processo
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contínuo que permite processar compostos termolábeis e passíveis de degradação pela humidade e por solventes.

O processo de compactação por rolos inicia-se pela introdução da mistura de pó no granulador, através de uma tremonha de alimentação. As partículas de pó ao chegarem à zona de alimentação sofrem um rearranjo e densificam, devido à pressão exercida pelo parafuso rotativo no sentido descendente e ao afunilamento desta zona, a qual se prolonga na seguinte. A mistura de pó é então forçada a continuar pela zona de compressão, onde numa primeira fase, devido à pressão exercida sobre as partículas, ocorre deformação ou quebra das mesmas. À medida que as partículas avançam nesta zona, a força de compressão aumenta até que ao atingirem o termo da zona, a força de compressão exercida pelos dois rolos em contra-roteação provoca a fragmentação das partículas e, logo em seguida, a sua ligação até formarem fitas compactas. Por fim, as fitas são expelidas pelos rolos, cortadas e moídas, de modo a formarem grânulos.

O NIR é uma ferramenta PAT que devido ao facto de a interação da radiação com a matéria ocorrer na região de 780-2500 nm, permite uma interação direta com a amostra sem causar a sua destruição. O NIR tem a capacidade de monitorizar o processo em tempo real, fornecendo dados para a construção de modelos multivariados. O modelo PCA ao desvendar as combinações de variáveis que descrevem a maior tendência nos dados, fornece informações sobre o “comportamento” de todo o processo. O modelo PLS é utilizado para prever as propriedades do produto final.

Este trabalho pretendeu identificar os atributos críticos do processo responsáveis pelas alterações nos atributos críticos de qualidade dos grânulos. Além disso, procurou estimar as propriedades dos grânulos (tamanho e densidade) com base em dados espetrais e dados do processo.

Este trabalho foi realizado utilizando a Linha de produção contínua de comprimidos do PROMIS Centre (University of Eastern Finland, School of Pharmacy) em Kuopio, Finlândia. Neste trabalho, recorreu-se a alimentadores gravimétricos, um misturador contínuo e um compactador por rolos (Hosokawa Bepex Pharmapaktor® L200/30P, FC 200). A monitorização do processo foi seguida em linha por um sistema de infravermelho próximo (Specim RHNIR, Spectral Imaging Ltd, Oulu, Finland) e por um medidor do tamanho de partículas (Eyecon™, Innopharma Labs, Dublin, Ireland). A densidade dos grânulos foi medida por deslocamento do volume dentro de uma proveta e o tamanho dos grânulos foi medido num equipamento por dispersão de luz (método padrão).
A relação entre os possíveis CPP’s e os CQA’s dos grânulos foi estabelecida através de um delineamento experimental, onde a velocidade dos rolos variou de 3 rpm a 8 rpm, a força de compressão variou de 15 kN a 35 kN e a velocidade do moinho variou de 50 a 250 rpm. Considerou-se a densidade (areada e batida) e a dimensão dos grânulos como CQA’s.

O processo foi monitorizado por infra-vermelho próximo tendo os espetros adquiridos sido processados para remoção de variabilidade de linha de base e escala. A identificação de espetros atípicos (ou outliers) e a trajetória do processo de acordo com a informação espectral foi avaliada através de modelos de análise de componentes principais, esta última através do primeiro componente principal.

A velocidade do parafuso alimentador, a velocidade dos rolos e a velocidade do moinho estabilizaram cerca de 2 minutos após o início do processo. A força de compressão variou sempre ao longo de todo o processo, independentemente da força de compressão alvo.

A densidade dos grânulos aumentou (ex. areada, 0,62 g/ml – 0,64 g/ml) com o aumento da força de compressão (35 kN) e diminuiu (ex. areada, 0,54 g/ml – 0,55 g/ml) com a diminuição da força de compressão (15 kN). O valor intermédio de força de compressão (25 kN) originou grânulos com densidade intermédia (ex. areada, 0,58 g/ml – 0,60 g/ml).

O tamanho dos grânulos foi influenciado sobretudo pela força de compressão. Assim, quanto maior a força de compressão aplicada, maior o tamanho dos grânulos (ex. 1009 μm); e quanto menor a força de compressão aplicada, menor o tamanho dos grânulos (700 μm). A aplicação de uma força de compressão intermédia produziu grânulos de dimensão intermédia entre as duas anteriores (881 μm).

Na medição da dimensão das partículas, o método por análise de imagem revelou um desvio significativo em relação ao método por dispersão de luz (método padrão), não constituindo por isso um método preciso para a monitorização em linha do tamanho dos grânulos.

Foram construídos dois modelos de regressão multivariada baseados em mínimos quadrados parciais para prever a densidade e a dimensão dos grânulos. O primeiro modelo, construído com os dados NIR, teve o intuito de prever a dimensão dos grânulos. Uma vez que o modelo apresentou um RMSEP elevado (50.5 μm) e um coeficiente determinação de previsão muito baixo (0.19), considerou-se que este modelo não é aceitável para a previsão do tamanho dos grânulos.

A segunda abordagem de regressão utilizou os parâmetros do processo para prever as respostas do processo. Foram modeladas a densidade areada (BD), a densidade batida...
(TD) e a dimensão dos grânulos (GS). Pela análise estatística dos modelos, os coeficientes de determinação de previsão foram: 0,89 para GS, 0,90 para TD e 0,91 para BD. Estes, indicam uma boa capacidade de previsão das respetivas respostas. Cada um dos modelos demonstrou, também, que a força de compressão foi a variável que mais influenciou, e de forma positiva, tanto a densidade como a dimensão dos grânulos.

**Palavras-chave:** Compactação por Rolos; Espetroscopia de Infravermelho próximo; Granulação; Quimiometria; Produção Contínua.
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List of abbreviations

ANOVA, Analysis Of Variance
API, Active Pharmaceutical Ingredient
BA, Bonding Area
BD, Bulk Density
BS, Bonding Strength
cGMPs, Current Good Manufacturing Practises
CM, Continuous Manufacturing
CPP, Critical Process Parameters
CQA, Critical Quality Attributes
DG, Dry Granulation
DoE, Design of Experiment
EMA, European Medicines Agency
FDA, Food and Drug Administration
LV, Latent Variable
MS, Mean Square
MSPC, Multivariate Statistical Process Control
NIR, Near-Infrared
NIRS, Near-Infrared Spectroscopy
PC 1, Principal Component 1
PC 2, Principal Component 2
PCA, Principal Component Analysis
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PAT, Process Analytical Technology

PLS, Partial Least Square

PMP, Pharmaceutical Manufacturing Process

PSD, Particle Size Distribution

QbD, Quality by Design

RC, Roller Compactor

RMSECV, Root Mean Square Error of Cross Validation

RMSEP, Root Mean Square Error of Prediction

RMT, Raw Materials Traceability

RSD, Relative Standard Deviation

RTD, Residence Time Distribution

RTRT, Real-Time Release Testing

SavGol, Savitzky-Golay

SD, Size Distribution

SE, Square Error

TD, Tapped Density

TRU, Traceability Resource Unit
Chapter 1

Motivation

The continuous manufacturing (CM) approach for medicines offers immense benefits over traditional batch processing. Not only because it affords flexibility and economic advantages but also because the higher knowledge-based and control level drives the process straight into the highest quality standards.

A CM line built to produce immediate release tablets has been among the most studied processes in the endeavor for making CM a reality. The roller compaction process plays an important role in this context, since dry granulation is more suitable to CM processes and has known advantages as preserving heat and moisture sensitive compounds, among others.

The CM approach for the manufacturing of drug products lays on top of the quality-by-design (QbD) principles, which demand the implementation of process understanding methodologies and requires full adoption of process analytical technologies (PAT). In this context, the widely adopted near-infrared spectroscopy method, as a PAT tool, enables real-time monitoring of the process, feeding process models with frequent and high quality data. Statistical models can be adjusted to deal with these data to monitor and to estimate in real-time drug product properties.

Thus, this work aims at providing knowledge on powder granulation by roller compaction, as a continuous process, to support its future implementation in pharmaceutical industry.

The experimental work was performed in the research and development continuous tableting line (PROMIS-line), constructed at the School of Pharmacy of the University of Eastern Finland.
Chapter 2

Objectives

This written thesis is the result of the experimental work performed in the PROMIS-line (School of Pharmacy of the University of Eastern Finland).

Therefore, the main objectives of this work are:

1) identify the critical process parameters affecting the critical quality attributes of granules produced by RC;

2) implement an analytical method (near infrared spectroscopy) to monitor in real-time the quality of granules in the RC process;

3) build predictive models for estimating the properties of granules (size and density) from spectral and process data.
Chapter 3

Introduction

3.1 Continuous manufacturing

The pharmaceutical manufacturing sector is characterized by a traditional way of manufacturing drug products (batch production), that has been revealed often inefficient at several levels. Thus, the lack of agility, flexibility and robustness in pharmaceutical processes leads to failure in production units which is in the origin of drug shortages, high production costs and waste. Since shortages are mainly related to a supply disruption caused by non-conformities in the quality of whole facility or drug product, regulatory authorities have been looking for promoting the adoption of more scientific mechanistic understanding of processes and methods applied on pharmaceutical industry.(1)(2) This endeavour is among the aims of regulatory authorities, such as Food and Drug Administration (FDA) or the European Medicines Agency (EMA) as they regulate pharmaceutical drug products and promote a flexible pharmaceutical sector that reliably produces high-quality drugs without extensive regulatory oversight.(3)

In general, in a batch process, the raw materials are loaded into the equipment at the beginning and final products are discharged at once, at the end of the process. Nothing comes in and nothing comes out of the equipment during the process run.(1) Some adopted processes are indeed fed-batch as during the production cycle some components are added in a continuous or discrete way.

In contrast, in a continuous process, the materials and products are continuously charged and discharged over time.(1)

So far, a pharmaceutical manufacturing process (PMP) rather consists of a combination of batch and continuous unit operations, such as in a tablet production line, where powder blends are made in batch mode and tablets are produced continuously in a tablet press. The PMP as a whole is globally considered to operate in batch mode.(4)

The future of PMP lies in continuous manufacturing (CM), a breakthrough over the standard batch concept. In CM, single unit operations are all connected together in a logic sequential order – integrated process. Process Analytical Technology (PAT) tools are implemented to
provide real-time acquisition data for process monitoring and control. Multivariate analysis is performed to extract information and to gain scientific knowledge about the process. Engineering process control systems are designed to reduce the impact of raw materials and process variability on the quality of drug products. (1) An overview of those two methodologies is represented in Figure 1.

![A conceptual integrated continuous manufacturing process](image)

![A typical batch manufacturing process](image)

**Figure 1** – The integrated continuous manufacturing process concept versus the more widely adopted batch processing concept. (Adapted from (1))

Batch manufacturing has been applied for the production of pharmaceutical products since pharmaceutical industry’s fast expansion in 80s. (5) Batch processing requires that samples from one unit operation should be taken according to previously settled in-process controls. Samples are tested off-line and stored, while they wait for quality control approval, and finally they are sent to the next processing step. However, if the in-process product does not meet quality specifications, then it may be discarded, or even reprocessed, before moving to the next process step. (1)

In CM, materials obtained from each process step are sent directly and continuously to the next step until the end of the process. This means that in-process material is produced within quality specification limits, at a given time, straight through the final product. (1) Hence, CM shows up as an integrated system approach built in with a model-based control placed throughout the process flow. CM is, indeed, designed as a whole, so any distinction between upstream and downstream or drug substance and drug product, as currently used, can be eliminated. (5)

Although the aforementioned description is the best known for CM, some authors advocate that the integration of several unit operations into a single line is a mere heterogeneous process, since there’s still significant powder transport challenges, unnecessary process
steps and higher risk of process issues. Genuine CM involves “homogeneous processes”, that is, the active-exciptient combination is engineered so to have the key properties needed with the view to directly make the final dosage form (e.g. extrusion, spray drying, thin film formation). From this point of view, heterogeneous processes constitute the first step in the transition from batch to homogeneous continuous processing. (5)

3.1.1 Advantages of CM over batch manufacturing

The overall advantages of CM embrace three main fields: 1) product development and quality; 2) costs; and 3) footprint. (6) As these fields are intimately related with each other, their benefic effects are felt as a whole over the CM concept.

CM offers a sort of opportunities to increase flexibility of PMP and to provide high quality drug products. In fact, CM can increase production volume without scale-up concerns, yielding a quicker response capacity. Scale-up deliberations, like process operating time, number of parallel processing lines and flow rate set up are introduced into the process design and control. Besides, the small volumes of raw materials needed to run the CM process allow operating with smaller equipments, thus eliminating scale-up. (7) (4) Hence, CM is able to reduce the costs regarding expensive active pharmaceutical ingredients (APIs) and excipients needed for process development studies and optimization efforts. Also, CM puts forward the streamlining of the whole process by excluding work-up unit operations. (1) (5) Removing scale-up bottlenecks from process development, reduces time to market, enhancing the opportunities to promote fast and efficient clinical development of new drugs. (1)

CM is able to reduce supply chains. As production can be accomplished at different scales, APIs, process intermediates and drug products are manufactured in-place, in a continuous sequence operation, without any further storage or shipping steps. This is a major improvement since removal of hold times between steps assures that sensitive materials are not degraded; in addition, being manufactured in a small scale production line, less risks can be associated with highly energetic or reactive materials. So, CM rises as a more flexible and safe method even when applied to a non-specialized manufacturing facility. (4) (8)

CM is built under the regulatory authorities guidelines regarding quality-by-design (QbD) approach for pharmaceutical development. According to the FDA, QbD is “a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management.” (4,9,10). Over the last decade the International Conference on Harmonisation
A continuous manufacturing model for the production of granules by roller compaction

(ICH) has released a few guidance documents in order to clarify how to implement this new concept. The ICH Q8(R2) – Pharmaceutical Development, ICH Q9 – Quality Risk Management, ICH Q10 – Pharmaceutical Quality System, ICH Q11 –Development and Manufacture of Drug Substances, as well as ICH Quality Implementation Working Group on Q8, Q9, Q10 Questions & Answers (R4) and Points to Consider (R2), documents consist of high-level guidelines concerning the scope, definition and implementation of QbD in pharmaceutical industry.(9)(11–15) A robust process is capable of producing drug products with acceptable quality. However, only through a strategy for process control, can its variability be controlled. Process control aims at achieving variability control by reducing input variation and/or adjusting for input variation during production. Such a strategy should be set up based on product and process understanding. Since PAT enhances process understanding, a forward control strategy can afford real time analysis and control of the output quality.(10) Thus, processes are controlled with robust and advanced process models, leading to a much lower risk of going out of specification, when compared to batch processes.(5)(16)

In short, CM process line is usually more efficient than its traditional batch counterpart. The manufacturing footprint is reduced whereas intermediates flow from one processing step to the other without concerning isolated rooms or dedicated modules. Consequently, CM requires smaller equipment, thus on the one hand reduces both capital and operation expenses and on the other increases throughput.(1)(17)

3.1.2 Challenges and barriers for CM

Despite of the greatest advantages of CM, it hasn’t become, yet, the gold standard for pharmaceutical industry, mainly because of a “business as usual” perspective tied to a highly conservative industry. Firstly, pharmaceutical industry is highly regulated: companies are cautious regarding regulatory aspects of unconventional procedures; companies seek approval for their products worldwide and CM may not be approved by regulators in other different countries. Secondly, it has been found that new manufacturing concepts must be proven both technologically and financially superior and applied to a product before widespread implementation can occur. So, because technologies must be already adopted for the industry to adopt them, the introduction of CM has been rather slow.(5)

However, this is starting to change. Whilst benefits of CM are being perceived by management, more investments are made so that CM is gradually becoming more prevalent.

In the meantime, there are some challenges for the implementation of CM:
1) Business and organizational. The established batch asset-base, wherein a huge capital was invested during the 80s and 90s, is a hurdle for introduction of CM. The capital invested in new CM facilities can be compensated by significant savings, once that continuous process monitoring and control assure lower energy consumption, higher production yield and shorter cycle times. Also, CM requires a smaller, highly skilled workforce and a smaller footprint, enabling flexibility in plant settlement in order to meet local demand for diverse products or proximity to R&D centres.(5) It’s foreseen that new therapeutic entities or approved drugs with high market share should be the potential candidates for the introduction of CM.(1)

2) Manufacturing and development. The CM paradigm requires a new mindset from scientists who develop formulation and process, through quality units within the company, until government regulators supervising the industry. Consequently, engineers, scientists and regulators must have to upskill in statistics to better analyze and understand process data. To reap the benefits of CM, continuous process must be adopted at the earliest possible stage of product development. In addition, to expand CM technologies, a new generation of equipment, sensors and automation have to be developed, as well as system integration in order to let operation units communicate and provide process control.(5)

3) Technical aspects. There are two main tricky situations. One is the development of accurate process operation models of various steps in a continuous process, together with powder characterization and handling, especially for low-dose production. Another is how to operate start-up and shutdown as fast as possible with minimal waste. Several solutions are being proposed for the first case, whereas for the second one, a smart sequencing of unit operations during start-up and shutdown was suggested to decrease losses. (5)

In CM, intermediate products flow between unit operations and drug products are generated continuously over a certain period of time. In CM, as in any other manufacturing process, process, raw materials, quality and environmental conditions can vary over time and so those variations have to be considered when developing the CM control strategy. In order to do that, it’s mandatory to understand the impact of process dynamics as well as to recognize which materials attributes and which process variables have a significant impact on final product quality. This gained knowledge should be applied to the design of measurement systems for process monitoring and control.(20,21) Regulators and industry will have to keep developing knowledge and experience with those systems-approach methodologies with the view to achieve expertise in supporting and approval of a wider implementation of CM processes.(1)
3.1.3 Quality considerations for CM

Process understanding

Design of Experiments (DoE) is a powerful tool to gain process understanding since as “a structured, organized method for determining the relationship between factors affecting a process and the output of that process”(9), it establishes the operational boundaries of the process. Continuous process response to changes in process parameters is swift, thus enabling a huge collection of data in a short period of time from a small amount of in-process materials. These data are introduced into mathematical models to get process knowledge, whilst predictive process models are applied as a simulation tool to generate experiments and enhance process understanding, in the course of process development.(21)

Regulation of CM requires a batch definition for continuous processes and a method to obtain raw material traceability (RMT) – the competence to maintain and access the identity and attributes of the raw materials throughout the process.(22) Comprehension of how raw materials flow through the process is crucial to RMT. This knowledge can be achieved by characterization of residence time distribution (RTD), following a tracer experiment or a process modelling.(23,24) RTD is a probability distribution that depicts how a material moves within different unit operations of a continuous process system. The RTD curve is very useful to predict the diffusion of raw materials, the disturbances over the system and to determine when substances were introduced into the manufacturing system. RTD is influenced by several factors like processing time, equipment parameters and raw material properties. A suggested method to report material travelling over the system is a traceability resource unit (TRU).(25) A TRU acts as a segment of material flowing through the process together with other raw materials and can be used as a unique identifier to the process history point of view. If the CM process is integrated with packaging units, unique package identifiers must connect drug product supply chain traceability to process traceability, in order to trace any packaged drug product from marketing to its original raw materials and vice-versa.(1)

Current Good Manufacturing Practises (cGMPs) guidelines define «batch» as a specific quantity of final or intermediate product, featured by uniform properties and within specified quality limits, which is fabricated according to an individual manufacturing order through the same production cycle. Likewise, it’s expected that CM process produces batches. In fact, for CM a «lot» is equivalent to «batch» and corresponds to a specific identified amount of final product generated in a particular time or in a certain quantity in a way that both uniform character and quality specified limits are warranted.(1)
In CM, RMT is closely linked to the definition of batch. When a process demonstrates an ongoing state of control, a batch can be determined according to production time period, quantity of raw materials processed, equipment run time capability or process variation (e.g. different lots of incoming raw materials). Hence, batch concept is directly associated with process control strategy, designed to deliver uniform quality within the batch. (1)

**Control strategy**

A control strategy for CM is built to control the quality of final product throughout the manufacturing process, in response to potential variations like equipment conditions, incoming raw materials or environmental factors. (26) Usually, three levels of control strategy implementations are described:

- **Level 1 control** (engineering control) takes an active process control system to monitor, in real-time, raw materials quality attributes and then to use that information to adjust automatically process parameters with the view of conforming those quality attributes to the acceptance criteria;
- **Level 2 control** (pharmaceutical control) assumes the definition of a process design space, in which raw materials attributes and process parameters are established, and also implements an adequate end-product testing;
- **Level 3 control** is exclusively based on raw material attributes and process parameters with extensive end-product testing. (1)

Usually, in CM, the most convenient level of control is Level 1, although a hybrid perspective of different levels of control is possible for some CM process designs. (16) (27)

Process knowledge gained from monitoring and control strategies supports process state of control, a condition in which a continuous process is able to ensure that a final product is consistently delivered with the desired quality. (1) However, in the course of start up and shutdown procedures, at some point, there may be in-process materials or final products that do not meet the target quality specifications. Therefore, the competence to isolate and reject materials out of specification, as a consequence of a process no longer under a state of control, is one of the main responsibilities of a CM control strategy. Once again, RTD models are powerful tools to track non-conforming materials over the process from deviation point. The settlement of a disposition strategy when products provide from a process that is not under control together with the implementation of adequate process monitoring criteria, constitute important issues to ensure quality through the production run. (1)
The increased amount of total data collection during a continuous process run motivates the adoption of multivariate process monitoring methodologies. Multivariate statistical process control (MSPC) constitutes a process monitoring methodology applied to determine whether the variability in the process is stable over time. MSPC is used to detect abnormal events in the process that may potentially cause severe consequences and unveils which process variables may be in the origin of the event. MSPC also enhances detection of abnormal process operations by identifying changes in the relationships between process parameters and quality attributes.\(^\text{(28)}\)

Since CM process holds in-process materials and discloses a fast process dynamics, real-time monitoring of both process parameters and intermediates quality attributes shows up as a crucial stage for the settlement of a state of control. Moreover, PAT tools and multivariate models are used to build process understanding. Applying PAT tools enables the measuring of the final product quality attributes, some of which may have already been integrated into the control strategy for process monitoring and control.\(^\text{(1)}\)(\text{5}) In-line PAT tied to the control system, explains why real-time release testing (RTRT) comes up naturally for CM, as “the ability to evaluate and ensure the quality of in-process and/or final product based on process data, which typically include a valid combination of measured material attributes and process controls”.\(^\text{(9)}\)(\text{6}) So, whenever process perturbations occur, real-time rejection of non-conforming products can be performed without losing the whole batch.\(^\text{(5)}\) However, a risk analysis should be accounted to assist on PAT failure and efforts should be done to establish contingencies for process monitoring and batch release.

Innovation in pharmaceutical development follows the direction of manufacturing a high quality product (highly suitable for its intended use), built by a scientific-based design, whose production process is capable of consistently providing the desired performance of the product. The information gathered during process development (through design of experiments, PAT tools and prior knowledge) supports process knowledge and that, along with product knowledge, provides the scientific basis to define the design-space, specification boundaries and production controls.\(^\text{(9)}\) The design-space represents the relationship between both material attributes and process parameters, i.e. process inputs, and the critical quality attributes (CQA). A CQA is a specific property that should be within an adequate range to assure the intended product quality. A critical process parameter (CPP) is a process parameter which variability influences the CQA and thus, should be monitored and controlled to assure the production of a product with the expected quality.\(^\text{(9)}\)
3.2 Roller compaction

Granulation is a unit operation that consists of particle size enlargement and densification by agglomeration of small particles into larger ones. In pharmaceutical technology, the principal reasons to granulate powders are: to improve powder flow properties for further dosage filling and compression purposes; to improve product stability; to prevent powder mixture from segregation; to reduce bulk volume so that storage is minimal and transport is facilitated; to reduce potential environmental and safety hazards. (29)

There are several methods to perform granulation, even though they are usually classified as either dry or wet. In wet methods, powder mixture particles are agglutinated by spraying an appropriate solution to form a mass. After that, the wet mass is dried and larger particles, named granules, are calibrated to get the adequate size for further downstream processing. In modern pharmaceutical manufacturing, wet granulation has been by far the most common powder granulation technology. (29)

Dry granulation (DG) was first applied to pharmaceutical industry in the late 1940s, but has drawn particularly attention in the last 25 years as research in new API has increased. Some of these new therapeutic compounds are either sensitive to heat or moisture and, therefore, cannot undergo wet granulation. (29)

DG process began by producing uniform densified granules, called slugs, during a process named slugging. Nowadays, DG is mostly performed using roller compaction technology, whereas it offers many advantages over other granulation methods: (29)

1) it is among the most cost-effective granulation processes, since it requires less space, personnel, energy and time consumption;

2) it is the only efficient and safe process for formulations with drug substances sensitive to heat, moisture or solvents, since no liquid nor additional heat are needed;

3) it is a continuous process with higher throughput and lower energy consumption;

4) it is able to produce more homogeneous products, when compared to other DG techniques;

5) it lends itself to a higher level of control, with implementation of on-line monitoring and control tools, as well as to automation of process settings, in order to minimise variations between batches and to improve product quality. (29–32)
3.2.1 Roller compaction process

The process of dry granulation is dependent upon bond formation between particles in order to produce granules. The aggregation of particles, stuck together due to interparticulate bond formation, is described by four distinct stages that occur accordingly to a specific order.

1) **Particle rearrangement** takes place when particles start to fill void spaces and air begins to move out from interstitial spaces inside powder mixture. Then particles start to come closer together and powder mixture’s density increases. Spherical particles tend to pack to one another, moving less than particles with other different shapes. Thus, particle shape and size are crucial in rearrangement process.

2) **Particle deformation** is considered to be a plastic deformation, as a result of increasing compress forces applied on powder particles. This deformation enhances points of contact between particles, which boosts their bonding.

3) **Particle fragmentation** comes up at higher compression forces, creating multiple new particle surface sites and thus potential bonding points.

4) **Particle bonding** ensues as a consequence of plastic deformation and fragmentation, particularly due to van der Waals forces.(29)

When powder granules undergo an applied force, a stress force is released from granules and they tend to return to their original form – elastic deformation. Albeit, granules may not completely recover from deformation and so plastic deformation occurs. Elastic and plastic deformation can occur at the same time, though only one of them predominates.(29)

Roller compaction process starts when powder mixture enters into the feeding zone, through a hopper, where particles are rearranged and densified. At this stage, press force over particles is too low. These powders then go through the compaction zone, beginning by nip region, where brittle particles break and plastic particles deform as a result of a sharp increase in compaction force. At the end of nip area, the going up further compression force exerted by two counter-rotating rolls causes particles fragmentation and particles bond to form ribbons (Figure 2).(30)
A continuous manufacturing model for the production of granules by roller compaction

Figure 2 – Representation of compaction zone with horizontal rolls, inside the roller compactor. (1) Feed Zone; (2) Compaction Zone (Nip zone + Grip Zone); (3) Extrusion Zone. (Adapted from [33])

The higher pressure occurs at neutral nip angle, which usually is slightly before the lower roll gap. The nip angle is the angle where pre-densified powders enter the nip zone, and it hinges on the material friction angle and the roll surface friction angle. (34) The nip angle is large for compressible material, but small for incompressible material. (35)

After the roll gap, the ribbons are extruded from the rolls, then chopped and milled to produce granules with adequate particle size. (30)

3.2.2 Roller compactor features

The main components of a roller compactor are: feeder, rolls, and mill. (30)

1) Feeder. Feeding system is critical to regulate powder flow, powder densification and powder deaeration. The head pressure, a pressure differential established between the bottom and top of the hopper, induces continuous densification and deaeration of incoming particles. (30)

There are two types of feeders: gravity feeder and force feeder. The gravity feeder has an adjustable tongue and a distributor at the end of hopper, working without an external driving force. The force feeder has a rotating screw, with a single flight, installed in the centre of the hopper. The rotating flight pushes the powder toward the nip area. Force feeders offer several advantages: adequate for poor flowing powders, provide continuous and consistent flowing to the nip region and prevent powder feeding disruption from trapped compressed air. (30)

Feeders design is important to get positive pressure in powder feeding. The orientation of feeder can be vertical, horizontal or inclined; for feed screw only straight (most common) and tapered designs are available (Figure 3). Vertical feeders are favoured with
head pressure from the hopper. Horizontal feeders minimize leakage and improve compactibility. Inclined feeders use also gravity to introduce powder, but show less powder leakage; they are used for multi-screw feeders in large scale equipment.\(^{(30)}\)

![Figure 3 – Feeder orientations. (a) Vertical, straight; (b) Inclined; (c) Vertical, tapered; (d) Horizontal. (Adapted from (30))](image-url)

Screw feeders unveil non-uniform feeding. The cross section of the nip area is rectangular, but the rotating screw generates a circular deliver area. As a result, the centre region of the nip is overfed, while the edges are scarcely fed, producing ribbons with thinner and more fragile edges.\(^{(36)}\) Also, as single rotating flight exerts pressure on the compact in the roller gap, the feed pressure is irregular and induces an uneven distribution of the powder in the nip area. Hence, ribbons may be more compacted in one area than the other.\(^{(37)}\) This effect can be reduced, following one of these suggestions: round off the end of screw flight, select double flight screws to get a uniform force distribution, choose multiple feeder screws and elevate the position of the screw.\(^{(30)}\)

Feed screw affects granules characteristics by controlling the roll gap, which further regulates the amount of material coming between the rolls.\(^{(38)}\) Hence, the roll gap defines the ribbon thickness and, consequently, the product quality. It has been understood that when the roll gap is reduced, powder is compressed at a much higher compaction force, so more densification occurs. As a result, the average density of the ribbon is inversely proportional to the roll gap.\(^{(39)}\) Besides, if the two rolls are fixed, the compaction force will
vary enormously with the fluctuating mass flow, throughout the process. On the contrary, if the rolls are movable, roll compaction force can be kept constant by changing the gap width according to the mass flow.(40)

2) Rolls. Rolls are key components that exert compression force. Rolls are characterized by their orientation, mounting, arrangement and pressurizing system. The rolls orientation determines the feeder orientation. Therefore, rolls can be horizontal (most common), inclined or vertical (Figure 4). Horizontally aligned rolls are equipped with vertical or inclined feeders; vertically aligned rolls are equipped with horizontal feeders.(30)

![Figure 4 – Roll orientations. (A) Horizontal; (B) Inclined; (C) Vertical. (Adapted from (30))](image)

The surface of rolls can be smooth, corrugated or fluted (Figure 5). Smooth and corrugated rolls are the most common. Smooth rolls are advantageous in overcoming sticking problems and also can reduce the amount of lubricant needed. Corrugated rolls are selected to give more gripping force to the powder, in order to solve the inadequate feeding and uneven compact, though powder sticking may be a problem.(30)

![Figure 5 – Roll surface. (a) Smooth roller; (b) Corrugated; (c) Fluted. (Adapted from (30))](image)
3) Mill. The milling step intends to obtain granules from the ribbon. In general, the mill consists of a moving rotor and a fixed sieve of a chosen mesh size. Not only the rotor speed, but also the rotation direction (clockwise direction, counter-clockwise direction or a combination of both) can be adjusted, according to the equipment. Some authors have proposed that operating in oscillating mode (clockwise/counter-clockwise) yields higher throughput than rotation (clockwise). Concerning the mill speed, it is reported that, typically, the higher the mill speed, the higher percentage of fines is got at the end of the process. Other studies have shown that the effect of milling conditions on granules mechanical properties, obtained from die compaction, is irrelevant.

Roll compactors are built with a sealing system to prevent the loss of powder from the sides. The most common sealing systems are: cheek plates, with a fixed side sealing, and rimmed-roll, in which side sealing is integrated with the bottom roll. In cheek plates assembly, roll pressure and density distribution are non-uniform, whereas for rimmed-roll, the reverse effect is observed. In order to reduce the amount of fines produced during roller compaction, it is preferable to work at high roll force and use rimmed-roll as a sealing system.

Other factors like deaeration, temperature control and feeder vibration are important as well to keep the process feasible. In deaeration, the air trapped between particles may damage the new-formed ribbon: when ribbon porosity is high, air continues to leave and ribbons get weaker; when ribbon porosity is low, the trapped air may cause the ribbon to break horizontally into pieces. The air usually escapes in three ways: between the feeder base and the top of the roller, between the rolls and the cheek plates, against the flow of feed through the loose bulk material. To minimize this problem, applying a vacuum at the top and bottom level of the powder bed induces the trapped air out.

The feeder vibrator can improve the powder flow, providing a continuous driving force to break the stagnant powder bed, thus helping densification and deaeration.

The screw flight can generate excessive heat when rotating in the powder bed. This heat may elevate the local temperature and cause the powder to be partially melted and stuck to the flight. To avoid this situation, a special flight with a cooling jacket can be used.
3.2.3 Impact of process parameters

In roller compaction process, the critical process parameters needed to be optimized to assure process feasibility, ribbon quality and granule tabletibility are: compaction force, roll speed and feeder screw speed.(40)(45–47)

1) Compaction force. When subject to press force, solid particles densify, deform or fracture and bond to form ribbons. At high compaction force, a strong ribbon with low porosity and less fines is produced.(48–50) Over-compaction may break the ribbon and generate poor quality granules.(30)

Once the granules from RC are to be compressed, one of the main issues regarding a DG process is the phenomenon of loss of tabletibility of granules.(51–53) Tabletibility or compactibility (tablet tensile strength versus pressure) describes the capacity of a powder to be transformed into tablets with defined strengths under determined pressures. Tablet tensile strength is the result of the interplay between bonding area (BA) and bonding strength (BS).(54,55) Obviously, larger BA amidst granules or higher BS benefits stronger tablets.

Several mechanisms have been proposed to explain the loss of tabletibility in DG. One of the earliest hypotheses put forward is the “work hardening”, defined as the production of harder granules with markedly increased resistance to deformation.(56) Since work hardening is difficult to measure in granules, some authors have proposed its replacement by “granule hardening”(57) (under a compaction force, the granules porosity is reduced and the granule strength increases). Because of granule hardening, higher compaction forces lead to harder ribbons, harder granules and lower tensile strength tablets.(49)

It has been concluded that BA and BS influence mechanisms that determine tabletibility. In the case of plastic materials, the main mechanisms are: lubrication, granule size enlargement and granule hardening. Adding more lubricant, especially when blended in the mixture, leads to lower BS and reduced tabletibility. Thus, granules with a higher porosity are more deformable when subjected to compaction force and promote large BA and a stronger tablet. In brittle materials, granule hardening is the most important mechanism for tabletibility. However, the dominating mechanism for each situation depends upon material properties and process parameters.(58)

Some authors have pointed out that compaction force is the most important factor that affects the quality of the compact,(59) mostly for plastic materials. As for brittle materials, they seem to be less susceptible to compactibility loss. Thereby, since powder mixtures often contain plastic and brittle materials, an optimum operating range of compaction force should be determined on a case-by-case base throughout process development.(30)
2) **Screw speed.** The rotating flight generates a force which induces a downward compression force, pushing the powder into the compaction zone and causing its pre-densification. (36) Screw speed operating range should be determined based on powder flow, aeration condition and roll speed. Low screw speed may provoke scant feeding to the nip zone and poor ribbon strength. High screw speed may cause a highly densified zone in the nip area and eventually induce melting of particles on the flight, which may stop powder flow. A proper formulation modification, adequate deaeration or addition of feeder vibrator may be necessary to improve process feasibility. (30)

3) **Roll speed.** The roll speed controls the dwell time of the ribbon and the throughput of the roller compactor. Roll speed is defined according to the flowability, plasticity and elasticity of the powder.

For plastic materials, sensitive to dwell time, a low roll speed is prone to produce granules with better flow and lower friability. (60) But longer dwell time may also cause the material to lose compactibility, generating tablets with low hardness and high friability. The impact of dwell time on plastic or partially plastic deforming materials can be reduced with high roll speed and low screw speed. (59)

In case of elastic recovery materials, the compact strength depends on the dwell time in the compaction zone, as elastic recovery may occur upon the release of the ribbon. High roll speed or short dwell time may provoke cracking, weakening or even the destruction of the ribbon. Hence, for highly elastic materials, the overall process throughput is hedged by physical properties of raw materials. (30)

For brittle materials, the compact strength reveals independence from dwell time, once fragmentation occur in short time and so exposure to compaction force tends to have a limited effect on the ribbon strength. (61–63)

4) **Relationship between roll speed and screw speed.** The production of granules with desirable compression capacity is achieved by controlling the ratio of roller speed to screw speed. At constant roll speed, a low screw speed may lead to insufficient feeding and thus to thinner ribbons and weaker ribbon strength. On the contrary, high screw speed may induce overfeed and produce thicker ribbons. (48) When roller speed and screw speed ratios are kept constant, both the ribbon density and strength are independent of roller speed. (60)

The definition of roll speed to screw speed ratios hinges mostly on the properties of powder blend. Generally, for plastic materials, a higher roll speed to screw speed ratio gives better quality granules and tablets (best tablet friability, hardness and dissolution rate). (30)
Finally, the most important critical quality attributes are:

1) **Granule particle size distribution.** Small particle size of both raw materials and granules have a positive effect on enhanced tablet strength.(51) Large granules may induce weight variation during compression and because less BA is exposed, tablets exhibit low tensile strength. (45)(58)

2) **Granule/ribbon density.** Ribbon is not homogeneous in terms of density distribution, showing lower density at the edges and higher density at the centre.(31)(45)(39)

3) **Granule/ribbon porosity.** Recent studies have highlighted the importance of granule porosity. In fact, granules with high porosity, under a compression force, breakdown and above a critical porosity value disintegrate completely into primary particles, producing a tablet which microstructure resemble that formed from the original powder.(64,65) For that reason, critical porosity should be lower at higher compaction force.(58)

   Harder ribbons (resulted from higher compaction force) exhibit low porosity, and leads to harder granules and lower tensile strength tablets.(45)(49)

4) **Amount of fines produced.** When there are too much fines, problems regarding poor flow, weight variation and picking may occur during tablet compression. Moreover, fines generated during RC are undesirable as they frequently cause material loss and reduce granule flow properties. Also, it is strongly discouraged to recycle fines in the process, since the regranulation of fines has a negative influence on API-conformity.(42,45)(51)
3.3 Process monitoring tools

3.3.1 Near-infrared spectroscopy

Near infrared spectroscopy (NIRS) refers to the interaction of light with wavelength from 780 to 2500 nm with matter. The observed spectral bands are overtones and combinations of fundamental bands occurred in the mid-infrared region. The NIR bands are combinations of hydrogen atoms with larger atoms, mainly, C–H, N–H, O–H bonds. The overtones of these fundamental bands are close to NIR region, and that’s why they can be seen. However, NIR bands are 10-100 times weaker than the corresponding mid-IR bands. Thus, NIR spectra have been extensively used to identify raw materials as they are able to discriminate compounds with resembling structures.(66)

Diffuse reflectance measurements derive from interaction of NIR radiation with solid samples. The sample is illuminated directly, without any pre-treatment, and the incoming radiation is absorbed or scattered by the particles in many angles and then collected through mirrors. The scattered radiation that returns to the detector is called remitted fraction. The obtained spectrum is a result of the intensity of the radiation measured by the detector. An adequate software processes the detector measured intensities, generating a final spectrum and stores the spectral data in a convenient format (Figure 6).(66)

Figure 6 – Main components of an off-line NIR instrument. (a) radiation source; (b) sample–radiation interaction device; (c) wavelength selector; (d) detector; (e) data collector, processing, storing and control device. (Adapted from (66))

Overview of the main NIR components

(a) radiation source – the most common is a tungsten filament source with a trace of iodine inside a quartz bulb. Typical power and temperatures are in the range 25–100 W and 2000–3000 K, respectively.

(b) sample-radiation interaction device – promotes the interaction of the polychromatic or monochromatic NIR radiation with the sample.

(c) wavelength selector – determines the resolution of the NIR spectra.
(d) detector – measures the intensity of the radiation scattered by the sample. InGaAs devices (an alloy of gallium arsenide and indium arsenide) demonstrate a quick response and a high detectivity over the range of 1000-2500 nm.

(e) data collector, processing, storing and control device – consists of a microcomputer running a program able to control the spectrophotometer, to collect and to process the detector measured intensities in order to build the final information in terms of a spectrum (absorption intensities versus wavelength).(66)

In a continuous process, the use of a single or a bundle of fibers to carry the NIR radiation toward the sample and back to the NIR detector is a smart choice to perform monitoring at long distances. The optical fiber has the ability to conduct electromagnetic radiation between two points through a nonlinear path with low losses at distances of 10-100 m.(66)

3.3.2 Chemometrics tools

Chemometric techniques are generally required to the treatment of spectral data for process data analysis. Due to the capability of processing vast amounts of data, algorithms are able to extract the multivariate information needed to better understand the process.

NIRS has the ability not only to identify a certain compound, by comparing it with those existent in the “spectral library” (qualitative method), but also to determine the amount of compound present in a sample (quantitative method). One of the most common multivariate quantitative methods is the partial least squares (PLS), as it’s been widely used to predict product properties from NIR spectra.(66–72) PLS estimates its model components (latent variables) by maximising the covariance between two matrices: the system inputs and the system response.

Principal component analysis (PCA) is a powerful tool for data compression and information extraction. It provides an interpretable model of a data set by finding combinations of variables that describe major trends in data. PCA model is the result of compressed data in few components (principal components) in terms of the scores, which contain information on how the samples relate to each other, and loadings, that contain information on how the variables relate to each other.(73)
3.3.2 Process analytical technology

Accordingly to the ICH Q8, PAT is “a system for designing, analyzing, and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw materials and in-process materials and processes with the goal of ensuring final product quality”. The objective of PAT is to design and develop dynamic manufacturing processes able to compensate for variability in both raw materials and equipment. Thus, generating process and product quality information in real-time, operations can be immediately adjusted. Through PAT any source of variability affecting a process is identified, explained and managed. This relates to the key principle that quality cannot be tested, but should rather be built into the product by design. Therefore, production under QbD principles involves PAT strategies to reduce identified manufacturing risks linked to product quality.(9)

The successfully establishment of PAT requires a careful selection of methods with the ability to measure the CPP, preferably in an in-line or on-line mode – PAT monitoring tools. In this context, NIR is one of the most flexible tools, since it’s a fast and non-sample-destructive technique that measures samples without previous preparation in a real-time basis.(66)

Process monitoring within PAT should use samples, in their native state, ideally taken on-line or in-line, through continuous measurements, in order to get a faithful representation of the real process. Thus, NIRS is capable of describing process trajectory trend through the whole spectra treated by multivariate analysis.(66)
Chapter 4

Materials and methods

4.1 The continuous manufacturing line

The equipment used to produce the granules was part of the PROMIS continuous tablet manufacturing line (University of Eastern Finland, School of Pharmacy, Kuopio, Finland) (Figure 7).

![Figure 7 – Depiction of complete continuous line. A – powder loss in weight feeders; B – continuous mixer; C – roller compactor; D – screw conveyer; E – vacuum conveyer; F– tableting machine. (Adapted from (74))](image)

This line is able to operate in complete line configuration, double blending/direct compression and direct compression configuration. In complete line configuration, up to four powder loss-in-weight (LIW) feeders feed API and excipients to the continuous mixer. From the continuous mixer, a screw conveyer transfers the powder mixture to the RC. From the RC, a vacuum conveyer transfers granules to the granule LIW feeder. This last feeder together with LIW microfeeder (for lubricant) feed the second continuous mixer. At last, a vacuum conveyer transfers granules to the tableting machine.
Table 1 – Description of the equipment used in complete continuous line.

<table>
<thead>
<tr>
<th>Equipment</th>
<th>Brand and manufacturer</th>
<th>Specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 Loss-In-Weight powder feeders</td>
<td>K-Tron, K-ML-D5-KT20</td>
<td>500 g/h - 24 kg/h</td>
</tr>
<tr>
<td>Loss-In-Weight granule feeder</td>
<td>K-Tron, K-CL-24-KT24</td>
<td>300 g/h - 40 kg/h</td>
</tr>
<tr>
<td>Loss-In-Weight micro feeder</td>
<td>K-Tron, K-CL-SFS-MT24</td>
<td>32 g/h - 300 g/h</td>
</tr>
<tr>
<td>Modified Loss-In-Weight feeder for lubricant and low dose API</td>
<td>K-Tron, K-CL-24-KT24 modified</td>
<td>X - 150 g/h</td>
</tr>
<tr>
<td>Two continuous blenders</td>
<td>Hosokawa, Modulomix</td>
<td>300 - 1450 rpm</td>
</tr>
<tr>
<td>Roller compactor</td>
<td>Hosokawa, Pharmapaktor L200/30P, with flake crusher FC 200</td>
<td>Screw speed: 0 - 53 rpm; Roll speed: 0 - 19 rpm; Roll pressure: 0 - 50 kN; Flake crusher: 32 - 313 rpm</td>
</tr>
<tr>
<td>Tableting machine</td>
<td>PTK, PT-100 with PISCon</td>
<td>96 000 tablets/h</td>
</tr>
<tr>
<td>Screw conveyer</td>
<td>Entecon Spiral Screw</td>
<td>Constant speed</td>
</tr>
<tr>
<td>Vacuum conveyer</td>
<td>K-Tron, P10-BV-100-VE</td>
<td>Constant speed</td>
</tr>
<tr>
<td>Vacuum conveyer</td>
<td>Volkmann, VS200 Eco</td>
<td>Constant speed</td>
</tr>
</tbody>
</table>

The optimum throughput tested in complete continuous line is 20 kg/h. It was realized that the tableting is the rate limiting equipment in the line. Moreover, it is known that upper and lower limits of the line are dependent on the formulation (flowability, cohesiveness and adhesiveness of powder/granule mixture).

Each equipment unit of the line (except the tableting machine) is connected to the control-PC. The Labview control software (University of Eastern Finland, School of Pharmacy, Kuopio, Finland) controls, collects and stores the data from every equipment unit (Figure 9 and Figure 9). Data are also stored in the Datain Server (Kuava, Finland). Data can be shown in graphs for monitoring purposes.
A continuous manufacturing model for the production of granules by roller compaction

4.2 Equipment

The equipment used to perform the experimental work is described below.

1) Production of granules

- Three LIW powder feeders K-Tron, K-ML-D5-KT20 (for excipients and API) (Figure 10);
- One LIW micro feeder K-Tron, K-CL-SFS-MT12 (for lubricant) (Figure 10);
- One continuous mixer, Hosokawa Modulomix (Figure 11);
- One Roller Compactor Hosokawa, Pharmapaktor L200/30P, with a flake crusher FC 200 (Figure 12, Figure 13, Figure 14).
The LIW powder feeder K-Tron has a feeding device with a hopper placed on a platform scale. The weight of the feeding device and hopper is electronically tared. The feeder is filled through its hopper and the raw materials are discharged from the hopper by twin-screws. The resultant weight loss per unit of time is determined by weighing and control system. The actual weight loss per unit of time is compared with the desired weight loss per unit of time. Any difference between those two values induces a correction in the speed of the feeding device. (75)

![Assembly of the four LIW feeders that feed the mixer.](image)

continuous mixer, Hosokawa Modulomix, is a tubular blender with a horizontal cylinder and a bladed shaft that rotates along its central axis. Powder is fed in one end and the impeller moves the powder to the other end of the cylinder and out of the mixer. The homogeneity of the mixture depends on the axial and radial movements of the particles in the mixer. (74)
The RC Hosokawa Pharmapaktor L200/30P, with a flake crusher FC 200, consists of: a feeding unit with a vertically oriented screw; a compaction unit with two counter-rotating rollers, horizontally oriented, with a ribbed surface and a fixed gap between the rollers and a milling unit with a mesh screen of 1.25 mm.

The force transducer (Figure 14 A) measures and regulates the pressing force between the rollers. If the maximum allowable pressing force is exceeded, the machine switches off. A pre-stressing force must be adjusted in order to approximate the pressing force to the target value (i.e., if the target pressing force is 35 kN, the pre-stressing force should be adjusted to 30 kN). Usually, the pre-stressing force (called actual value) is 5 kN lower than the target pressing force.
Figure 12 – RC Hosokawa Pharmapaktor L200/30P. On the top left: RC prepared to operate; on the top right: detail of the vertical screw; bottom, on the bottom: detail of the milling screen.
Figure 13 – The RC rollers. On the top: the two disassembled rollers of 25 Kg each; on the bottom: top view of the two horizontal assembled rollers showing the fixed gap between them.

Figure 14 – The compaction system. A) The force transducer. B) The Hexagonal nut on the right roller arm. C) The roller shoulder. The force transducer measures the pressing force between the rollers. The hexagonal nut is tightened to increase the pre-pressing force or is loosened to reduce the pre-pressing force. The roller shoulder fixes the rollers and is connected to the roller arms by eye bolts.
2) Monitoring of produced granules

- The NIR-sphere system (Specim RHNIR, Spectral Imaging Ltd, Oulu, Finland) (Figure 15). consists of an integrated sphere with a tube inside, through which powder flows, surrounded by six fibers placed in different angles. The fibers collect the signals to the Specim’s Spectral Camera, which consists of an ImSpector N17E imaging spectrograph for the wavelength region 900–1700 nm and a temperature stabilized InGaAs detector and a monochrome camera. This system collects 100 spectra per second. The image resolution and rate are 320 pixel and 35 Hz, respectively. The light source is a halogen lamp.

- Eyecon™ system (Eyecon™, Innopharma Labs, Dublin, Ireland) (Figure 16) is a particle sizing system, based on direct imaging. It provides real-time particle size and shape information, with a maximum material speed of 10 m/s and a measurement time of 2 seconds per image. The light source is 15 x high intensity/low energy LEDs (red, green and blue). The measured size range is 50 μm – 3000 μm.
A continuous manufacturing model for the production of granules by roller compaction

Figure 16 – Configuration of the NIR sphere and Eyecon to on-line monitoring of the granules. On the top left: the NIR sphere attached to the outlet of the RC and the glass frame through which Eyecon collects images of the granules; on the top right and on the bottom: Eyecon capturing granules’ images.

3) **Measurement of granules’ physical properties**

- **Malvern Mastersizer 2000 equipment** (Figure 17) measures off-line the particle size through the principle of light scattering. A laser beam impinges on the particles and they scatter light at an angle that is inversely proportional to their size. The measured size range is 0.02 μm – 2000 μm. It is able to measure wet (Hydro Unit) or dry materials (Scirocco Unit).
The light source is composed of a helium-neon laser (red light) and a solid-state light source (blue light).

![Figure 17 – Malvern Mastersizer 2000, with Scirocco Unit (on the left) and Hydro Unit (on the right). (Adapted from (76))](image)

### 4.3 Raw materials

The powder mixture consisted of:

- **Microcrystalline cellulose (MCC)** (AVICEL PH 102, FMC, Cork, Ireland) is an excipient, with the chemical name cellulose, the chemical formula \((\text{C}_6\text{H}_{10}\text{O}_5)_n\), where \(n \approx 220\) and the molecular weight 36,000 g/mol. In tablet manufacturing MCC is used as diluent and disintegrant and leads itself to direct compression. MCC is a purified, partially depolymerised cellulose, commercially available in different particle sizes and moisture grades. MCC PH 102 is suitable for direct compression. MCC is slightly soluble in sodium hydroxide solution, and practically insoluble in water, dilute acids and most organic solvents. (77) MCC deforms mainly by plastic deformation.(30)

- **Lactose α-monohydrated** (Lactochem, DOMO, The Netherlands) is an excipient, with the chemical name O-β-D-Galactopyranosyl-(1→4)-α-D-glucopyranose monohydrate, the chemical formula \(\text{C}_{12}\text{H}_{22}\text{O}_{11}.\text{H}_2\text{O}\) and the molecular weight 360.31 g/mol. Lactose α-monohydrated is a natural disaccharide, obtained from milk and it is composed by one galactose and one glucose moiety. In tablet manufacturing it is used as binder, diluent and filler and is able to undergo direct compression. It is practically insoluble in chloroform, ethanol and ether and soluble in water. (77) Lactose is mostly brittle and partially plastic.(30)

- **Paracetamol** (Xiamen Forever Green Source Biochem Tech. Co., Ltd, Xiamen, China) is an API with analgesic and antipyretic therapeutic effects. Its chemical name is N-(4-Hydroxyphenyl)-acetamide, with chemical formula \(\text{C}_9\text{H}_9\text{NO}_2\), and molecular weight of 151.16 g/mol. It is very slightly soluble in cold water, considerably more soluble in hot water; soluble
in methanol, ethanol; practically insoluble in petroleum ether, pentane, benzene. (Index Merck) It is a highly brittle material that deforms mainly by elastic deformation.

- **Magnesium stearate (Mg.Stearate)** (Peter Greven, Venlo, The Netherlands) is an excipient with the chemical name octadecanoic acid magnesium salt, the chemical formula C\(_{36}\)H\(_{70}\)MgO\(_4\), and the molecular weight 591.24 g/mol. Mg.Stearate is used in tablet manufacturing as lubricant. It flows poorly and is a cohesive powder. It is practically insoluble in ethanol, ether and water; and slightly soluble in warm benzene and warm ethanol.(77)

The raw materials were characterized according to the physical properties described in Table 2 and Figure 18. The size, the bulk density and the tapped density were measured according to the procedure described in Methods (points 4.3.5 and 4.3.6). The angle of repose was measured in Hosokawa Micron Powder Characteristics Tester PT-X equipment. The Carr index was determined by the formula:

\[ CI = \left(1 - \frac{BD}{TD}\right) \times 100 \]  

(4.1)

Lactose α-monohydrated shows the highest bulk density and poor flow properties (Carr Index 24.9). Paracetamol has the worst flowability (Carr Index 28). MCC is the material that flows the best (Carr Index 16.7).

<table>
<thead>
<tr>
<th>Raw material</th>
<th>Amount used in formulation (%)</th>
<th>Size (90%)/μm</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>True density (Literature) (g/ml)</th>
<th>Angle of repose</th>
<th>Carr Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avicel PH 102</td>
<td>60</td>
<td>275.30</td>
<td>0.36</td>
<td>0.43</td>
<td>1.440(78)</td>
<td>39.3</td>
<td>16.7</td>
</tr>
<tr>
<td>Lactose Lactochem</td>
<td>24.5</td>
<td>148.62</td>
<td>0.49</td>
<td>0.65</td>
<td>1.545(77)</td>
<td>55.8</td>
<td>24.9</td>
</tr>
<tr>
<td>Paracetamol</td>
<td>15</td>
<td>353.6</td>
<td>0.33</td>
<td>0.46</td>
<td>1.293(77)</td>
<td>60.0</td>
<td>28.0</td>
</tr>
<tr>
<td>Mg Stearate</td>
<td>0.5</td>
<td>17.83</td>
<td>0.26</td>
<td>0.35</td>
<td>1.092(77)</td>
<td>53.3</td>
<td>25.2</td>
</tr>
</tbody>
</table>

Table 2 – Some physical properties of the raw materials.
Figure 18 – Particle size distribution (PSD) of raw materials.
4.4 Methods

4.4.1 Design of experiments

In order to determine the relationship between the possible CPP’s and granules’ CQAs, a design of experiments (DoE) was performed in Modde (MKS, US). In this DoE, the following three CPP’s were selected and their corresponding variation was: roll speed (from 3 rpm to 8 rpm), compression force (from 15 kN to 35 kN) and mill speed (from 50 rpm to 250 rpm) (Error! Reference source not found.). The DoE yielded 13 experiments. The experiments order assured that the three centre points (run 11, run 12 and run 13) took place in three different moments of the experimental design: in the beginning, in the middle and in the end of the DoE. Besides, the experiments’ run order also interchanged in terms of target compression force, to avoid having two consecutive runs with the same compression force (see detail in Table 4, given in Chapter 5).

Table 3 – Design of experiments obtained by Modde.

<table>
<thead>
<tr>
<th>Experience Name</th>
<th>Run Order</th>
<th>Roll Speed (rpm)</th>
<th>Compression Force (KN)</th>
<th>Mill Speed (rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1</td>
<td>2</td>
<td>3</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>N2</td>
<td>3</td>
<td>3</td>
<td>35</td>
<td>250</td>
</tr>
<tr>
<td>N3</td>
<td>5</td>
<td>8</td>
<td>15</td>
<td>250</td>
</tr>
<tr>
<td>N4</td>
<td>10</td>
<td>8</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>N5</td>
<td>11</td>
<td>3</td>
<td>15</td>
<td>250</td>
</tr>
<tr>
<td>N6</td>
<td>12</td>
<td>3</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>N7</td>
<td>4</td>
<td>8</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>N8</td>
<td>8</td>
<td>8</td>
<td>25</td>
<td>150</td>
</tr>
<tr>
<td>N9</td>
<td>9</td>
<td>5.5</td>
<td>35</td>
<td>150</td>
</tr>
<tr>
<td>N10</td>
<td>7</td>
<td>5.5</td>
<td>25</td>
<td>250</td>
</tr>
<tr>
<td>N11</td>
<td>1</td>
<td>5.5</td>
<td>25</td>
<td>150</td>
</tr>
<tr>
<td>N12</td>
<td>13</td>
<td>5.5</td>
<td>25</td>
<td>150</td>
</tr>
<tr>
<td>N13</td>
<td>6</td>
<td>5.5</td>
<td>25</td>
<td>150</td>
</tr>
</tbody>
</table>
4.4.2 Preparation of the mixture

Each one of the four LIW feeders was manually filled in with its raw material. The feeders were remotely controlled by the Labview control software.

After ensuring that the feeders had been filled in with enough amount of raw materials, the mixing process was ready to start. The rotating hopper (that helps the powder flow continuously from the feeders into the mixer) was turned on, followed by the feeders and the mixer. Each feeder flow rate was adjusted according to both the mixture throughput (20kg/h) and the proportion of the respective raw material in the mixture. The mixer speed was set to 1300 rpm. The first operating minutes of the mixer were considered a purge and that mixture was wasted. After that, the mixture was collected to a big plastic bag attached to the outlet of the mixer.

4.4.3 Granulation process

The RC was remotely controlled by the Labview control software. This software commanded the switching on/off operations of the RC. However, the parameters' settings were introduced manually by the RC onsite control panel. The RC feeding was done manually throughout the process. At the beginning of each run, the parameters were set gradually, following the order: mill speed, roll speed and screw speed. On the other hand, when the process was about to end, the process parameters were slowed down gradually by the opposite order: screw speed, roll speed and mill speed. The process variables variation was followed by graphs exhibited by the control software and the data (measured once per second) were stored by the same software.

4.4.4 On-line monitoring of the properties of granules

The granules’s size was monitored on-line by NIRS and direct imaging (Eyecon™ system). The NIR-sphere was attached to the outlet of the RC, collecting the in-coming granules. The NIR signals were sent to the detector and stored by the software. The granules then fell onto a tilted ramp where they were exposed to the Eyecon LED’s and photographed (Figure 19). The camera information was sent to the software and data were stored.
4.4.5 Granules’ size measurement

During the run, four granules samples were collected (one sample at the beginning, two samples in the middle and one sample at end of the process) onto a tray and then stored in a labeled plastic bag for future measurement. These samples were weighed, one by one, and given the total run time of each experiment, the respective throughput was computed.

The size of the granules was measured off-line by light scattering in the Scirocco unit of the Malvern Mastersizer 2000. The diameters of the particles shown in the reports of the light scattering method are displayed as d(0.1), d(0.5) and d(0.9). These results correspond to the mass median diameter of the volume of distribution and are expressed in microns. For instance, d(0.9) indicates that 90% of the sample has a size smaller than that value, whereas 10% has a larger size. To facilitate the understanding of this terminology, in next chapters, d(0.9) was translated by 90% fraction of the granules’ size distribution.
4.4.6 Granules’s density measurement

The granules’ samples collected throughout the process were used to determine the bulk density (BD) and the tapped density (TD). The BD was determined by reading the bulk volume of the granules in a graduated cylinder and measuring the corresponding mass on an analytical scale.

\[
BD = \frac{Mass}{Bulk\,Volume}
\]  

(4.2)

In order to determine the TD, the bulk volume inside the beaker was tapped by an Erweka tapped density tester apparatus. The tapped volume was read and the corresponding mass was measured on an analytical scale.

\[
TD = \frac{Mass}{Tapped\,Volume}
\]  

(4.3)

4.4.7 Exploratory data analysis

Data collected from NIR spectrometer were introduced in Matlab (The MathWorks Inc. Natick, MA). The spectra obtained were pre-processed with Savitzky-Golay (first derivative, first order, 15 points). Before PCA or PLS modelling all datasets were subjected to mean-centring. After that, a PCA model was built in PLS toolbox software (Eigenvector Research, Inc., Manson, WA).

4.4.8 Prediction models

The prediction of density and size of the granules was performed by two models: one built upon NIRS data and the other built upon process variables and process responses. For the first NIRS based model, the spectra were used to calibrate a model against the granule size. Thus, the NIR data that matched with their respective granules’ sampling times was selected. Those data were introduced in Matlab and in PLS toolbox software. The spectra were preprocessed with Savitzky-Golay (first derivative, second order, 15 points) and mean centring. The response data matrix consisted of information regarding 90% fraction of the
granules size distribution (SD) obtained off-line by light scattering. This matrix was preprocessed with mean centring. Besides that, many other models were built and several different preprocessing were tested. The number of latent variables was optimized with cross-validation. The model error is given as the root mean square error of prediction (RMSEP), and is relative to an unseen part of the data (the prediction set).

The second PLS model was built using Modde. The selected variables were: compression force (or roll force), roll speed, mill speed and flow rate. The selected responses were: bulk density, tapped density and granule size (90% fraction of the granules SD). The value of each response was determined by the aforementioned methods. So, the values of variables and their corresponding responses were introduced in Modde and a PLS model was built. The capability of the model in predicting the granules’ physical properties was evaluated by the analysis of variance (ANOVA). A similar strategy to compute model errors was followed in Modde.
Chapter 5

Results and discussion

5.1 Exploratory data analysis

The data collected by the NIR spectrometer was introduced in Matlab, where the mean of 100 spectra per second was calculated, in order to have 1 average spectrum per second. Then the spectra were plotted against the wavelength. The spectral region 927 nm–1085 nm was cut off, because they exhibit essentially noise and didn’t have any relevant information (Figure 20, top). The spectra were preprocessed with derivative (Savitzky-Golay (SavGol) algorithm), to remove irrelevant baseline drift. The SavGol was used with the first derivative. This subtraction removes the same signal between the two variables and leaves the part of signal that is different, removing any offset from the sample. Derivatives tend to accentuate noise, that’s why SavGol algorithm smoothes the data. Smoothing is used to remove high-frequency noise from samples and it’s an operation that acts separately on each row of the data matrix. Smoothing fits single polynomials to windows around each point in the spectrum. Then the size of the window (filter width) and the order of the polynomial are selected. In this case, the filter width has 15 points and the polynomial order is 1 (Figure 20, bottom). At last, the spectra were mean-centered, in order to build the PCA model. Mean-centring calculates the mean of each column in the data matrix and subtracts it from the column.

The following discussion will make use of the first run (run N1) of the DoE as an example for considerations on this subject over the other runs. As it can be seen, the region that reveals more information goes from around 1320 nm to 1540 nm and from around 1580 nm until the end of the spectra.
After preprocessing the spectra, a PCA model was built. Figure 21 shows the score plot with the PC 1, with 64.99% of variance captured, versus PC 2, with 34.05% of variance captured. The PC 1, the first component, describes the direction of the major variation in the data set, which is the greatest axis of the ellipse. The scores were colored according to the Hotelling’s $T^2$ statistic and labeled according to time. So, it can be seen a clear trajectory of the granulation process from its beginning (score 1, outside the ellipse, on the bottom, at right) until the end (score 2005, inside the ellipse). Following the scores along the PC 1 axis, the process starts with positive scores, out of the ellipse, then approaches the centre of the model with some negative scores deviated from that central cluster (intermediate process stage), and finally returns to the positive domain, where some of the last scores remain outside the ellipse (end of the process). The scores retained on the second and on the forth quadrants are negatively correlated, and refer to different stages in the granulation process.

The Hotelling’s $T^2$ statistic is the sum of normalized squared scores and a measure of the variation in each sample inside the PCA model. The limit defines the ellipse seen on the plane within which the data are projected (assuming that data is normally distributed which is not the case). The samples colored by the Hotelling’s $T^2$ value represent their distance to the centre of the model. So, the blue cluster of scores inside the ellipse is the core that better describes the model. The scores painted in yellow, orange or red, outside the ellipse, are far away from the centre of the model, which means that the model is not able to explain these
samples. As it will be explained later, these last scores are related to specific times of the process, where the variables varied more.

\[ \text{Scores on PC 1 (64.99\%)} \]
\[ \text{Scores on PC 2 (34.05\%)} \]

Figure 21 – The score plot for run N1, depicting PC 1 versus PC 2. The total variance captured by both components is 99.04\%. The ellipse’s border represents the 95% confidence limit.

The error matrix (E) is obtained by the difference between the original data and the model predictions (residuals). Q is the sum of squares of each row in matrix E. The Q statistic points out how well each sample conforms to the PCA model. In Figure 22 the plot represents the Hotelling's T² statistic versus the Q statistic. The dotted lines are their respective 95% confidence limit. The intersection of the confidence limits defines the region beyond which the scores distributed over this area are the most distant from the model and behave like possible outliers. Likewise the score plot, the statistic plot reveals the same samples as possible outliers: 1-12, 17, 19, 271, 893, 1485 and 1926.
Figure 22 – The statistic plot for run N1, depicting Hotelling’s T2 statistic versus Q statistic. The dotted lines represent the 95% confidence limit for both Hotelling’s T2 statistic (horizontal dotted line) and Q statistic (vertical dotted line).
5.2 Analysis of process variables

Table 4 shows the experiments' order performed. The screw speed was adjusted to the roller speed target value, in order to get the target compression force. The lag time ended when all variables (roll speed, screw speed, mill speed and compression force) stabilized. Even though the compression force has not kept constant, it was considered “stable” when the mean variation around the target compression force was about 10%.

Table 4 – Detail of the DoE performed, showing the order by which the experiments were done. The screw speed was adjusted to the roll speed in order to obtain the target compression force. The lag time was the time considered for the variables to stabilize.

<table>
<thead>
<tr>
<th>Experience name</th>
<th>Run order</th>
<th>Roll speed (rpm)</th>
<th>Compression force (kN)</th>
<th>Mill speed (rpm)</th>
<th>Screw speed (rpm)</th>
<th>Lag time (min)</th>
<th>Total run time approx (min)</th>
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<td>18</td>
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<td>1.5</td>
<td>16</td>
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<td>25</td>
<td>150</td>
<td>18.5</td>
<td>2</td>
<td>18</td>
</tr>
</tbody>
</table>

The variation of the process variables is depicted in Figures 23-28. The graphs selected are representative of the process behaviour within each target compression force. The graphs describe the process variables behaviour when the compression force is set to 15 kN (Figures 23-24), 25 kN (Figures 25-26) and 35 kN (Figures 27-28). The roll force mean line exhibited in Figures 23, 25 and 27 smooths the fluctuations in the data to show a trend more clearly. Each point of the line is the mean of the roll force values every 50 seconds.

Generally, the mill speed was the first variable to stabilized (between 15 s and 24 s after the process onset), followed by roll speed (between 21 s and 28 s after the process onset), screw speed (between 110 s and 140 s after the process onset) and compression force. In
fact, the compression force was the variable that most varied in all runs, regardless of its target value. The applied compression force is expressed in kN/cm and is the result of the interaction of both screw speed and roll speed over the materials, within a fixed gap width between the rollers. However, this force merely represents the pressure within the hydraulic system and so it’s not a precise measure of the force applied onto the powder. Moreover, as the gap width is fixed, the powder flow rate drawn into the gap is not constant, which results in the variation of the force applied to the powder.

The compression force variation can be associated with the “outliers” identified in Figures 21-22. Actually, in Figure 24, the compression force varied significantly up to 153 s. This variation was exposed by the outliers numbered from 1 to 19. In addition, the compression force peaks that occurred at 265 s (18 kN), 893 s (11 kN), 1940 s (17 kN) can be linked, respectively, to the outliers labelled with 271/272, 893 and 1926.

The screw speed, roll speed and mill speed stabilized at about the first 2 min of the process (Figure 23) and after that they were kept constant until the process finish. On the other hand, the compression force took more time to approach the target value, though it kept fluctuating throughout the process run time.

Therefore, these results demonstrate that the compression force is one of the CPP’s that most affects the granulation process. So it is expected that the compression force fluctuation will affect the granules’ physical properties.
A continuous manufacturing model for the production of granules by roller compaction

Figure 23 – Process Variables Variation for Run N1. The target compression force was the lowest of the DoE (15 kN). After about 2.5 min all process variables reached their target values, except the compression force, which fluctuation lasted until the end of the run. The Mill Speed stabilized at 24 s, Roll Speed at 28 s and Screw Speed at 140 s.

Figure 24 – Compression force fluctuation showing the roll force mean line. The mean value stood below the target, at 13 kN-14 kN. The target of 15 kN was reached at about 154 s. After that the compression force varied between 10 kN (645 s, 1030 s, …) and 20 kN (1281 s).
A continuous manufacturing model for the production of granules by roller compaction

Figure 25 – Process Variables Variation for Run N12. The target compression force was the highest of the DoE (25 kN). After about 2.2 min all process variables reached their target values, except the compression force, which fluctuation lasted until the end of the run. The Mill Speed stabilized at 24 s, Roll Speed at 21 s and Screw Speed at 110 s.

Figure 26 – Compression force fluctuation showing the roll force mean line. The mean value stood below the target, at 22 kN-24 kN. The target of 25 kN was reached at about 131 s. After that the compression force varied between 17 kN (285 s, 992 s,...) and 35 kN (572 s).
A continuous manufacturing model for the production of granules by roller compaction

Figure 27 – Process Variables Variation for Run N4. The target compression force was the intermediate value of the DoE (35 kN). After about 2 min all process variables reached their target values, except the compression force, which fluctuation lasted until the end of the run. The Mill Speed stabilized at 15 s, Roll Speed at 24 s and Screw Speed at 118 s.

Figure 28 – Compression force fluctuation showing the roll force mean line. The mean value stood close to the target, at 34 kN-36 kN. The target of 35 kN was reached at about 120 s. After that the compression force varied between 27 kN (276 s, 556 s,…) and 44 kN (388 s).
5.3 Analysis of the granules

Table 5 displays the values of the granules’ density (BD and TD). The table was divided in three blocks to make the interpretation easier. In fact, sorting the densities by target compression force, it is realized that when the compression force is higher (35 kN), the density of the granules is also higher (0.62 g/ml – 0.64 g/ml); when the compression force is lower (15 kN), the density of the granules is also lower (0.54 g/ml – 0.55 g/ml). The intermediate compression force value (25 kN) gave rise to granules with and intermediate density (0.58 g/ml – 0.60 g/ml). The variation on density seems not to be so affected by single changes on roll speed, screw speed or mill speed. Thus, the compression force is the variable that most influences the density of the granules.

Once almost all of the granules produced were collected, it was possible to calculate the process throughput. As the Table 5 shows the process throughput depends upon the screw speed: when the screw speed increases, the process throughput increases (see run 12 and run 13).

Table 5 – The granules’ densities determined for each run and the process throughput. The table was split in three blocks, according to the target compression force (from the highest compression force, on the top, to the lowest compression force, on the bottom).

<table>
<thead>
<tr>
<th>Run</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>Process throughput (kg/h)</th>
<th>Roll speed (rpm)</th>
<th>Screw speed (rpm)</th>
<th>Target compression force (kN)</th>
<th>Mill speed (rpm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>0.63</td>
<td>0.72</td>
<td>9.24</td>
<td>3</td>
<td>10.5</td>
<td>35</td>
<td>250</td>
</tr>
<tr>
<td>4</td>
<td>0.64</td>
<td>0.74</td>
<td>20</td>
<td>8</td>
<td>31.5</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>0.62</td>
<td>0.73</td>
<td>9.12</td>
<td>3</td>
<td>10.5</td>
<td>35</td>
<td>50</td>
</tr>
<tr>
<td>9</td>
<td>0.62</td>
<td>0.72</td>
<td>17.16</td>
<td>5.5</td>
<td>20.5</td>
<td>35</td>
<td>150</td>
</tr>
<tr>
<td>8</td>
<td>0.59</td>
<td>0.68</td>
<td>20.17</td>
<td>8</td>
<td>28.5</td>
<td>25</td>
<td>150</td>
</tr>
<tr>
<td>10</td>
<td>0.59</td>
<td>0.69</td>
<td>15.52</td>
<td>5.5</td>
<td>18.5</td>
<td>25</td>
<td>250</td>
</tr>
<tr>
<td>11</td>
<td>0.58</td>
<td>0.67</td>
<td>15.52</td>
<td>5.5</td>
<td>18.5</td>
<td>25</td>
<td>150</td>
</tr>
<tr>
<td>12</td>
<td>0.58</td>
<td>0.69</td>
<td>14.37</td>
<td>5.5</td>
<td>17.5</td>
<td>25</td>
<td>150</td>
</tr>
<tr>
<td>13</td>
<td>0.60</td>
<td>0.70</td>
<td>15.55</td>
<td>5.5</td>
<td>18.5</td>
<td>25</td>
<td>150</td>
</tr>
<tr>
<td>1</td>
<td>0.55</td>
<td>0.64</td>
<td>6.77</td>
<td>3</td>
<td>7.5</td>
<td>15</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>0.55</td>
<td>0.65</td>
<td>18.4</td>
<td>8</td>
<td>23.5</td>
<td>15</td>
<td>250</td>
</tr>
<tr>
<td>5</td>
<td>0.54</td>
<td>0.64</td>
<td>6.85</td>
<td>3</td>
<td>7.5</td>
<td>15</td>
<td>250</td>
</tr>
<tr>
<td>7</td>
<td>0.54</td>
<td>0.65</td>
<td>18.3</td>
<td>8</td>
<td>23.5</td>
<td>15</td>
<td>50</td>
</tr>
</tbody>
</table>
The size of the granules collected during each run was measured by light scattering. This method was considered the gold standard for subsequent methods’ comparisons. Figures 29-31 exhibit the PSD for each run. Regardless of its distribution, the size profile is quite similar for this set of runs. Runs where the target compression force was higher (35 kN), runs 2, 4, 6 and 9, correspond to higher granules’ size. Runs where the target compression force was lower (15 kN), runs 1, 3, 5 and 7, show lower granules’ size. Runs with the intermediate compression force (25 kN), runs 8, 10, 11, 12 and 13 revealed intermediate granules’ sizes.

The effect of the roll speed and the mill speed on granules’ size is not clear (Figure 29). Keeping the target compression force and the mill speed constant, the size of granules decreases when roll speed increases (see run 6 and run 4, run 13 and run 8, run 5 and run 3). This result may be because the powder stays longer in the nip zone (when the roll speed is lower), where particles rearrange and start to deform as a consequence of the pre-compression stage. Once the particles are closer together for more time, they feel the pre-compression force for longer time and that’s why their compressed ribbon is denser and the correspondent granules are harder and larger. However, in the case of runs 1 and 7, that logic reasoning is true for the first sample, but in the last three samples the size decreases as the roll speed decreases.

Concerning the mill speed, now keeping the target compression force and roll speed constant (see run 6 and run 2, run 13 and run 10, run 1 and run 5), the size of the granules decreases when the mill speed increases. As the rotor speed increases the impact force of the granules against the sieve is higher which results in smaller granules. However, in the case of the run 13 and run 10, that logic reasoning is true for the first three samples, but in last sample the size increases as the mill speed increases.

Therefore, the compression force is the variable the most affects the size of the granules produced by roller compaction.
Figure 29 – 90% fraction of the granules size distribution (SD) obtained off-line by light scattering. The runs are ordered from the highest target compression force to the lowest target compression force.
Figure 30 – 50 % fraction of the granules size distribution (SD) obtained off-line by light scattering. The runs are ordered from the highest target compression force to the lowest target compression force.
The results from the on-line method (Eyecon) used to monitor the size of granules are represented in Figures 32-34. The run 5 is missing because an error prevented the collection of data. The size profiles are identical within each run, despite of their distribution.

In Figure 32 the runs with the lowest target compression force are the ones with the highest granules’ size. The run 6 has the lower granules’ size. The run 4 and the run 9 are among the ones that show lower sizes too. The runs with intermediate target compression force appear in middle of the graph, with intermediate sizes. The run 2 is the one that looks close to its real size, measured by light scattering.
Figure 32 – 90% fraction of the granules size distribution (SD) obtained on-line by direct imaging. The size of each sampling point corresponds to the average of sizes captured by Eyecon during the sampling time settled for each run. The runs are ordered from the highest target compression force to the lowest target compression force.
Figure 33 – 50% fraction of the granules size distribution (SD) obtained on-line by direct imaging. The size of each sampling point corresponds to the average of sizes captured by Eyecon during the sampling time settled for each run. The runs are ordered from the highest target compression force to the lowest target compression force.
The Eyecon results show a great deviation from their mean value. This deviation is represented by RSD value. Thus, the granules’ sizes obtained with the on-line method exhibit a great RSD when considering 90% of granules (Figure 35). In 50% fraction of the granules SD, the RSD is higher for runs 2, 3 and 7 (Figure 36). In 10% fraction of the granules SD, the RSD is lower for runs 1, 2, 6 and 7, but run 3 keeps its high RSD (Figure 37).
Figure 35 – The RSD determined for 90% fraction of the granules size distribution (SD) obtained by Eyecon.
Figure 36 – The RSD determined for 50% fraction of the granules size distribution (SD) obtained by Eyecon.
The granules’ size obtained on-line by Eyecon were compared to the gold standard off-line method. Each sample was individually compared within the both methods by determining the square error (SE) (Figures 38-40). In Figure 38 it can be seen that run 2 has the lowest SE, in accordance with the closest results to the off-line method, and the run 6 has the highest SE, once its sizes are greatly deviated from the true ones. Run 3 has the second highest SE, which corroborates with the high sizes captured by Eyecon during this run.
Figure 38 – Comparison between off-line and on-line methods for granules' size measurement. Square Error between the both methods regarding 90% fraction of the granules size distribution (SD).
Figure 39 – Comparison between off-line and on-line methods for granules’ size measurement. Square Error between the both methods regarding 50% fraction of the granules size distribution (SD).
The direct imaging method demonstrated a great deviation in granules’ size, comparing to the ones measured by light scattering. These results might be due to the inappropriate flow rate of the granules that reached the Eyecon camera and its image acquiring speed. The flow rate was inconstant, with periods of high flow rate interchanging with periods of a very low flow rate. Besides, the direction of the granules fall did not always favor the camera, and sometimes it was not possible the collect focused images. These acquired blurred images might have contributed for the wrong size measurements. As the images were captured each 2 seconds, the information lost between the collection times might have improved the size measurements.

So, the on-line method did not reveal to be accurate enough for granule’s size monitoring.
5.4 Predictive models

Two predictive models were built in view of estimating the granules’ physical properties. The first PLS model was built with the NIR data collected throughout the process to predict the granules’ size.

A summary of the performance of the first model is displayed in Table 6. Different models were built testing several pre-processings and applying a cross-validation method. The best model obtained was chosen by minimizing both the number of latent variables and the RMSE of cross-validation.

The chosen model is simple, with only one LV. The pre-processing applied differed from the one used in the all spectra for the PCA model by selecting a polynomial of second order in the Savitzky-Golay filter. The performance of the model was assessed by an internal validation (cross-validation) and an external validation. The model was built with NIR data from runs 1, 3, 4, 5, 7, 8, 10, 11, 12 and 13. Spectral data from runs 2, 6 and 9 had some sort of problems regarding data processing and that is why those were not used in the model.

The 40 samples (because each run had 4 granules’ samples) of the model were divided in 2 groups: one with 32 samples was used to calibrate the model and the other with 8 samples was used to test the model. The calibration set underwent an internal validation method, cross-validation (contiguous-blocks). The calibration set was split into 8 blocks, where 1 block was used to “test” the subset and the remaining blocks were used to build a subset calibration model. This internal validation provides an estimate of the model’s prediction performance, which can be assessed by the RMSECV (Root Mean Square Error of Cross Validation) and the coefficient of determination for cross validation ($R^2_{(cv)}$).

In the external validation, the calibration model was tested using data that was not used to build the model: the test set with 8 samples. This method provides a reasonable assessment of the model’s prediction performance on new other samples. The external validation is evaluated by the RMSEP and the coefficient of determination for Prediction ($R^2_{(P)}$).
Table 6 – Description of the PLS model to predict granules’ size based on NIR spectra.

<table>
<thead>
<tr>
<th>Spectral range</th>
<th>Pre-processing</th>
<th>Cross-validation method</th>
<th>LV</th>
<th>RMSECV (μm)</th>
<th>$R^2$ (cv)</th>
<th>RMSEP (μm)</th>
<th>$R^2$ (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>950-1650 nm</td>
<td>1st derivative (order 2; 15 points); mean centring</td>
<td>contiguous blocks (8)</td>
<td>1</td>
<td>146.3</td>
<td>0.14</td>
<td>50.5</td>
<td>0.19</td>
</tr>
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</table>

The calibration model has a high RMSECV (146.3 μm) and a poor $R^2$ of CV (0.14), both foreseeing that the model will not work well when predicting the granules’ size. The prediction model has also a high RMSEP (50.5 μm), even though with a lower magnitude order than RMSECV, and a very low $R^2$ of prediction (0.19), thus the model is not acceptable for predicting the granules' size.

The figures 41-42 show the scores of the calibration set and the test set. Only one sample of the test set is out of the 95% confidence limit and cannot be described by the model, so it is probably an outlier.

Figure 41 – The scores of the calibration set and the test set used in the PLS prediction model.
A continuous manufacturing model for the production of granules by roller compaction

Figure 42 – The statistic plot for the PLS model, depicting Hotelling’s T2 statistic versus Q statistic. The dotted blue lines represent the 95% confidence limit for both Hotelling’s T2 statistic (horizontal dotted line) and Q statistic (vertical dotted line). Both the scores of the calibration set and the test set are represented.

Figure 43 exhibits the correlation between the observed and the predicted data. It is seen the great dispersion over the regression line, which explains the weak link between the experimental and the predicted data. The green line shows the ideal regression line (a strong association between observed and predicted data) and the red line shows the real regression line.

The model’s lack of accuracy in predicting the granules’ sizes is due to the inadequate quality of NIR data. Despite the missing three runs, which would contribute to give more information on the process, the interaction between the sample and the radiation was not ideal. The granules flow rate into the glass tube might influence the ability to gather information with better quality. Maybe the diameter of the glass tube should be reduced to provide a better flow rate. Moreover, the spectral range from 950 nm to 1680 nm used is too narrow, even if searching only the physical information. A wider spectral range, from 1000 nm to 2500 nm would benefit the collection of better process information.

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The second PLS model was built with the values of the process variables (factors) and their respective responses. The variables chosen were the same as in the DoE’s: the roll speed, the mill speed and the compression force. This second approach used the three process responses (the process results) – BD, TD and GS – to build three PLS models capable of predicting each of those responses (Table 7).
Table 7 – The overview of the factors and the responses used to build the second PLS model.

<table>
<thead>
<tr>
<th>Experience name</th>
<th>Run order</th>
<th>Screw speed (rpm)</th>
<th>Roll speed (rpm)</th>
<th>Target compression force (kN)</th>
<th>Mill speed (rpm)</th>
<th>Bulk density (g/ml)</th>
<th>Tapped density (g/ml)</th>
<th>Granules size/90% fraction/last sample (μm)</th>
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</thead>
<tbody>
<tr>
<td>N1</td>
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<td>7.5</td>
<td>3</td>
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<td>0.64</td>
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<td>35</td>
<td>250</td>
<td>0.63</td>
<td>0.72</td>
<td>1009.40</td>
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<tr>
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<td>15</td>
<td>250</td>
<td>0.55</td>
<td>0.65</td>
<td>655.53</td>
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<tr>
<td>N4</td>
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<td>35</td>
<td>50</td>
<td>0.64</td>
<td>0.74</td>
<td>1120.33</td>
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<tr>
<td>N5</td>
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<td>7.5</td>
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<td>15</td>
<td>250</td>
<td>0.54</td>
<td>0.64</td>
<td>648.58</td>
</tr>
<tr>
<td>N6</td>
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<td>35</td>
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<td>0.54</td>
<td>0.65</td>
<td>729.22</td>
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<td>N8</td>
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<td>25</td>
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<td>0.68</td>
<td>881.36</td>
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<tr>
<td>N9</td>
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<td>5.5</td>
<td>35</td>
<td>150</td>
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<td>0.72</td>
<td>1028.87</td>
</tr>
<tr>
<td>N10</td>
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<td>5.5</td>
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<td>0.69</td>
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</tr>
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<td>1</td>
<td>18.5</td>
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<td>150</td>
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<td>0.67</td>
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<td>N12</td>
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<td>150</td>
<td>0.60</td>
<td>0.70</td>
<td>860.53</td>
</tr>
</tbody>
</table>

The plots depicted in Figure 44 show the variation of the responses so that the raw data may be seen as a whole. The values of the responses are plotted against the experimental runs and also the variation in the response for replicated experiments is displayed. The replicates are experiments with the same factor values plus or minus the replicate tolerance of 10%. Ideally, the variability of the repeated experiments should be much less than the overall variability. The variability of the replicates in BD and TD models is low, but in the case of the GS the replicates 11 and 12 show a greater variability. Nevertheless, this variation is not higher than the overall variation for the responses (see reproducibility in Figure 45).

When a set point is defined for the responses, the plot shows the upper bound and the lower bound (dotted red line), as well as the target value (dotted black line). Therefore, the experiment points should not be above the upper limit or under the lower limit. In this case, however, those limits are merely indicative, so it is not important whether the points are above or under the marked limits.
The Table 8 exhibits the analysis of variance (ANOVA) regarding the three models, as well as their regression equations. The ANOVA splits the total variation of the response (sum of squares corrected for the mean) into a component due to the regression model and a component due to the residuals. The residual sum of squares is further divided into Replicate Error and Model Error. The model is evaluated by comparing the Mean Square (MS) Model Error to the MS Replicate Error.

Only two components were used to build the model, so its absence of complexity favors the prediction performance.

The $R^2$ denotes the fraction of the response that is explained by the model. Once it is an optimistic indicator of the model prediction ability, $R^2$ could be considered an upper bound of the estimate for how well the model predicts the outcomes of new experiments. In these three models the $R^2$ is high varying from 0.93 (for GS) to 0.96 (for BD), which means a strong association between the variables and the predicted response.

The $Q^2$ estimates the predictive ability of the model and is used to validate the regression models. A $Q^2$ value higher than 0.70 indicates a very good predictive ability and a very low prediction error on new samples. The computed $Q^2$ for the three models ranged from 0.89 (GS) to 0.91 (BD), which suggests a model with good prediction ability.

The p-value for the regression model should be inferior to 0.05 and the three models satisfy this criterion. The p-value for the lack of fit (the model error, i.e., the non modeled part of the model) should be greater than 0.05, which is also true for all of the three models. The model
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is also evaluated by the MS for the model error and the MS for the replicate error. The prediction performance of the model is good if the MS for model error is lower than the MS for replicate error. All of the three models satisfy this criterion.

Table 8 – Summary of the PLS Model built with the process parameters. BD, Bulk Density; TD, Tapped Density; GS, Granule Size; RS, Roll Speed; CF, Compression Force; MS, Mill Speed. MS, Mean Square; p, probability.

<table>
<thead>
<tr>
<th>Response</th>
<th>PLS Model equation</th>
<th>Components</th>
<th>$R^2$</th>
<th>$Q^2$</th>
<th>p (Regression)</th>
<th>p (Lack of Fit)</th>
<th>MS (variance) Model error ($\mu^2$)</th>
<th>MS (variance) Replicate error ($\mu^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD</td>
<td>$BD=0.0034RS+0.0343CF+0.59$</td>
<td>2</td>
<td>0.96</td>
<td>0.91</td>
<td>&lt; 0.001</td>
<td>0.898</td>
<td>3.9x10^{-5}</td>
<td>1.3 x10^{-4}</td>
</tr>
<tr>
<td>TD</td>
<td>$TD=0.0306CF-0.0051MS+0.69$</td>
<td>2</td>
<td>0.95</td>
<td>0.90</td>
<td>&lt; 0.001</td>
<td>0.843</td>
<td>5.1 x10^{-5}</td>
<td>1.3 x10^{-4}</td>
</tr>
<tr>
<td>GS</td>
<td>$GS=139.383-27.8055+894.379$</td>
<td>2</td>
<td>0.93</td>
<td>0.89</td>
<td>&lt; 0.001</td>
<td>0.918</td>
<td>1342.4</td>
<td>4912.2</td>
</tr>
</tbody>
</table>

The Figure 45 presents the summary statistics for each response in four parameters: $R^2$, $Q^2$, model validity and reproducibility, where 1 is the perfect outcome.

The first two columns, $R^2$, $Q^2$, should be close in size, which is true for the three models. The model validity usually indicates statistically significant model problems, such as the presence of outliers, when its value is inferior to 0.25. However if the replicates are identical (the pure error is rather small) the model validity can be very low, even though the model is good and complete. As Figure 45 shows, in the case of the three models, the model validity is higher than 0.25.

The reproducibility is the variation of the replicates compared to overall variability and should be greater than 0.5. The three models also satisfy this criterion.
Figure 45 – Summary of the basic model statistics for every response: R2, Q2, model validity and reproducibility.

The significance of the regression model coefficients is represented in Figure 46. A model term is deemed to be significant when it exhibits a large distance from y=0 (either positive or negative) and has an uncertainty level that does not extend across y=0.

All three models included the three coefficients concerning the three variables: roll speed, mill speed and compression force. However, in BD model, the mill speed was considered non significant and in both TD model and in GS model, the roll speed was considered non significant. Thus, only the model terms displayed in the coefficient plot were considered significant for the prediction performance of the model. The compression force coefficient is the most significant model term for each model.
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Figure 46 – The coefficient plot depicting the model terms for each response. RolSp, Roll Speed; ComFc, Compression Force; MilSp, Mill Speed.

The observed values versus predicted values for each model plot are displayed in Figure 47. All three plots show their points close to the straight line, which means a strong match between observed and predicted data. These plots indicate the capacity of the model in predicting the new values. The best model is the BD with $Q^2=0.91$, followed by TD, with $Q^2=0.90$ and finally GS with $Q^2=0.89$.

Figure 47 – The observed versus predicted plot for each model. Bulk Density: $R^2=0.96$, $Q^2=0.91$; Tapped Density: $R^2=0.95$, $Q^2=0.90$; Granule Size: $R^2=0.93$, $Q^2=0.89$. 
The plots represented in Figure 48 illustrate the relation between scores for the factors (t1) and the responses (u1) for the first component. Within each model, it can be seen the presence of three groups: scores 1, 3 and 5 (with compression force equal to 15 kN), scores 8, 10, 11 and 12 (with compression force equal to 25 kN) and scores 2, 4 and 6 (with compression force equal to 35 kN). So the score plot can clearly reveal the existence of three clusters within each model. However, the scores 7, 8 and 9 are not well described by the model, as the plot shows.

![Figure 48](image.png)

**Figure 48** – The score plot for each model, depicting the relationship between the scores (t1) and the responses (u1).

The loading plot correspondent to each of the three models is represented in Figure 49. This plot explains how the responses vary in relation to each other and which ones provide similar information.

Similarly to the information gathered in the Figure 46, for the BD model the compression force is the variable that most affects the BD of the granules in a positive way while the roller speed affects less the BD of granules and in a negative way. For the TD model the compression force is the variable that most affects the TD of the granules in a positive way while the mill speed affects less the BD of granules and in a negative way. And finally, for the GS the compression force is the variable that most affects the GS of the granules in a positive way while the mill speed affects less the BD of granules and in a negative way.
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The Figure 50 represents the standardized residuals from each model. The standardized residuals are the raw residuals (difference between the observed and the predicted values) divided by the residual standard deviation. The residuals account for the non modeled part of the model. The residuals have to demonstrate a normal distribution in order to ground the predictive ability of the model. If all the points of the residual plot are on a straight line on the diagonal, the residuals are normally distributed noise. For the BD and the TD models, residuals tend to be on a straight line, so they are considered normally distributed. For the GS model, a diagonal can also be drafted through the points.
Chapter 6
Conclusions

In this experimental work, the CPP’s proposed and their respective variations were: roll speed, from 3 to 8 rpm; mill speed, from 50 to 250 rpm; and compression force, from 15 kN to 35 kN. The granules’ CQA’s measured were: bulk density, tapped density and granule’s size.

The NIR sphere, as a PAT tool, looked inside the process and unveiled not only the process trajectory, but also the sources of variability that influenced the process. Thus, the PCA model built with NIR data revealed that the variance of the scores far from the centre of the model was due to abnormal variation in the compression force, during the process.

Although the roll speed, the screw speed and the mill speed were kept constant few seconds after the process onset, the compression force fluctuated throughout the process run time. The compression force variation was due to the unstable flow rate coming through the fixed gap between the rollers. Since this fixed gap could not be adjusted to the flow rate variation, the compression force exerted by the rollers over the powder varied significantly.

The bulk and tapped density of the granules were strongly influenced by the compression force. The higher the compression force achieved, the higher the bulk and tapped density of the granules; and the lower the compression force achieved the lower the bulk and the tapped density of the granules. Likewise, for granules’ size, the compression force was the variable that most affected this response. The granules’ size increased when compression force increased and the granules’ size decreased as the compression force decreased.

The granules’ size on-line monitoring with Eyecon showed a great deviation from its off-line measurement and therefore did not provide accurate results. The Eyecon system was strongly influenced by the granules flow rate. As it was not constant, Eyecon’s camera was not able to capture a clear real-time image of the granules’s shape and therefore the size was wrongly determined.

Two PLS prediction models were built in order to predict the size and the density of granules. The first PLS model, built upon NIR data, had a high RMSEP (50.54 μm) and a very low R² of Prediction (0.19), thus the model was not acceptable for predicting the granules’ size. Data collected through the NIR-sphere was sensitive to granules flow rate variations, and that
affected the quality of spectral data obtained. In addition, the spectral range used (950 nm – 1700 nm) was a drawback concerning information on the granules’s properties.

The second PLS model, built upon the values of the process parameters and the process responses predicted three responses: the bulk and the tapped density of the granules and the size of the granules. In these three models the $R^2$ was high, yielding 0.93 for GS, 0.95 for TD and 0.96 for BD. The $Q^2$ was also high: 0.89 for GS, 0.90 for TD and 0.91 for BD. Together, both values account for three models with good prediction ability.

Besides, these last three models pointed out that the compression force was the variable that most influenced each model response. While the compression force exerted a strong and a positive influence on the responses, the roll speed and the mill speed, on the opposite, performed a slight and negative influence over the responses.

Thus the compression force was the variable that should be kept under control in order to produce granules with the desired density and size.
Future perspectives

One of the main variables that affects the granulation process is the formulation. In this experimental work, the formulation was kept constant in terms of its composition and the proportion of raw materials. So, in a first trial varying the composition by exchanging one component of each kind and in a second trial keeping the composition and varying the amount of one or two components would provide more information regarding the influence of the formulation on the final product.

The flow rate had a strong impact on the compression force variation and on the quality of NIR data. Thus, in the next DoE, including the flow rate as a CPP would yield a better understanding of how this variable affects the process responses. Therefore, taking the flow rate into consideration as an input variable, might improve the prediction models, especially in the case of the prediction of the granule size.

Moreover, in what concerns NIR spectroscopy, improving the interaction between the sample and the radiation, as well as providing a wider spectral range, would yield more and better NIR data and so better prediction models. As a result, the changes in the granules’ density could also be followed by the shift in the NIR spectra baseline.(46)

The ribbon, as an intermediate product of the granulation process, should be evaluated mostly by its porosity. A NIR probe could be attached to the ribbon sampling window so that data could be collected in order to follow the porosity variation by the shift in the NIR spectra baseline.(46)(72)

Finally, the granules produced should be compressed at different compression forces and the tablets produced should be characterized by their tensile strength and friability. This study should clarify which granules yield the higher tensile strength tablets with lower friability. This information should be used in the granules prediction models in order to adjust the CPP’s for the production of the desired granules, i.e, with the intended CQA’s (the most suitable for future compression into tablets).
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