Multivariate Synergies in Pharmaceutical Roll Compaction

The quality influence of raw materials and process parameters by design of experiments

Nabil Souihi
“Do not follow where the path may lead. Go instead where there is no path and leave a trail”

~ Ralph Waldo Emerson

Dedicated to my parents, Manuela, Laila, Zineb and Amina
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Abstract

Roll compaction is a continuous process commonly used in the pharmaceutical industry for dry granulation of moisture and heat sensitive powder blends. It is intended to increase bulk density and improve flowability. Roll compaction is a complex process that depends on many factors, such as feed powder properties, processing conditions and system layout. Some of the variability in the process remains unexplained. Accordingly, modeling tools are needed to understand the properties and the interrelations between raw materials, process parameters and the quality of the product. It is important to look at the whole manufacturing chain from raw materials to tablet properties.

The main objective of this thesis was to investigate the impact of raw materials, process parameters and system design variations on the quality of intermediate and final roll compaction products, as well as their interrelations. In order to do so, we have conducted a series of systematic experimental studies and utilized chemometric tools, such as design of experiments, latent variable models (i.e. PCA, OPLS and O2PLS) as well as mechanistic models based on the rolling theory of granular solids developed by Johanson (1965).

More specifically, we have developed a modeling approach to elucidate the influence of different brittle filler qualities of mannitol and dicalcium phosphate and their physical properties (i.e. flowability, particle size and compactability) on intermediate and final product quality. This approach allows the possibility of introducing new fillers without additional experiments, provided that they are within the previously mapped design space. Additionally, this approach is generic and could be extended beyond fillers. Furthermore, in contrast to many other materials, the results revealed that some qualities of the investigated fillers demonstrated improved compactability following roll compaction.
In one study, we identified the design space for a roll compaction process using a risk-based approach. The influence of process parameters (i.e. roll force, roll speed, roll gap and milling screen size) on different ribbon, granule and tablet properties was evaluated. In another study, we demonstrated the significant added value of the combination of near-infrared chemical imaging, texture analysis and multivariate methods in the quality assessment of the intermediate and final roll compaction products. Finally, we have also studied the roll compaction of an intermediate drug load formulation at different scales and using roll compactors with different feed screw mechanisms (i.e. horizontal and vertical). The horizontal feed screw roll compactor was also equipped with an instrumented roll technology allowing the measurement of normal stress on ribbon. Ribbon porosity was primarily found to be a function of normal stress, exhibiting a quadratic relationship. A similar quadratic relationship was also observed between roll force and ribbon porosity of the vertically fed roll compactor. A combination of design of experiments, latent variable and mechanistic models led to a better understanding of the critical process parameters and showed that scale up/transfer between equipment is feasible.
Abbreviations and notations

Vectors are denoted in bold.
Matrices are denoted by capital letter and in bold.

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<td>EMA</td>
<td>European Medicines Agency</td>
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<td>QbD</td>
<td>Quality by Design</td>
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<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
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<td>RC</td>
<td>Roll Compaction</td>
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<tr>
<td>DCP</td>
<td>Dicalcium phosphate</td>
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<tr>
<td>DOE</td>
<td>Design Of Experiments</td>
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<td>NIR-CI</td>
<td>Near-Infrared Chemical Imaging</td>
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<td>ICH</td>
<td>International Conference for Harmonization</td>
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<tr>
<td>CPP</td>
<td>Critical Process Parameters</td>
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<td>CQA</td>
<td>Critical Quality Attributes</td>
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<tr>
<td>DS</td>
<td>Design Space</td>
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<td>DC</td>
<td>Direct Compression</td>
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<td>MCC</td>
<td>Microcrystalline cellulose</td>
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<tr>
<td>ODT</td>
<td>Orodispersible tablets</td>
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<td>SEM</td>
<td>Scanning Electron Microscopy</td>
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<tr>
<td>CCF</td>
<td>Central Composite Face centered</td>
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<tr>
<td>CCC</td>
<td>Central Composite Circumscribed</td>
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<tr>
<td>MLR</td>
<td>Multiple Linear Regression</td>
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<tr>
<td>OLS</td>
<td>Ordinary Least Squares</td>
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<td>PLS</td>
<td>Partial Least Squares</td>
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<tr>
<td>DPMO</td>
<td>Defects Per Million Opportunities</td>
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<tr>
<td>LVR</td>
<td>Latent Variable Regression</td>
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<td>LV</td>
<td>Latent Variable</td>
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<td>PCA</td>
<td>Principal Component Analysis</td>
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<tr>
<td>OPLS</td>
<td>Orthogonal Projections to Latent Structures</td>
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<td>O2PLS</td>
<td>Bidirectional OPLS</td>
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<td>PC</td>
<td>Principal Component</td>
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<tr>
<td>SVD</td>
<td>Single Value Decomposition</td>
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<tr>
<td>NIPALS</td>
<td>Non-linear Iterative Projections by Alternating Least Squares</td>
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<tr>
<td>$Q^2$</td>
<td>Goodness of prediction</td>
</tr>
<tr>
<td>$R^2$</td>
<td>Goodness of Fit</td>
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<tr>
<td>RMSEP</td>
<td>Root Mean Square Error of Prediction</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
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<tr>
<td>RMSEcv</td>
<td>Root Mean Square Error of cross-validation</td>
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<tr>
<td>TS</td>
<td>Tensile Strength</td>
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<td>p</td>
<td>Loading value</td>
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<td>t</td>
<td>Score value</td>
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<td>X</td>
<td>Matrix of observation values</td>
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<td>T</td>
<td>Matrix of score values</td>
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<tr>
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<td>T&lt;sup&gt;T&lt;/sup&gt;</td>
<td>Transpose</td>
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<td>E</td>
<td>Matrix of X residuals</td>
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<td>Y</td>
<td>Matrix of response values</td>
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<td>Matrix of predictive scores (OPLS)</td>
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<td>Matrix of predictive loadings (OPLS)</td>
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<td>Matrix of orthogonal scores (OPLS)</td>
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<td>Matrix of orthogonal loadings (OPLS)</td>
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<td>C</td>
<td>Matrix of y-related loadings</td>
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<td>F</td>
<td>Matrix of Y residuals</td>
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<td>p&lt;sub&gt;P&lt;/sub&gt;</td>
<td>Vector of predictive loadings (OPLS)</td>
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<td>y</td>
<td>Vector of responses</td>
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<td>Vector of weights</td>
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<td>Vector of score values</td>
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<td>Vector of y-related loadings</td>
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<td>Vector of loadings</td>
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<td>w&lt;sub&gt;O&lt;/sub&gt;</td>
<td>Vector of orthogonal weights (OPLS)</td>
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<td>Vector of orthogonal loadings (OPLS)</td>
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<tr>
<td>X&lt;sub&gt;E&lt;/sub&gt;</td>
<td>Residual X matrix</td>
</tr>
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</table>
Johanson’s model nomenclature

\[ c_s \] Screw constant
\[ D \] Roll diameter
\[ F \] Force factor
\[ ffc \] Flow function
\[ K \] Material compressibility
\[ N_R \] Roll speed
\[ N_S \] Screw speed
\[ P_{\text{max}} \] Peak pressure
\[ R_f \] Roll force
\[ S \] Roll gap
\[ W \] Roll width
\[ \alpha \] Nip angle
\[ \gamma \] Relative density
\[ \gamma_0 \] Preconsolidation relative density
\[ \gamma_R \] Ribbon relative density
\[ \delta_E \] Effective angle of internal friction
\[ \rho \] Ribbon/bulk density
\[ \rho_{\text{true}} \] Material true density
\[ \phi_w \] Angle of wall friction
\[ \theta \] Roll angle
\[ \sigma \] Normal stress
\[ \mu \] Friction coefficient
List of Publications

This thesis is based on the following papers, which in the text will be referred to by their Roman numerals and bold text. The papers were reprinted with kind permission from the publishers.


List of papers by the author not included in the thesis

V. N. Souihi, A. Lindegren, L. Eriksson, J. Trygg. OPLS in batch process monitoring – opens up new opportunities. Accepted for publication in Analytica Chimica Acta, 2014.


#These authors made equal contributions.
Introduction

Recently, the pharmaceutical industry has encountered significant changes in the existing economic and regulatory environments. Increased global competition, mainly from manufacturers of generic products, has resulted in decreasing competition-free lifespan of products and reduced profit margins as drugs come off-patent.\(^1\)\(^2\)

The pharmaceutical industry is a highly regulated industry. Traditionally, manufacturing processes are considered as fixed and based on time-defined end points. The approach “if it isn’t broke, don’t fix it” has been dominating with frequent batch rejections. The reason is that the uncertain consequences from regulatory submissions of process changes as well as the high price of submitting post approval changes overcome the possible benefits from optimising the manufacturing processes.\(^3\)

However, nowadays the Food and Drug Administration (FDA) of the USA and the European Medicines Agency (EMA) have started to adopt the quality by design (QbD) paradigm. QbD requires that companies show understanding of the way in which variability in raw materials, process design and operating conditions affect product quality and use this knowledge to implement effective quality control strategies.\(^3\)\(^-\)\(^6\) Within this new QbD concept there is a big need for tools to understand the properties and the interrelations between raw materials, process parameters and the final quality of the product. Most of the interrelations have a multivariate nature, i.e. it will be difficult to catch these properties if the industry is working with only univariate tools.

Pharmaceutical manufacturing processes remain relatively inefficient and poorly understood as compared with other chemical process industries.\(^3\) This can be ascribed to some extent to the special challenges associated with pharmaceutical process design.
During the drug development process, availability of materials, physical and chemical properties of the active pharmaceutical ingredient (API) and excipients can affect the success of various drug product formulations and manufacturing routes.\(^3\), \(^7\) Under the current process development paradigm, manufacturing costs consume a large portion of revenue for many pharmaceutical companies, as much as 27% by some estimates.\(^8\) In many cases more is spent on manufacturing than on research and development.\(^7\)-\(^8\) Moreover, insufficient process understanding and lack of robust process development can also result in variability in product quality.\(^9\)

Currently, pharmaceutical manufacturing is dominated by batch processing for which scale up to commercial volumes can encounter several technical difficulties and for which studies to provide detailed process understanding can be resource intensive and time consuming.\(^10\) The future competitiveness of many pharmaceutical manufacturers may depend on the selective transition from batch driven production to continuous or, at least, to a semi-continuous or flexible batch processing.\(^9\)

Continuous processing has a great deal of opportunity to address issues of cost and robustness in the development of pharmaceutical manufacturing processes.\(^11\) Continuous processes tend to contain smaller equipment than batch processes. This may decrease capital investments in equipment and plant space as well as decreased utility requirements. Additionally, continuous processes scale readily to a certain extent through increases in operating time, total flow rate or parallelization, reducing the need for scale-up studies throughout the development process. This can reduce time to market, which in turn may increase competition-free lifespan. Continuous processing at small scale also allows rapid data generation across a wide range of processing conditions thus minimizing experimental time and reducing API demand in development.\(^2\), \(^9\)-\(^12\) Finally, continuous processing can mitigate problems of product variability through implementation of on-line process control.\(^10\)
Roll compaction (RC) is a continuous process for solid dosage form manufacturing, increasingly popular within the pharmaceutical industry. It is used to compress mixtures of materials in different smaller particle size ranges into larger agglomerates with better powder handling properties. In pharmaceutical manufacturing, this technique is employed to produce ribbons or briquettes ready for subsequent milling and tableting processes. It is important to look at the whole manufacturing chain, from raw materials to tablet properties using the appropriate data analysis methods. Although roll compaction has become an established technique for dry granulation, some of the process variation and the influence of material properties are still not fully understood.

This thesis describes the methods used, the problems encountered, and the results obtained in my work in mapping and understanding raw materials and process parameters variation in roll compaction. It starts with an introduction to the aims of the studies of the thesis, followed by an introduction to the relevant pharmaceutical formulation, processing, computational and mathematical methods used in the studies. The thesis concludes with a discussion part as well as the results of the four composing studies and the future of roll compaction process.
Aims of this work

The main aim when commencing this work was to investigate the impact of raw materials, process parameters, and system design variations on the quality of intermediate and final roll compaction products as well as their interrelations. In retrospect, the aims of each study can be defined more clearly:

1) To understand the influence of different qualities of mannitol and dicalcium phosphate (DCP) on roll compaction, and to predict critical quality attributes of the drug product based solely on the material properties of those fillers (Paper I).

2) To demonstrate the applicability of statistical design of experiments (DOE) and multivariate modeling principles to identify the Design Space of a roll compaction process using a predictive risk-based approach (Paper II).

3) To explore the use of near-infrared chemical imaging (NIR-CI) for the study of roll compacted drug products and evaluate the increased process and product understanding that could be gained from this technology (Paper III).

4) To explore the utilization of instrumented roll technology for a roll compactor to measure normal stress on ribbons, and to relate the operating parameters to the normal stress exerted on the material, which will then be related to the ribbon densification (Paper IV).

5) To investigate the performance of roll compaction process equipment at different scales, and while using horizontal and vertical force feed mechanisms (Paper IV).
Background

Quality by Design

Improving and producing guarantees about the overall quality of a process is at the core of *Quality by Design (QbD)*. Nowadays, the concept of QbD is one of the most recurrent ideas in the pharmaceutical literature.\(^{14}\) QbD has been first applied in industries such as the automotive industry.\(^{15-16}\) An example of successful application is the automotive industry in Japan. It is known that the quality of the production chains has enabled the Japanese companies to manufacture high quality and low cost cars. The aim of QbD is to improve the quality of the products by understanding the products and the process setup to build it.\(^{14,17}\) The development provided by QbD should lead to the production of less “rejected products or bad products” since the mechanisms leading to good quality are known.\(^{17}\)

Recently, the FDA and International Conference for Harmonization (ICH) have clearly recognized the advantages of applying QbD to gain more knowledge and understanding about pharmaceutical products and processes.\(^{17}\) The ICH Q8, Q9 and Q10 guidelines describe principles and tools for the implementation and improvement of QbD.\(^{4-6}\)

QbD is a systematic, scientific, risk based, holistic, and proactive approach to pharmaceutical development that starts with predefined objectives and emphasizes product and process understanding.\(^{17}\) QbD identifies characteristics that are critical to quality from the perspective of patients, and translates them into the attributes that the drug product should possess and establish how the critical process parameters (CPPs) can be varied to consistently produce a drug product with the desired characteristics.\(^{14}\) In the QbD paradigm, when designing and developing a product, a company is required to define desired product performance and to identify critical quality attributes (CQAs).\(^{17}\)
Based on this information, the company designs the product formulation and process to meet those product attributes. This leads to a better understanding of the impact of raw material attributes and process parameters on the CQAs, and to the identification and control of sources of variability. This systematic approach to product development varies a lot from the traditional approach *Quality by Testing*, which was extremely empirical.14

The concept of *Design Space (DS)* is gaining popularity as a tool for implementation of QbD. DS concept is defined as “the multidimensional combination and interaction of input variables (e.g., materials attributes) and process parameters that have been demonstrated to provide assurance of quality”.5-6 Working within the design space is not considered as a change. However, movement out of the design space is considered to be a change and would normally require a regulatory post-approval-change process.

**Formulation development of tablets**

Drugs are seldom administered as the pure active pharmaceutical ingredient alone. They are given in a mixture with appropriate excipients to provide an appropriate dosage form for administration, also called drug product or just formulation.18 The design of the formulation and the process that results in the most preferable dosage form is the central concept of formulation development. Formulation development specially concerns drug product and process development, which generally means designing the dosage form composition and manufacturing process.18-19

Tablets accounts for more than 60 % of all the pharmaceutical dosage forms administered to people.19 A tablet is a compressed unit of a powder mixture of the API and a number of excipients that usually have no pharmacological effect. Excipients help in the manufacturing process and handling of the API to achieve an optimized production process.
Also, excipients control the release of the API in order to reach the target (e.g. a certain region of the gastro-intestinal tract). Examples of excipients are fillers or diluents, binders, disintegrants, lubricants and glidants. In earlier days, excipients were considered inactive constituents. Over the years, pharmaceutical scientists learned that excipients are not inactive and often have considerable impact on the manufacture, safety, quality and efficacy of the drug substance in the dosage form.

Tablets are dosage forms preferred by patients and manufacturers. Major advantages compared to other dosage forms are:

I. Better drug stability
II. High accuracy in dosing of API
III. Easy packaging process and distribution
IV. Economically beneficial manufacturing process
V. Suitable to handle and administer for the patient

For most people a tablet does not conceal any mystery. It is a solid object that can be obtained in pharmacies and that will aid in recovering from a medical event after being taken. After deeper inspection, what in a glance seems like a simple pharmaceutical product becomes a really complex process in terms of formulation and R&D. Tablets are prepared by compressing either powders or granules. Granules are prepared by granulation, a process in which powder particles are made to adhere to form larger agglomerates. Direct compression is the most simple and frequently preferred process for manufacturing tablets. It is simply mixing the API with the excipients and compressing the powder mixture directly into tablets. However, direct compression has its limitations: segregation can happen if the API and excipients differ in particle size and poorly flowing drugs and excipients are generally unsuitable for direct compression. This would negatively influence mass and content uniformity. Another drawback can be dust exposure, especially while handling high potency APIs.
A better approach to overcome these problems is to include an additional unit operation: the granulation of the powders. The aim of the granulation process is to create agglomerates or granules of powder blends. These granules are of higher bulk density than the original bulk powder and therefore tend to have better flow properties. Granulation also contributes to improve control of content uniformity and compactibility. Granulation methods can be divided into two types: wet and dry granulation. Wet granulation includes combining a dry powder blend with a liquid binding solution, in the presence of some sort of agitation. After the granulation process the granules are usually dried, sieved, mixed with other excipients and compressed into tablets. There are several advantages of using the wet granulation process for example to provide better flow characteristics, improve compaction, prevent segregation, better control of drug content uniformity at low drug concentrations, reduce powder volume and to reduce dust from toxic powders. Disadvantages of the commonly used wet granulation process are the huge amount of space, energy and air to dry the granules after the granulation process. Moreover, wet granulation is not the best choice for moisture, solvent or heat sensitive APIs.

Granulation can also be achieved via dry granulation. Dry granulation differs from wet granulation in that granules are formed only through compression. Dry granulation is carried out continuously through roll compaction. A detailed description of the roll compaction process will be presented in the next section. The tablets manufactured in the work underlying this thesis were all made by direct compression of powders or roll compaction.
Roll compaction

Basic principles of roll compaction

Roll compaction is a dry granulation method commonly employed in the chemical and pharmaceutical industries. It is a quick and efficient way to provide pre-densification and improve the flowability of the primary powders. It compresses small sized particles into larger agglomerates. This technique is used to produce ribbons ready for subsequent milling and tableting processes. Throughout the roll compaction process, the initial powder mix passes through the gap between two counter-rotating rolls under gravity or screw feeding forces. The powders are gripped in the decreasing gap by the friction forces on the roll surfaces. In the region close to the minimum roll gap, the powder undergoes compression and forms a compact ribbon. The ribbon is then conveyed forward and released from the rolls.

It is usual to consider that there are three zones of material behavior in roll compaction, which correspond to the slip, nip and release regions (Figure 1). When the particles are fed to the rolls they are originally considered to be in the slip region of the process, characterized by the particles slipping at the surface of the rolls. Particle rearrangements occur and relatively little pressure is exerted on the powder in the slip region. The nip region starts at a roll angle \( \alpha \), termed the nip angle, when the wall velocity of the powder becomes equal to that of the rolls. In this zone, the powder is dragged to the smallest gap and compressed by the substantial increase in the pressure developed during the process. Powder densification mainly takes place in this region. The nip angle \( \alpha \), defines the angle at which the powder transitions from the slip region to the no-slip (nip) region. The release region is initiated when the roll gap begins to increase again and in which elastic recovery could happen.
Figure 1. Schematic diagram of the roll compaction process showing the slip, nip and release regions defined by Johanson’s theory. $\alpha$ and $\Theta$ are the nip and the roll angles, respectively.

**Classification of the roll compactor**

Figure 2 illustrates the major parts of a roll compactor. Although the general layouts of roll compactors look similar, there are some features that differ:

- Sealing: side cheek plates or rim roll assembly.$^{25}$
- Roll assembly: fixed or movable rolls.$^{25}$
- Feeding systems: gravity feed and force fed (single or double screw) (Figure 3).$^{26}$
- Roll layout: vertical, horizontal and inclined (Figure 4).$^{27}$
- Powder de-aeration system.$^{28}$
- Roll surface conditions: smooth, pocketed and knurled rolls.$^{28}$
Three roll compactors have been utilized during the course of this thesis:

1. Rolls mounted in a horizontal position
   - Vector TFC-Labo (Vector Corporation, Marion, IA, USA) (Paper I)
   - Hosokawa Bepex roll compactor (Pharmapaktor C250, Hosokawa Bepex GmbH, Germany) (Paper II-IV)

2. Rolls mounted in a vertical position
   - Alexanderwerk WP 120×40V roll compactor (Paper IV)

![Figure 2](image)

**Figure 2.** (a) Alexanderwerk WP 120×40V roll compactor, (b) Hosokawa Bepex roll compactor.

![Figure 3](image)

**Figure 3.** Feeding methods: a) gravity, b) single screw and c) double screw (adapted from Guigon et al. 29).
Advantages and drawbacks of roll compaction

Roll compaction is designed to produce free flowing, dust free granules with improved bulk density and uniformity of particulate formulations by preventing the segregation of the constituents of the powder. This technique offers unique advantages compared to wet granulation regarding moisture, solvent, or heat sensitivity of the drug substance, since neither a liquid binder nor a drying stage is required. Moreover, roll compaction is an increasingly more attractive option for manufacturing oral dosage forms for many reasons: it facilitates continuous manufacturing, reduces floor space, saves energy, yields high throughput with reduced operator presence, and scale up efforts are minimized.\textsuperscript{30-31}

One important factor in roll compaction is that binding of particles results only from the compaction forces requiring a certain degree of compactability of the powder blend.\textsuperscript{31} Therefore materials with good compactability have to be selected for roll compaction and following tableting. Kleinebudde\textsuperscript{13} has listed possible limitations and drawback areas with regard to processing using roll compaction. The main problems are: high amount of fines/leakage of uncompacted material; loss in compactibility (loss in reworkability); homogeneity of the ribbon; and extensive sticking of material to the rolls.\textsuperscript{13}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{figure4.png}
\caption{Different roll layout: a) inclined, b) horizontal and c) vertical.}
\end{figure}
Roll compaction in pharmaceutical manufacturing

Roll compaction is used in secondary pharmaceutical manufacturing of tablets (Figure 5), in which the blends of APIs and excipients were transformed to dosage forms. The roll compactor is usually combined with a milling system. The ribbons produced can subsequently be milled to obtain appropriately sized granules which are ready for tablet manufacture. Roll compaction is intended to increase bulk density and to improve both flowability and uniformity of particulate formulations.32

Figure 5. Roll compaction in pharmaceutical manufacturing.
Fillers in roll compaction

Roll compaction differs from wet granulation in that granules are formed only through compression. Therefore, the powder properties of the raw materials are important in determining if roll compaction is an acceptable approach.\textsuperscript{13} Compactability and flowability are considered as key material attributes for fillers in roll compaction, therefore well flowing direct compression (DC) qualities of fillers are commonly used in the roll compaction process.\textsuperscript{33-35} The choice of filler depends on the feeding system of the equipment, but even more on the properties and proportion of the active substance in the formulation. If the active substance is very cohesive, free flowing excipients as direct compression qualities are preferred. When flowability is not an issue in the formulation, traditional filler qualities not designated to one specific use such as direct compression or roll compaction, are also usable.\textsuperscript{36} Microcrystalline cellulose (MCC) is a plastic deforming material and one of the most popular fillers for roll compaction due to its high tensile strength. Several authors have studied the effect of MCC quality on the roll compaction.\textsuperscript{37-41} In contrast, there are only few studies describing the effect of brittle filler qualities such as lactose, mannitol and dicalcium phosphate (DCP) on roll compacted granules and tablets. Inghelbrecht and Remon \textsuperscript{42} investigated the influence of different lactose qualities on roll compaction. In their study, spray-dried lactose caused problems due to its high flowability and only low pressures could be used, which resulted in a lower granule quality. In a recent study published after the work underlying this thesis (Paper I), Wagner et al. \textsuperscript{43} investigated and compared the roll compaction behaviour of pure, unprocessed, crystalline mannitol and five various spray-dried mannitol grades.

In the work underlying this thesis (Paper I), mannitol and DCP, two brittle fillers, have been investigated. Mannitol is a naturally existing sugar alcohol. Mannitol shows high stability to chemical reactions and low hygroscopicity. It is widely used in pharmaceutical formulations mainly as filler in tablets but also in lyophilizates or as a drug carrier in dry powder inhalers.\textsuperscript{44}
Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution and sweetness. As the main component in ready-to-use excipients or in spray-dried quality for direct compression, mannitol plays an important role mainly in formulations of orodispersible tablets or orally disintegrating tablet (ODT), and dispersible tablets.\textsuperscript{45-46} ODTs differ from traditional tablets in that they are designed to be dissolved on the tongue rather than swallowed whole. Moreover, mannitol has low drug interaction potential. It is not absorbed significantly from the gastrointestinal tract and orally given laxative effects only occur at very high doses. In contrast to lactose no physiological intolerances are known and it is non-diabetic.\textsuperscript{44}

Various dicalcium phosphate qualities are widely used in tablet formulations both as fillers and as source of calcium and phosphorus in nutritional supplements. Some calcium phosphate salts can be anhydrous, meaning the water has been removed from the salt form. Other calcium phosphates are termed dibasic, meaning they have two replaceable hydrogen atoms. It is used in pharmaceutical products because of its compaction properties. The predominant deformation mechanism of DCP is brittle fracture. In the work underlying this thesis (Paper I), seven different DCP qualities and thirteen different mannitol qualities were characterized by several representative physical properties and the effect of these qualities on roll compacted granules and tablets has been studied.
Raw material, powder blend, ribbon, granule, and tablet characterization

Characterization of excipients is an essential step at the preformulation phase of product development. It creates a body of information that is very valuable in the development of pharmaceutical products. The lack of such information leaves the formulator with little freedom and flexibility for action when a problem arises from the production process or from the quality of the finished product.\(^\text{20}\) The knowledge derived from the characterization of raw materials can also help to allow better specifications to be defined for acquiring materials, with the aim of either reducing cost or improving a product’s quality. Furthermore, material characterization results can provide a good database for the assessment of suppliers which can provide a consistent quality of materials.\(^\text{20, 47}\)

Pharmaceutical raw material companies (vendors) may provide materials with their detailed specification. However, the information provided by different suppliers may vary. The type of tests performed or the techniques used for the characterization of a particular physical property such as flowability or particle size distribution may be different. Therefore, comparison of materials from different suppliers can be challenging.\(^\text{20, 44, 48-49}\)

The method of raw material characterization varies significantly, because it depends on many factors for instance the nature and form of material used as the process utilized in the conversion of the raw materials to the final products. For example, information about particle size distribution of a drug material may be less important if the end product is a solution, more important when the material is to be granulated, and most critical when preparing an inhalant.\(^\text{20}\)
Many compendial tests are concerned with the chemical aspects of testing and seldom address the physical characterization of excipient materials. However, it is more likely that the physical aspects of raw materials rather than the chemical properties will have a great influence on the roll compaction process as well as the quality of the finished products.

Roll compaction greatly depends on the properties of the feed powders. In the work underlying this thesis, raw materials, powder blends and granules were characterized by measuring their rheological properties (dynamic methods)\textsuperscript{50}, bulk density, true density, compressibility and permeability\textsuperscript{51}, frictional and flow properties\textsuperscript{52}, particle size\textsuperscript{48-49}, compactability and particle morphology (SEM). Ribbons were characterized by measuring densities, thickness and near-infrared chemical imaging (NIR-CI). An instrumented roll compactor\textsuperscript{53} was employed for roll compression in Paper IV (Figure 6). Tablets were characterized by measuring diameter, thickness, weight variation, content uniformity, disintegration time, tensile strength and NIR-CI.

\textbf{Figure 6.} Instrumented roll installed along the roll width (back (P1), center (P2) and front (P3)) on an Alexanderwerk WP120 roll compactor.
Computational tools and Mathematical modeling

Models can be seen as tools to describe reality in a simplified way, and to facilitate both interpretation and prediction of the studied properties. In general, mathematical modeling approaches can be divided into two categories:

- The hard modeling approach uses models derived from first principles (fundamental models), representing scientifically-stated laws of nature, usually using a system of differential equations. For example, the rolling theory of granular solids developed by Johanson.
- The soft modeling approach represents knowledge gained from experiments. Projection methods produce models based on the data. This is also termed semi-empirical modeling. Semi-empirical models are not a substitute for first principle models (mass balance, kinetics), but complement them.

In contrast to soft modeling, the experiments in hard modeling are performed to support or test the underlying theory. When working with models it is essential to remember that they are approximations of reality. Therefore, all models contain errors, but they can still be highly useful. It is important to use good sense and experience concerning the reliability of the models and to utilize them while applying objective criteria and good scientific standards.
Johanson’s model

The theoretical modeling of the roll compaction unit operation was pioneered by Johanson (1965). Johanson’s model is based on several assumptions, including cohesive, isotropic material, no-slip between the powder and the roll surface in the nip region (the material is frictional) and that all material within the nip region is compressed to a ribbon with a thickness equal to the exact gap between the rolls. Johanson’s model describes the pressure gradients for the slip and nip regions according to Equations (1, 2).

In these equations, $\theta$ denotes the roll angle, $S$ denotes the roll gap, $D$ indicates the roll diameter, $\mu$ is the friction coefficient between the powder and the roll, $\delta_E$ is the effective angle of internal friction, the constant $K$ indicates material compressibility and $\sigma$ is the normal stress applied to the powder. The parameter $A$ can be calculated from Equations (3, 4), where $\phi_w$ is the angle of wall friction.

$$\frac{d\sigma}{dx}_{\text{Slip}} = \frac{4\sigma\left(\frac{\pi}{2} - \theta - \nu\right)\tan \delta_E}{D\left(1 + \frac{S}{D - \cos \theta}\right)\cot(A - \mu) - \cot(A + \mu)}$$  \hspace{1cm} (1)

$$\frac{d\sigma}{dx}_{\text{Nip}} = \frac{K\sigma_\theta\left(2\cos \theta - 1 - \frac{S}{D}\right)\tan \theta}{D\left(1 + \frac{S}{D - \cos \theta}\right)\cos \theta}$$  \hspace{1cm} (2)

Where

$$A = \frac{\theta + \nu + \frac{\pi}{2}}{2}$$  \hspace{1cm} (3)

$$2\nu = \pi - \arcsin\left(\frac{\sin \phi_w}{\sin \delta_E}\right) - \phi_w$$  \hspace{1cm} (4)
The nip angle ($\alpha$) is estimated based on the assumption that the pressure gradients at the boundary between the no-slip and nip regions are equal. By solving the equation where the expressions in Equations (1, 2) are equal to one another, it is possible to calculate $\alpha$.\(^{23}\)

The value of the model is the link between process parameters and material attributes. The pressure is normally applied to the rolls as an overall hydraulic pressure, or press force ($R_f$). The relationship for the pressure distribution between the rolls can be used to relate this process parameter with the peak pressure ($P_{\text{max}}$) applied at minimum separation as in Equations (5, 6):

$$R_f = \frac{P_{\text{max}} WDF}{2} \quad (5)$$

Where

$$F = \int_{\theta=0}^{\theta=\alpha(\delta_E, \phi_F, K)} \left[ \frac{S}{D} \right]^K \left[ 1 + \frac{S}{D} - \cos \theta \cos \theta \right] \cos \theta \ d\theta \quad (6)$$

This represents a relationship between process parameters (press force ($R_f$), roll separation ($S$), geometric parameters (roll diameter ($D$), roll width ($W$)) and material properties (effective angle of internal friction ($\delta_E$), angle of wall friction ($\phi_w$) and compressibility ($K$)).

Based on Johanson’s model, the relative ribbon density exiting the process can be calculated from Equation (7), where $\gamma_0$ is the pre-consolidation relative density.

$$\gamma_R = \left( \frac{2R_f}{WD} \right)^{\frac{1}{K}} \int_{\theta=0}^{\theta=\alpha(\delta_E, \phi_F, K)} \left[ \frac{S}{D} \right]^K \left[ 1 + \frac{S}{D} - \cos \theta \cos \theta \right] \cos \theta \ d\theta \quad (7)$$
In summary, to use the Johanson’s model the following input parameters are needed:

1) Roll width and diameter  
2) Roll gap  
3) Effective angle of internal friction and angle of wall friction  
4) Compressibility factor  
5) Pre-consolidation relative density

Using Johanson’s model we can predict:

1) Pressure profile in the nip region  
2) Nip angle  
3) Roll force and Torque  
4) Effect of material and process parameters on the roll compaction process.

Reynolds et al. 24 used a modified version of the Johanson model to predict the relative ribbon density as a function of screw speed to roll speed ratio, press force \((R_f)\), and pre-consolidation relative density \((\gamma_0)\). The Johanson model expression was modified to incorporate press force \((R_f)\), screw speed to roll speed ratio \((N_s/N_R)\), and screw speed constant \((c_s)\). These changes were made to eliminate the need for accurate gap measurements by relying on actual roll speed and screw speed data. The screw constant \((c_s)\) can be estimated using Equation (8). Johanson’s model is easy to implement and computationally economical. However, there are limitations due to the simplification of the powder behavior in the nip region. Johanson’s model and Reynolds approach were used in Paper IV.

\[
\frac{N_s}{N_R} = \frac{\pi}{c_s \rho_{\text{true}} \gamma R} DWS
\] (8)
Chemometrics

Measured data is not the same as information. Hence, a main subject in all empirical sciences, including pharmaceutical sciences, is how to reveal the relevant information in the data. The term “chemometrics” was coined by Svante Wold in 1974 when he wrote:

The art of extracting chemically relevant information from data produced in chemical experiments is given the name of ‘chemometrics’ in analogy with biometrics, econometrics, etc. Chemometrics, like other ‘metrics’, is heavily dependent on the use of different kinds of mathematical models […]. This task demands knowledge of statistics, numerical analysis, operation analysis, etc., and in all, applied mathematics. […]; in chemometrics the main issue is to structure the chemical problem to a form that can be expressed as a mathematical relation.

Therefore, chemometrics is an interdisciplinary field of science that combines tools and ideas from chemistry, mathematics and statistics. By definition, chemometrics deals with two main topics (aims): designing and performing experiments, and the following analysis of the measured multivariate data. The first topic can be achieved by using design of experiments to provide a small number of information-rich experiments, while multivariate data analysis is used to analyse the measured multivariate data. This thesis will cover both topics.
Design of Experiments (DOE)

Design of Experiments is the basis of data generation in chemometrics. The main aim of DOE is to maximize the information output from a minimum number of experiments.\textsuperscript{62-64} In DOE, variation is introduced into the data in a systematic way so that the effects of investigated factors and their interactions on one or many responses can be explained by means of statistical analysis and more easily separated from the noise.\textsuperscript{62, 69}

The two most commonly used designs are the two-level factorial and fractional factorial designs. Factorial designs are box-like designs with one dimension per factor, usually investigated in two levels for each factor where all combinations of these factors are investigated.\textsuperscript{63} The number of experiments in a two-level factorial design will be $2^k$, $k$ being the number of factors to be investigated. As a rule, centre points and replicates are added to the design. These experiments are normally three and will give the model additional degrees of freedom. Moreover, the centre points will reveal possible non-linearity in the experimental domain and the experimental error can be calculated from the replicates. With increasing number of factors ($k>5$), the number of experiments required for full factorial design increases rapidly, to a number impractical to conduct with a limited amount of time and resources. In such cases reduced alternatives of the factorial design are often used, so called fractional factorial designs. The number of experiments in two-level fractional factorial designs is $2^{k-p}$ where $p$ can be 1, 2, 3,....k-2. However, depending on the level of reduction, a certain number of factor and interaction effects get confounded, and their individual effect cannot be distinguished.\textsuperscript{62, 64} In the work underlying this thesis, factorial design was used in \textbf{Paper I and IV}.

Factorial designs can be either extended or reduced depending on the objective of the study. Generally, design points are added for optimization.
Examples of designs used in optimization (also called response surface modeling designs) are the central composite designs, Central Composite Face centered (CCF) and Central Composite Circumscribed (CCC) designs. They consist of three parts, namely the corners from a full or fractional factorial design, axial points located on the factor axes, and replicated center points. In the CCC design the axial points are located on the surface of a circumscribed sphere, while in the CCF design the axial points are located on the face sides of the design cube. Central composite designs provide the possibility to calculate more complex mathematical models, including quadratic terms. In Paper II, a reduced CCF design was used. Data obtained from experimental designs are usually evaluated with Multiple Linear Regression (MLR) or Partial Least Squares (PLS).

Establishment of the Design Space - Risk based Predictive Approach

Design space is defined by ICH (2008) as “the multidimensional combination and interaction of input variables (e.g., materials attributes) and process parameters that have been demonstrated to provide assurance of quality”. In other words, a link between the critical process parameters (CPPs), the process inputs and the critical quality attributes (CQAs) should be established. The process should be controlled in a way that the CQAs reach their expected values. It is also clear from the definition of design space that the actual values for CPPs and process inputs are unimportant, only the combination between process inputs and CPPs make the design space. Figure 7 illustrates the concept of DS. The design space is the region established by the operating conditions where the corresponding predicted outputs will exhibit acceptable quality level. DOE can be used to explore the operating conditions. The concept of acceptance on the outputs of the process is determined with specifications, which are some acceptance limits that are used to give some values of minimal acceptable quality.
Figure 7. Demonstration of the concept of Design Space (DS) as the area of the operating conditions for x in which there is assurance that the responses $Y_1$ and $Y_2$ are within acceptance limits (adapted from Lebrun\textsuperscript{72}).

DOE is useful in translating how the combination of CPPs affects the product CQAs. DOE helps in defining the combination of process parameters that will keep the product performance within the specifications with a quantified guarantee for the future use of the process. However, the basic use of DOE for optimization is generally not adequate to achieve the risk-based perspective recommended to achieve the “assurance of quality” as stated in the DS definition.\textsuperscript{72, 74}

The optimization of multiple response surfaces uses the overlapping mean responses approach to find the so-called sweet spot. The sweet spot reflects a volume in subspace, situated in the total multidimensional experimental design, in which the combination and interactions of process inputs reliably deliver a product with the desired performance according to the profile of critical quality attributes defined for that product.\textsuperscript{62} The sweet spot plot represents one approach toward finding a suitable operating condition. However, there are number of limitations with the sweet spot approach: 1) It can be interpreted too optimistically since it is only based on point estimates and uncertainty in Y-predicted is not taken into account. 2) It does not indicate how sensitive the sweet spot is to factor disturbances. 3) No risk estimation.\textsuperscript{62} These limitations represent a major drawback since ICH Q8 is clearly asking for a level of assurance guaranteeing that the product specifications will be met.
In this perspective, predictive probability is essential since it allows quantifying the risks that specifications will (or will not) be met in the future runs of the process. Specifications express the minimal satisfying quality that the experimenters want to obtain.\textsuperscript{74-75}

In Paper II Monte Carlo simulations were utilized to estimate the risk of failure. Both the uncertainties in the process factors, as well as the model uncertainty (RSD, and the condition number of the design) were taken into consideration. The Monte Carlo simulations used a normal distribution to sample the random process factors settings based on an optimum value with set low and high limits. This was followed by 100 000 predictions of the responses. The results display a distribution of the predictions providing an estimated risk of being in or out of a defined specification. The results of the optimization were evaluated based on two parameters: defects per million opportunities (DPMO) and Log(D). DPMO shows how many response predictions are outside the response specifications based on one million simulations. DPMO indicates the sensitivity of the responses to the external perturbations applied on the factor settings (in our case 5%). The ideal outcome of DPMO is zero. The “overall distance to target”, D, was another parameter used to evaluate the optimization results and was calculated according to Equation 9,

$$D = \log_{10} \left[ \frac{\sum wi \left( \frac{y_i - T}{T - L} \right)^2}{M} \right]$$ \hspace{1cm} (9)

where $y_i$ is the response, $T$ is the desired target, $L$ is the worst acceptable response value(s), $w_i$ is the weight for each response and $M$ is the number of responses. A log (D) value below zero means that we are between the target and the maximum for each response. The data collected through a DOE plan were analyzed using a risk based predictive approach, allowing the uncertainties and interaction to be integrated into a multivariate statistical model. Integrating the variability of the process, which may more or less have an impact on the quality, is an efficient way of assuring quality.
**Multiple Linear Regression (MLR)**

The purpose of predictive modeling is to determine the relation between several x-variables and one or more y-variables (dependent or response variables). This can be accomplished by means of a model, where the observed result, i.e. response (y), is described as a function of the x-variables, usually called factors (x₁, x₂, . . ., xₙ) in DOE. The noise is left in the residual e (Equation 10). A regression model is written as

\[
y = Xb + e
\]

\[
y = b₀ + x₁b₁ + x₂b₂ + \ldots + xₙbₙ + e
\]  \hspace{1cm} (10)

The most frequently used method for finding b is the ordinary least squares (OLS) method⁵⁵ (also called Multiple Linear Regression, MLR), where

\[
b = (X^{T}X)^{-1}X^{T}y
\]  \hspace{1cm} (11)

In MLR, in order to estimate b, the OLS method requires that the data must satisfy the linearly independent criteria ((X^{T}X) of full rank), and the number of factors in X must be equal to or smaller than the number of observations.⁶⁸ Due to these criteria, MLR essentially requires designed data. Non-linearity can be handled to some extent by adding non-linear parameters, i.e. interaction or quadratic, in the model.⁵⁴

When the x-variables are not orthogonal or the number of x-variables is more than the number of experiments, co-linearity arises between x-variables. The matrix X^{T}X has no longer full rank implying that the usual full rank inverse of X^{T}X no longer exists.

In general, the measured data in pharmaceutical applications are normally multivariate and collinear and MLR cannot be used (except for cases where x-variables are controlled using a DOE. This is the main reason why latent variable regression (LVR) methods, for example PLS, have become popular in pharmaceutical applications.⁵⁸
Latent Variable Methods

Latent variables (LV) are variables that cannot be observed directly but which instead are defined as manifest variables inferred from directly observed variables. The goal is to represent the general properties of a phenomena or system with as few latent variables as possible regardless of the number of observed variables. A latent variable may for instance capture concepts such as quality of life, intelligence, disease, phenotype, size, molecular flexibility or hydrophobicity.

For example, quality of life is a latent variable that cannot be measured directly, so observable variables such as salary, employment, environment, education, physical and mental health variables are used to infer quality of life. Latent variable methods are attractive in pharmaceutical applications for a number of reasons, but mainly because they are designed for use with dataset describing correlated variables. Such correlations are common when characterizing pharmaceutical systems using common instrumental measurement methods. Furthermore, the use of latent variables facilitates the visualization of multivariate data sets by reducing their complexity. Three latent variable methods, principal component analysis (PCA), partial least squares (PLS) and orthogonal projections to latent structures (OPLS) were utilized in the work underlying this thesis.

An important difference exists between supervised and unsupervised modeling methods. Unsupervised modeling is used for single datasets (e.g. X or Y) with the aim of modeling the maximum of variance. With unsupervised modeling no priori information about the observations is used during model building. Alternatively, supervised modeling is performed pairwise (e.g. X and Y) with the aim of modeling the maximum covariance. When modeling using supervised methods the model is driven toward a specific solution by including one or more particular response variables of interest (Y).
Principle Component Analysis (PCA)

One of the oldest and most common latent variable projection methods is principal component analysis. PCA is an unsupervised method used for compressing high-dimensional multivariate data sets into a smaller number of dimensions (LVs) and thus making it easier to get an overview about trends, grouping, patterns and outliers.

The data matrix $X$ is decomposed into a number of principal components (PCs) that maximize explained variance in the data on each consecutive component under the constraint of being orthogonal to the previous PCs. PCA algorithm condenses the $X$ data into t-scores, $p$-loading and e-residuals as

$$X = TP^T + E = t_1p_{1}^T + t_2p_{2}^T + .... + t_Ap_{A}^T + E$$ (12)

The scores ($T$) provides an overview of the observations (e.g. process batches) and how they relate to each other. Interpretation of the patterns in the scores is found in the corresponding loadings ($P$). The loadings reveal how each variable contributes to the separation among the observations and express the relative importance of each variable. Some of the variation in $X$ is not structured and should not be included in the model, thus constituting the residuals $E$.

There are several algorithms for performing PCA. The most common are single value decomposition (SVD) and Non-linear Iterative Projections by Alternating Least Squares (NIPALS). The NIPALS algorithm is a sequential method, which means that the latent variables are calculated one at time. SVD is a non-sequential method, which means that all latent variables are calculated simultaneously. Furthermore, the NIPALS algorithm can handle missing values. All PCA calculations reported in this thesis were performed using the NIPALS algorithm. PCA has been used in Papers I and III.
Partial Least Squares (PLS)

One of the most common tasks in data analysis is to build a model which reveals how one or several response variables, can be explained by means of a set of predictor variables. PLS regression is a supervised projection method.\textsuperscript{80-82} It is an extension of the previously described PCA, while PCA maximizes the variance within a single dataset, PLS maximizes the covariance between two sets of data (i.e. X and Y). The X and Y matrices are decomposed into components as

\begin{align*}
X &= TP^T + E \\
Y &= TC^T + F
\end{align*}

where P and C are the loadings matrices, T is the scores matrix, E and F are the residuals matrices. PLS can handle both multiple responses and correlated variables making it a good choice for analyzing matrices with more columns than rows.\textsuperscript{68, 83-84} PLS has been used in Paper III.

Orthogonal Projection to Latent Structures (OPLS)

About a decade ago, a modification of the PLS method, named orthogonal PLS, OPLS, was introduced.\textsuperscript{85} OPLS was originally proposed as a pre-processing filter for PLS but was subsequently developed into a full modeling method.\textsuperscript{85-86} The driving force behind the development of OPLS was improved model interpretation.\textsuperscript{87-92} OPLS separates the systematic variation in X into two parts, one that is correlated (predictive) to Y and one that is uncorrelated (orthogonal) to Y. Using the same settings, the prediction properties for single-Y are the same for PLS and OPLS.\textsuperscript{85, 93-94}

In OPLS the X and Y matrices are modeled as

\begin{align*}
X &= T_p P_p^T + T_o P_o^T + E \\
Y &= T_p C_p^T + F
\end{align*}
where $\mathbf{P}$ and $\mathbf{C}$ are the loadings matrices, $\mathbf{T}$ is the scores matrix, $\mathbf{E}$ and $\mathbf{F}$ are the residuals matrices, and the subscripts indicate whether they explain the predictive (p) or the orthogonal (o) variation. When only a single $\mathbf{y}$ exists, all predictive variation is modeled by a single predictive vector ($\mathbf{p}_p$) that is directly related to the response. This improves interpretation without sacrificing predictive ability, which can be difficult to accomplish using PLS.\textsuperscript{85-86} Below, the OPLS method is described for a single $\mathbf{y}$ vector.\textsuperscript{86} The first five steps are identical for the NIPALS PLS.

1) $\mathbf{w} = \mathbf{X}^\mathbf{T} \mathbf{y} (\mathbf{y}^\mathbf{T} \mathbf{y})^{-1}$
2) $\mathbf{w} = \mathbf{w} (\| \mathbf{w} \|)^{-1}$
3) $\mathbf{t} = \mathbf{X} \mathbf{w}$
4) $\mathbf{c} = \mathbf{y}^\mathbf{T} \mathbf{t} (\mathbf{t}^\mathbf{T} \mathbf{t})^{-1}$
5) $\mathbf{p} = \mathbf{X}^\mathbf{T} (\mathbf{t}^\mathbf{T} \mathbf{t})^{-1}$
6) $\mathbf{w}_o = \mathbf{p} - \mathbf{w} (\| \mathbf{p} - \mathbf{w} \|)^{-1}$
7) $\mathbf{t}_o = \mathbf{X} \mathbf{w}_o$
8) $\mathbf{p}_o = \mathbf{X}^\mathbf{T} \mathbf{t}_o (\mathbf{t}_o^\mathbf{T} \mathbf{t}_o)^{-1}$
9) $\mathbf{X}_E = \mathbf{X} - \mathbf{t}_o \mathbf{p}_o^\mathbf{T}$
10) Return to step 1, using $\mathbf{X}_E$ in place of $\mathbf{X}$

The basis for the OPLS method is the difference between the $\mathbf{p}$ and $\mathbf{w}$ loadings, as discussed by Stenlund.\textsuperscript{54} The $R^2_X$ values of the predictive and orthogonal components are measures of the structured fraction of the original data variation describing the response and the fraction not correlated with the response, respectively. The quality of an OPLS model is described by the $R^2_Y$ value, i.e. the correlation between the observed and predicted values for the studied response, and the $Q^2$ value, i.e. the correlation between the observed and cross-validated predicted response. The higher the $R^2_Y$ and $Q^2$ values the better the response can be described and predicted as a function of the descriptor variables, respectively. OPLS has been used in \textbf{Paper I, II and IV}. 

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O2PLS is an extension of OPLS. In contrast to PLS and OPLS, O2PLS is bidirectional, i.e. $X \leftrightarrow Y$. In other words, $X$ can be used to predict $Y$ (as with PLS and OPLS), but at the same time $Y$ can be used to predict $X$ (unlike PLS and OPLS). Moreover, O2PLS also allows the partitioning of the systematic variability in $X$ and $Y$ (as with OPLS) into three model compartments: the $X/Y$ joint variation; the unique variation in $X$; and the unique variation in $Y$.

The interpretational advantages of OPLS can be illustrated using the Raman dataset on pharmaceutical tablets produced using an experimental design. OPLS-DA and PLS-DA were used to classify two groups of batches; group 1 contains sodium stearyl fumarate as lubricant, while group 2 contains magnesium stearate. The important difference between PLS-DA and OPLS-DA was that with OPLS-DA the class discriminatory information was focused onto the single predictive component. This simplified model interpretation. The corresponding PLS-DA model required more than one PLS component to express this class difference and hence it was correspondingly more complicated to interpret. As seen in Figure 8, OPLS was used to target (rotate) all the systematic variation in the $X$ matrix related to the class discriminatory information in the first component. On the other hand, PLS modeling was not optimal in this; the systematic variation in the $X$ matrix related the class discriminatory information was observed in several components. Moreover, the vertical direction, the orthogonal component in the OPLS model, Figure 8, expresses the within class variability, that is uncorrelated (orthogonal) to the problem (to separate the two classes). This within-class variability can be interpreted through the orthogonal loadings (Figure 8) which arises from chemical composition differences due to running the experimental design at two different time occasions.
Figure 8. A) OPLS-DA (1+1 comp) model for the Raman dataset on tablets where group 1 contains sodium stearyl fumarate as lubricant while group 2 contains magnesium stearate, B) PLS-DA (2 comp) model for the same dataset and C) loadings for both models.
Results and Discussion of papers

This chapter discusses the results presented in Papers I-IV. The papers focus on presenting the data obtained in details which form the thesis’ foundation. By contrast, this section aims to clarify how things worked and present some unpublished results.

Paper I

Although roll compaction has become an established technique for dry granulation, the influence of material properties is still not fully understood. The QbD approach described in this paper aimed to understand the influence of different qualities of mannitol and DCP, but more importantly to understand the influence of brittle filler properties on product quality, and to enable to predict critical quality attributes of the drug product, based solely on the material properties of that filler. Each filler quality was described by several representative physical properties, e.g. flowability, particle size and compactability.

The work reported in Paper I was carried out at AstraZeneca, Mölndal Sweden. When starting the investigation, only few mannitol qualities were used in the site. It transpired that the different sites routinely used different excipients. As is often the case, people tend to stick with what they know. The characterization of twenty different DCP and mannitol qualities from different vendors by determining as many physical properties as realistically and practically possible creates a body of information that is very valuable in the development of pharmaceutical products. Furthermore, material characterization results can provide a good database for the assessment of suppliers which can provide a consistent quality of materials.\textsuperscript{20}

In a recent paper published after Paper I, Wagner et al.\textsuperscript{43} also investigated and compared the roll compaction behaviour of pure, unprocessed, crystalline mannitol and five spray-dried mannitol
qualities. The powder and granules were characterized with regard to their particle size distribution, flow properties and BET surface area. They concluded that the specific surface area is the key quality attribute. In Paper I, we characterized the qualities with regard to flowability, particle size and tensile strength of pure qualities tablets instead of BET surface area. Figure 9 illustrates a comparison between the five common qualities between both studies with regard to the BET surface area reported by Wagner et al.\textsuperscript{43} and tensile strength of pure qualities from our study. It can be seen that tensile strength decreases with decreasing BET surface area. A larger surface area available for bonding during tableting leads to tablets with higher tensile strength. The results confirm the investigation of Vromans et al.\textsuperscript{98}, who correlated the amount of binding sites in lactose qualities to the specific surface area.

![Figure 9. Specific surface areas of various spray dried mannitol qualities reported by Wagner et al.\textsuperscript{43} and tablets tensile strength of the same qualities reported in Paper I.](image)

Wagner et al.\textsuperscript{43} investigated the roll compaction behaviour of pure mannitol qualities. In Paper I, we investigated the roll compaction behavior of mannitol qualities in a mixture as formulations for roll compactions are most likely to contain mixtures of various excipients.
This helps in assessing whether the excipients would still retain their functional properties when mixed with other materials.

Following the physical characterization step, the raw material differences were visualized in a PCA score plot based on all raw material properties (Figure 10). This plot was then used to select the most different raw material qualities. It was observed in the loading plot (Figure 11) that particle size (d(0,1), d(0,5)), bulk density (BD), basic flow energy (BFE) and specific energy (SE) were in one cluster, implying that those properties were very correlated for the studied fillers; i.e. fillers with larger particle size exhibited higher density and better flowability. It should be noted that in **Paper I**, two PCA models were calculated, one for mannitol and one for DCP qualities and the selection was done based on separate PCA scores since originally the mannitol and DCP were two separate studies.

**Figure 10.** PCA of twenty mannitol/DCP qualities based on ten properties. PC1-PC2 score plot with training sets qualities indicated by squares, test sets qualities indicated by triangles and the rest of the characterized qualities by circles. The mannitol/DCP qualities abbreviations are listed in **Paper I**.
Figure 11. PCA of twenty mannitol/DCP qualities based on ten properties. PC1-PC2 loading plot indicating which properties are responsible for the extreme locations of the mannitol/DCP qualities in the score plot (Figure 10). Mannitol/DCP property abbreviations are listed in Paper I.

OPLS was then used to understand and predict how those properties affected drug product intermediates as well as the critical quality attributes of the final drug product. The interpretational advantages of OPLS allowed one to analyze the $R^2_X$ values of the predictive and orthogonal components, which are measures of the structured fraction of the original data variation describing the response and the fraction not correlated with the response. For example, it could be deduced that in the ribbon thickness model only 10.5% of the design variation correlated with changes in ribbon thickness ($R^2_{X_{\text{pred}}} = 0.105$), while a large part of the design variation (58%) did not influence the ribbon thickness, as opposed to the model for granule bulk density, where 40% of the variation in the design was related to the granule bulk density ($R^2_{X_{\text{pred}}} = 0.399$). An explanation for the low amount of $X-y$ correlating variation in the OPLS model describing ribbon thickness was found upon examination of the list of significant factors in the predictive component. Only the speed ratio was important in the case of ribbon thickness, while many of the material properties were
relevant for granule bulk density, thus representing a larger fraction of the variation in $\mathbf{X}$. The model validation performed with new filler qualities (independent from the model), resulted in good predictions of properties of drug product intermediates and quality attributes of the drug product.

In this work we demonstrated an approach that expanded the DOE from vendor identities in the design into an in silico OPLS model based on raw material properties. This approach allows the possibility of introducing new fillers without additional experiments, provided that they are within the previously mapped design space. Additionally, this approach is generic and could be extended beyond fillers, to include drug substance, disintegrant, etc. Thus any new compound/ingredient would just have to be characterized before a suitable formulation can be determined in silico, without running any additional experiments.

While several papers have described the loss in compactability by roll compaction, \cite{33,34,38,99,100} in Paper I, we observed that some of the investigated mannitol and DCP qualities showed an increase in tablet compactability while others showed the opposite. Unfortunately, due to the large amount of data presented in Paper I, no detailed discussion was presented concerning the loss or gain in compactability. In the following pages, I will discuss the phenomenon of loss in compactability and the results in more details.
The loss or gain in compactability after roll compaction

The phenomenon of loss in compactability by roll compaction was discussed by several authors: Malkowska and Khan 33 defined the reduced compactability as work hardening, which is defined as “the resistance to permanent deformation of a material, increasing with the amount of deformation”. They explained this phenomenon as a result of consumption of binding sites in the first compaction step. Sun and Himmelspach 38 related the reduction in compactability after roll compaction to an enlargement in particle size, leading to less available binding areas between the particles. Loss in compactability is more common in systems containing significant proportions of any plastically deforming material such as MCC or starch.34,99-101

Sun and Himmelspach 38 showed that compactability of brittle granules prepared by roll compaction is relatively insensitive to granule size enlargement, because extensive fracture of brittle granules during compaction minimizes differences in initial granules size. This explanation finds support from studies showing more extensive fragmentation of brittle particles than plastic particles especially at elevated compaction pressures.34 Therefore, brittle fragmenting materials are less prone to decrease in compactability after roll compaction.34

An increase in tablet compactability after roll compaction has rarely been reported. For crystalline lactose, Riepma et al. 102 found that dry granulation had only a small effect on compactability. Tablets made of α-lactose monohydrate and β-lactose showed comparable compactability when compressed directly or with previous dry granulation at the same pressure. Kuntz et al. 103 reported that the roll compaction step induced an increase in compactability for acetames. The increase in compactability observed was accompanied by an increase in specific surface area during roll compaction.
In **Paper I**, we observed that some of the investigated mannitol and DCP qualities showed an increase in tablet compactability while others showed a decrease in tablet compactability. All the investigated RC formulations in both mannitol/DCP designs were multi-component formulations. Compactability of multi-component formulations may be difficult to predict.

Figure 12, shows a value for gain or loss in compactability for DCP and mannitol qualities calculated using Equation 17

\[
\text{Loss or gain in compactability (\%)} = \frac{TS_{n_{RC}} - TS_{n_{DC}}}{TS_{n_{DC}}} \times 100 \tag{17}
\]

where \(TS_{n_{RC}}\) is the tensile strength of TS2 roll compacted tablets normalized with compaction pressure, and \(TS_{n_{DC}}\) is the tensile strength of TS2 direct compression tablets normalized with compaction pressure. It should be noticed that the batches are titled after the DOE, which in some cases the title does not reflect the major component in the formulation. In the mannitol and DCP designs, all the RC formulation are composed of 78% brittle fillers; a combination of different mannitol and DCP qualities. Compactability of some roll compacted MCC qualities (Av PH101, 105, 200)\(^{41}\) (Dumarey et al 2011) has been also added for comparison between plastic and brittle materials.
Figure 12. Percentage of gain or loss in compactability for mannitol/DCP qualities after roll compaction. The mannitol/DCP qualities abbreviations are listed in Paper I. Compactability of some roll compacted MCC qualities (Av PH101, 105, 200) reported by Dumarey et al. has been also added for comparison between plastic and brittle materials. (L: roll compacted at low ratio of the roll speed and the feed screw speed, H: roll compacted at high ratio). See Table 1 for further details.

Table 1 summarizes the main composition of each RC formulation and the dominant property which may led to either increase or decrease in compactability. All the RC formulations in the mannitol design which exhibited an increase in compactability contain 55% crystalline or granular brittle filler (Pear 400DC or Pharm16700 or Pear 50C). An increase in compactability was observed after roll compaction: the higher the applied roll compaction force, the higher the gain in compactability (Figure 12). A possible explanation to the improvement in compactability can be that the crystalline brittle filler fracture extensively during roll compaction, thus creating new surfaces for bonding during tablet compression. Pear 400DC exhibited the highest gain in compactability. We hypothesize this is due to its high bulk density and stronger structure integrity compared to spray dried mannitol.
Table 1. Summary of the main composition of each RC formulation in Paper I and the dominant property which led to either increase or decrease in compactability.

| Mannitol design (brittle) | | | | |
|---------------------------|------------------|-----------------|---------------|
| **A) Gain in compactability** | | | | |
| **RC formulation** | **Main composition (%)** | **Dominant property** | **d(0.5)g [µm]** |
| Pear 400DC | Pear 400DC (55%) Granular/high BD | Emc (23%) Spray dried/high BD | Granular+ High BD | 489 |
| Pharm 16700 | Pharm 16700 (55%) Crystalline | Emc (23%) Spray dried/high BD | Crystalline | 476 |
| Pear 50C | Pear 50C (55%) Crystalline/cohesive/high surface energy | Emc (23%) Spray dried/high BD | Crystalline | 416 |
| **B) Loss in compactability** | | | | |
| Part M100 | Part M100 (55%) Spray dried | Emc (23%) Spray dried/high BD | Spray dried | 570 |
| Part M200 | Part M200 (55%) Spray dried | Emc (23%) Spray dried/high BD | Spray dried | 642 |

| DCP design (brittle) | | | | |
|----------------------|------------------|-----------------|---------------|
| **A) Gain in compactability** | | | | |
| **RC formulation** | **Main composition (%)** | **Dominant property** | | |
| DCPD M | Part M200 (55%) Spray dried | DCPD M (23%) Crystalline/Dihydrate (surface energy) | Crystalline Dihydrate | 639 |
| **B) Loss in compactability** | | | | |
| Fuji | Part M200 (55%) Spray dried | Fuji (23%) Spray dried Anhydrous | Spray dried+ Spray dried Anhydrous | 381 |
| DCPA A | Part M200 (55%) Spray dried | DCPA A (23%) Crystalline Anhydrous | Spray dried+ Crystalline Anhydrous | 659 |
| Emc A | Part M200 (55%) Spray dried | Emc A (23%) Spray dried Anhydrous | Spray dried+ Spray dried Anhydrous | 692 |

| MCC design (plastic) | | | | |
|----------------------|------------------|-----------------|---------------|
| **Loss in compactability** | | | | |
| Av PH 105 or Av PH 101 or Av PH 200 | Av PH 105 or Av PH 101 or Av PH 200 (55 %) | Emc (23%) | Plastic deforming material (55 %) | |
On the other hand, all the RC formulations in the mannitol design which exhibited a decrease in compactability contain 78% spray dried brittle filler (Parteck M100 or Parteck M200+ Emc). A possible explanation to the loss in compactability can be that the highly porous spray dried fillers use some of their surfaces for bonding during roll compaction, thus leaving less surfaces remaining for tablets compression. Another possible cause is the breakage and collapse of spray dried particles during roll compaction. This is supported by the SEM images in Paper I for Fujicalin, a spray dried quality. This finding is consistent with Schlack et al. who noticed that the mean particle size of Fujicalin particles was only 7.7 µm after exposing them to ultrasound. The Fujicalin quality consists of spherical and highly porous particles, which are composed of very fine primary crystals.

Although the RC formulations in the mannitol design which exhibited an increase in compactability contain 23% spray dried filler (Emc), it seems that the 55% crystalline brittle filler compensate for the loss caused by the spray dried filler.

In the DCP design, the DCPD M formulations are the only ones that exhibited an increase in compactability, even though they contain 55% spray dried quality (Parteck M200). A possible explanation is that these formulations contain 23% DCPD M which is a crystalline dihydrate quality. Again, the crystalline brittle quality fractures extensively during roll compaction. Another factor on the gain in compactability in this case might be a change in surface energy of the starting material induced by roll compaction i.e. dihydrate vs anhydrous. Since highly energetic particles tend to agglomerate to reduce their surface energy, elevated compactability of roll compacted granules might be explained by an increase in surface energy after roll compaction. Chamarthy et al. reported differences in compactability of two batches of starch, which were virtually identical in common physical test procedures. Different compaction behavior was correlated with alterations in surface energy by an additional washing step in the manufacturing of one batch.
It was found that the washing step significantly altered the surface energetic properties of the excipient. The washed lot consistently produced stronger compacts. For spray dried lactose with varying amounts polysorbate, it was found that surface energy influenced compactability.\textsuperscript{107}

Furthermore, this hypothesis is supported by that all the other DCP qualities (Fuji, DCPA A and Emc A) which exhibited a reduction in compactability are anhydrous, more specifically the DCPA A quality, a \textbf{crystalline anhydrous} quality very similar in physical properties to DCPD M except for being anhydrous form. DCPD M being crystalline and dihydrate seems to compensate for the loss in compactability caused by the existence of spray dried filler (Part M200) in the formulation.

All the other DCP qualities (Fuji, DCPA A and Emc A) exhibited reduction in compactability due to a combination of high % of spray dried fillers and anhydrous qualities (Table 1). As expected, all MCC qualities showed reduction in compactibility: the higher the applied roll compaction force, the higher the loss in compactability (Figure 12).

Roll compaction typically induces an increase in particle size. As mentioned earlier, granule size enlargement is discussed as underlying cause for the observed reduced compactability by roll compaction.\textsuperscript{38} Therefore, the contrary relation might be expected for mannitol/DCP when formulations exhibited an increase in compactability or at least contribute partly to the observed effect. Table 1 illustrates granules median particle size (d(0,5)) for each formulation, produced at high roll compaction force. For the mannitol design, the highest increase in (d(0,5)) was observed for RC formulations which show loss in compactability (Part M100 and Part M200). For the DCP design, the relation is not clear. Alderborn and Nyström\textsuperscript{108} reported no influence of particle size on compactability could be determined for DCP and saccharose. The relationship between particle size and compactability is rather complex and depends strongly on material properties.
Thus, conflicting results might be found in the literature. However, a decrease in particle size can be fully or partially included to explain the increase in compactability after roll compaction for the mannitol batches.

Kuntz et al. reported that the roll compaction step induced an increase in compactability for acetames. The observed raise in compactability was accompanied by an increase in specific surface area during roll compaction. Supplementary experiments are required to deduce if granules specific area contribute to the observed effect.

Table 2 illustrates BET surface area, specific energy and tensile strength of pure mannitol and DCP qualities. It can be noticed that the brittle spray dried qualities of mannitol and DCP such as Parteck M200, Parteck M100 and Fujicalin, which suffered loss in compactability, exhibit high BET surface area, low specific energy and high tensile strength. On the other hand, the brittle crystalline filler qualities, like Pharm 16700 and Pearlitol 400DC, which showed an improvement in compactability following roll compaction exhibit low BET surface area, high specific energy and low tensile strength.

**Table 2.** BET surface area, specific energy and tensile strength of pure mannitol and DCP qualities. BET values are from vendor and literature.  

<table>
<thead>
<tr>
<th>Quality</th>
<th>Form</th>
<th>BET surface area [m²/g]</th>
<th>Specific energy [mJ/g]</th>
<th>Tensile strength [MPa]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fujicalin [DCP]</td>
<td>Spray dried</td>
<td>40</td>
<td>2.7</td>
<td>4.62</td>
</tr>
<tr>
<td>Parteck M100 [mannitol]</td>
<td>Spray dried</td>
<td>3.7</td>
<td>4</td>
<td>3.21</td>
</tr>
<tr>
<td>Parteck M200 [mannitol]</td>
<td>Spray dried</td>
<td>3.2</td>
<td>5</td>
<td>2.31</td>
</tr>
<tr>
<td>DCPD M</td>
<td>Crystalline</td>
<td>0.57</td>
<td>6.3</td>
<td>1.86</td>
</tr>
<tr>
<td>Pearlitol 400DC [mannitol]</td>
<td>Granular</td>
<td>0.5</td>
<td>12</td>
<td>1.22</td>
</tr>
<tr>
<td>Pearlitol 50 C [mannitol]</td>
<td>Crystalline</td>
<td>&lt;0.5</td>
<td>5.6</td>
<td>1.33</td>
</tr>
<tr>
<td>Pharma 16700 [mannitol]</td>
<td>Crystalline</td>
<td>0.2</td>
<td>9.1</td>
<td>1.42</td>
</tr>
</tbody>
</table>
In summary, roll compaction had a significant influence on the compactability of the investigated mannitol and DCP qualities. The results revealed that some of these qualities actually showed improved compactability following roll compaction. The observed effect seems to be a function of many factors, such as deformation characteristics; amount of crystalline and spray dried brittle fillers; particle size enlargement; and applied roll compaction force. Additionally, specific surface area and surface energy might be taken into account as important factors on compaction performance of mannitol and DCP qualities.

Spray dried qualities also demonstrated increased amount of fines when roll compacted at low speed ratio. This is likely caused by the collapse of their inherent porous structure, which ultimately had an effect on granule flowability. Their inherently better flowability may also lead to increased side seal leakage. The clearest example amongst the tested RC formulations is the one containing 78% spray dried brittle fillers combination of Parteck M200 and Fujicalin, where compaction properties and flowability were significantly reduced following roll compaction. These findings have been also observed in Paper II when using 55% mannitol (Parteck M200), a spray dried quality based formulation, and a roll compactor feeding the powder vertically. These qualities are often used in roll compacted formulation due to their excellent flowability and good compaction properties, but these results indicate that alternatives should be carefully considered.
Paper II

From a QbD perspective, the aim of this study was to demonstrate the applicability of DOE and multivariate modeling principles to identify the Design Space of a roll compaction process using a predictive risk-based approach. In Paper I, the focus was towards investigating the influence of material properties while in Paper II was to investigate roll compaction process parameters.

It is obvious that a holistic approach is required to map the process parameters interactions. In this context, DOE is perfectly adapted to collect the data and translate how the combination of CPPs affects the product CQAs. For this purpose, a reduced CCF design was used to evaluate the influence of roll compaction process variables (roll force, roll speed, roll gap, and screen size) on the different intermediate and final products (ribbons, granules, and tablets) obtained after roll compaction, milling, and tableting. The product CQAs were granule throughput, ribbon porosity, granules particle size, and tablets tensile strength.

After developing a regression model for each response, optimal settings were found which comply with the response criteria. Predictive probability is essential since it allows quantifying the risks that specifications will (or will not) be met in the future runs of the process. Therefore, a predictive risk based approach using Monte Carlo simulation of the factor variability and its influence on the responses was applied which fulfill the criteria for the responses in a space where there is a low risk for failure. As discussed in the background chapter of this thesis, the optimization of multiple response surfaces using the overlapping mean responses approach to find the so-called sweet spot has many limitations compared to the predictive risk based approach. In contrast to the overlapped mean response approach, the predictive risk based approach to define the Design Space takes into account the uncertainty in the process parameters as well as model uncertainty (RSD and condition number of the design).
O2PLS modeling for improved analysis and interpretation (not published)

A multidimensional dataset was presented in Paper II. O2PLS can be used as a multivariate tool to provide greater understanding of the interrelationships in this multidimensional dataset. The O2PLS tool was applied to the data set in Paper II. The DOE roll compaction parameters formed the $X$ matrix while the ribbon, granule and tablet properties formed the $Y$ matrix. The model resulted in 4+0+2 components. This notation means four joint components modeling the $X/Y$ information overlap, zero $X$-unique components, and two $Y$-unique components modeling information only found in $Y$. The zero $X$-unique component is expected since the $X$ block is constructed by DOE. The results show that:

I. 100 % of the variance in $X$ overlaps with 75 % of the variance in $Y$ ($R^2_X$(cum)=1, $R^2_Y$(cum)= 0.75, $Q^2$=0.61)

II. 15 % of the variance in $Y$ is unique.

The scores and the loadings of all these components can be interpreted. Compared to a PLS model, the difference is that one can avoid mixing joint and unique sources of variation. Consider Figures 13 and 14, which show the predictive (joint) scores $t$ and $u$ for the first two components. Of note is the fact that both models ($t$ and $u$) arrive at and display very similar patterns, directions and groupings.
Figure 13. O2PLS joint scores plot, where t represents the scores from the X block.

Figure 14. O2PLS joint scores plot, where u represents the scores from the Y block.
Figure 15 shows the loadings of the first two components. For example in the first component, the correlation between roll force (RF) and ribbon density (RD), granules bulk density (BD), particle size (D10, D50 and D90) and tablet tensile strength (TS) can be seen. In the second component, the correlation between roll gap (GW), roll speed (RS) and ribbon thickness (Th) and milled granules throughput (Prod). Figures 15 and 16 illustrate that each one of the four predictive components is dominated by a process parameter: roll force for the first component; roll gap for the second component; roll speed the third component; and screen size the fourth component. However, the third and fourth components only have a small contribution in explaining Y (R2Y=0.05 and 0.01, respectively).

Some variables will correlate even if there is no causality connection between them, e.g. relation between the milling parameter screen size and ribbon density and thickness. However, complementary scientific reasoning and application of pharmaceutical knowledge has to be included before judging the presence of causality.

![Figure 15. O2PLS joint loadings plot for the first two components, where p represents the loadings from the X block and q represents the loadings from the Y block.](image)
Figure 16. O2PLS joint loadings plot for the third and fourth components, where p represents the loadings from the X block and q represents the loadings from the Y block.

Most importantly, the scores and loadings for the unique part can also be interpreted. Consider Figures 17 and 18, which show the Y-scores and Y-loadings of the two Y-unique components, accounting for 15% Y-unique variance. The first orthogonal component illustrates that flowability (F) and permeability (Perm) carry unique information not related to the DOE process parameters. Likewise, the second orthogonal component also illustrates that permeability and D90 (coarse particles) carry unique information not related to the DOE process parameters. It should be noted that batches N7, 8, 18 and 19 (Figure 17) show what can be described as a combination of funnel arching and sudden flood (avalanche) during flowability measurements (sudden collapse of the granules bed when using the flow meter) and their measurements needed to be repeated many times. It is anticipated that this observation could be related to the unique variation in Y. The O2PLS model facilitates visualization of the interrelationships and improves model interpretability by separating joint and unique variations, which will add to the overall understanding of the process knowledge.
Figure 17. Score plot of the two Y-unique components of the O2PLS model.

Figure 18. Loading plot of the two Y-unique components of the O2PLS model.
Paper III

Near-infrared chemical imaging (NIR-CI) is an attractive technique within the pharmaceutical industry, where tools are continuously in demand to assess the quality of the intermediate and final products. The aim of this study was to demonstrate the feasibility of using NIR-CI in combination with multivariate methods to map; a) the spatial distribution of density/porosity of the ribbons, b) the chemical distribution of the API in the complex tablet matrix comprising five ingredients. Furthermore it was to show how textural features of the tablets can be related to a) the design parameters of the roll compaction process, b) the physical properties of the granules such as particle size. The ribbons and tablets manufactured in Paper II have been utilized in this study.

The results established the use of NIR-CI as a complementary nondestructive tool to determine ribbon density and to map the density distribution across the width and along the length of the ribbons in a complex chemical matrix. For the tablets, the compaction pressure developed during compression increased with the lateral distance from the center. Thus, the outer ring of the surface saw an increase in compaction pressure compared to the center of the tablet. Therefore, NIR-CI can be an effective tool to provide information about the spatial distribution of the compaction pressures on the surface of the tablet. Moreover, low roll force correlated to a heterogeneous type of texture in the API chemical image. Overall, texture analysis of the tablets enabled efficient investigation of the spatial variation and could be used to advance process understanding. Finally, O2PLS modeling facilitated the visualization of the interrelationships in this multidimensional data set and improved model interpretability by separating joint and unique variation.
Paper IV

Very limited work has been reported on comparing the performance of roll compaction process equipment operated at different scales and using different force feed screw mechanisms. In this paper the roll compaction of an intermediate drug load formulation was performed using horizontally and vertically fed roll compactors. The horizontally screw fed roll compactor was equipped with an instrumented roll technology allowing the direct measurement of normal stress at the roll surface. Furthermore, the characterization of the ribbons, granules and tablets was also performed.

Normal stress values recorded by the side sensor (P3) were lower than normal stress values recorded by the middle sensor (P2) and showed greater variability than the middle sensor which is in accordance with the near-infrared chemical imaging results reported in Paper III. Normal stress (P2) was used for data analysis and it was found to vary directly with hydraulic pressure and inversely with the ratio of screw speed to roll speed. The interaction term between hydraulic pressure and screw to roll speed ratio had also significant effect on normal stress (P2). It seems that the decrease in normal stress (P2) when increasing screw speed to roll speed ratio (or roll gap) is more prominent at high hydraulic pressure. The effect of roll speed on normal stress was absent for the formulation evaluated in this study which exhibited a good flowability (ffc=8.4) and using roll compactors with force feeding screw mechanism.

Ribbon porosity was primarily found to be a function of normal stress, exhibiting a quadratic relationship. A similar quadratic relationship was also observed between roll force and ribbon porosity for the vertically fed roll compactor.
Johanson’s model predicted a high value of peak pressure ($P_{\text{max}}$) compared to the measured normal stress ($P_2$). This discrepancy can be explained by the inadequate assumptions of Johanson’s model. For example, Johanson assumes that the powder mass entered into the nip region (upstream) will be 100% delivered downstream between the rolls (existence of mass continuity theory). Also, the nip angle calculation using Johanson’s model assumes a smooth roll surface of the same roughness as the shear cell measurement; however, it is not clear how knurled roll affects the calculation. In the current study, both roll compactors were equipped with one smooth and one cross knurled roll. The results suggested that the knurled roll surface is gripping the powder almost equivalent to having a more adhesive powder on a smooth roll surface. Overall, this suggests that different areas need to be improved in Johanson’s model such as nip angle prediction, compressibility constant and evaluating the impact of some of the assumptions in deriving the equations.

The estimated peak pressure ($P_{\text{max}}$) correlated with the ribbon relative density/porosity and the majority of downstream properties of granules and tablets such as granule particle size, granule bulk density and tablet tensile strength. $P_{\text{max}}$ takes into consideration various process and geometric parameters, such that the underlying pressure/density relationship of the formulation is revealed and shown to be consistent across different roll compactors. This demonstrates that $P_{\text{max}}$ can be used as scale–independent parameter.

Reynolds et al. $^{24}$ approach was utilized to transfer between both roll compactors. It was found that this approach provides very good predictions of ribbon porosity. For instance, this approach is very useful for predicting ribbon porosities of pre-blends for which the assumption of constant nip angle is valid and on a roll compactor for which model constants screw constant ($c_s$) and pre-consolidation relative density ($\gamma_0$) are determined using a calibration set.
An OPLS model was developed using the horizontal and vertical fed roll compactor datasets to express ribbon porosity as a function of geometric and process parameters. The model validation, performed with a new dataset, resulted in overall good predictions.

This study successfully demonstrated the scale up/transfer between two different roll compactors and revealed that the combined use of design of experiments, latent variable models and in silico predictions results in better understanding of the critical process parameters in roll compaction.
Conclusions and future perspectives

Regulatory and economic demands have created an increased interest in continuous processes such as roll compaction for solid dosage form manufacturing. Roll compaction is a complex process in which the dominating factors over the obtained products depend upon the feed powder properties, processing conditions, and system layout. Although roll compaction has become an established technique for dry granulation, some of the variability in the process remains unexplained. Predictive modeling is of special interest since it can enhance process understanding, contribute to the development of robust processes, and reduce costs. Within the new quality by design paradigm, modeling tools are needed to understand the impact of raw materials, process parameters, and system design variation on the quality of intermediate and final roll compaction products. The work described in this thesis represents a contribution towards this challenge.

In Paper I the development of a methodology to understand the influence of different brittle filler qualities of mannitol and DCP and their properties on product quality was described. This approach also allowed the prediction of critical quality attributes of the drug product based only on the material properties of that filler. The key advantage of this strategy is to expand the experimental design from vendor identities (qualitative factors) into an in silico OPLS model based on raw material properties. This would allow the possibility of introducing fillers from new vendors in the future without additional experiments, provided that they are covered within the range of the initial vendors. This modeling approach can generate fundamental understanding of the influence of raw material on any pharmaceutical unit operation.

With regard to the phenomenon of loss in compactability by roll compaction, the results revealed that some qualities of mannitol and DCP actually showed improved compactability following roll
compaction. The observed effect seems to be a function of many factors, such as deformation characteristics; amount of crystalline and spray dried brittle fillers; particle size enlargement; and applied roll compaction force. Additionally, specific surface area and surface energy might be taken into account as important factors on compaction performance of mannitol and DCP qualities.

In **Paper II** the application of DOE techniques combined with multivariate modeling were demonstrated to identify the design space for a roll compaction process using a predictive risk-based approach. The influence of different process variables on intermediate and final product properties was evaluated. DOE was beneficial to provide highly predictive models useful for the establishment of the design space, and to make it possible to identify interactions between the process variables. Multivariate analysis using OPLS enhanced understanding of the relations between intermediate and final product quality. Additionally, the use of O2PLS modeling facilitated visualization of the interrelationships and in comparison to PLS, it improved model interpretability by separating joint and unique variations. OPLS and O2PLS were found to be adequate for this analysis as they are predictive, interpretable and cope with multicollinearity in the measured data.

In **Paper III** the significant added value that the combination of NIR-CI and multivariate methods can provide was demonstrated in the quality assessment of the intermediate and final roll compaction products. The results established the use of NIR-CI as a complementary nondestructive tool to determine ribbon density and to map the density distribution across the width and along the length of the ribbons in a complex chemical matrix. Finally, this study also demonstrated the use of texture analysis as a method to numerically investigate the spatial variation in an image, in order to advance process understanding.
In **Paper IV** the performance of roll compaction process equipment was investigated when operated at different scales, and using horizontal and vertical force feed mechanisms. This study also presented the successful scale up/transfer between two different roll compactors and revealed that the combined use of soft (semi-empirical) and hard (mechanistic) modeling results in better understanding of the roll compaction process.

Within the roll compaction modeling community, an ongoing challenge in the development of mathematical models for roll compaction is the inherent trade-off between the level of detail included in a model and computational efficiency. Detailed models such as finite element models have been shown to describe roll compaction with a high degree of accuracy; however the utility of these models is limited by computational cost, at least when modeling is done down to the particle level. Therefore, the application of semi-empirical models, such as latent variable models, is necessary to supplement detailed process models for applications where computational efficiency is important. Additionally, semi-empirical models are particularly suited for the analysis of large volumes of data.

Finally, I believe that for a better understanding of the roll compaction process and for the development of robust in silico models, the future lies in combining 1) systematic experimental studies, such as the ones conducted in this thesis, where DOE can be a powerful tool for the improvement of the quality of the collected data 2) multi-scale modeling, using methods such as finite elements to predict bulk properties from particle properties, and 3) semi-empirical modeling to identify critical roll compaction and milling parameters and to use it where computational efficiency is important. This will require close collaboration between formulation and material scientists, data analysts and process engineers.
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