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ASTRAZENECA

MASTER'S THESIS

In-line monitoring of powder blend homogeneity in continuous drug manufacture using near infrared spectroscopy

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CHALMERS UNIVERSITY OF TECHNOLOGY

Abstract

Department of Chemistry and Chemical Engineering

Master of Science

In-line monitoring of powder blend homogeneity in continuous drug manufacture using near infrared spectroscopy

by Lisa RADOVANOVIC JANSSON

The pharmaceutical industry faces technical challenges in the near future when transitioning from the traditional batch wise manufacturing to continuous manufacturing. One issue that needs to be solved is how to obtain high-quality measurements of a moving solid powder sample. The aim of this work was to study this issue. The first part was to develop an in-line near-infrared spectroscopy (NIR) probe holder to improve the sample presentation directly after the first of the two consecutive blenders in continuous direct compression (CDC). The probe-holder collects the sample and momentarily holds it still during analysis. The second part of the work was to evaluate the in-house developed and commercial probe holder operating by the same principle. In-line measurements were conducted by simulating the discharge from the blend using a feeder. Both off-line and in-line orthogonal partial least-square (OPLS) prediction models were constructed using multivariate statistics. The models were pretreated using first derivative and standard normal variate (SNV) filters. The possibility of in-line monitoring the active pharmaceutical ingredient (API) using an off-line calibration through local centring was also investigated. The off-line prediction model overpredicted the concentration with approximately 2 %. Local centring was used as a solution to the overprediction. However, the NIR spectra obtained from the samples used for local centring indicated that segregation had occurred. Due to limited time, the powder blends could not be re-mixed and used to further investigate the possibility to use an off-line calibration to predict in-line measurements. The in-line calibrations could successfully predict the API concentration in powder blends measured in-line. The in-house made and commercial probe holders showed similar results and were both fit for purpose. Further investigation regarding for example cost and validation requirements should be made before deciding whether to continue with the solution of the in-house made probe holder or the commercial one.

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List of Abbreviations

API	**A**ctive **P**harmaceutical **I**ngredient
CMC	**C**arboxy**M**ethyl**C**ellulose
CDC	**C**ontinuous **D**irect **C**ompression
DoE	**D**esign **o**f **E**xperiments
FDA	**F**ood and **D**rug **A**dministration
ICH	**I**nternational **C**onference on **H**armonisation
MCC	**M**icro**c**rystalline **C**ellulose
MVA	**M**ulti**V**ariate **D**ata **A**nalysis
NIR	**N**ear-**I**nf**ra**red **S**pectroscopy
OPLS	**O**rthogonal **P**artial **L**east **S**quares
PAT	**P**rocess **A**nalytical **T**echnology
PAC	**P**rocess **A**nalytical **C**hemistry
SF	**S**tearyl **F**umarate
SNV	**S**tandard **N**ormal **V**ariate
QbD	**Q**uality **b**y **D**esign

Chapter 1

Introduction

1.1 Introduction

Traditionally, pharmaceuticals are manufactured in batch mode. However, in recent years, continuous manufacturing has emerged as a new opportunity, promising increased robustness and flexibility, lower footprint, reduced costs, and facilitated scale-up. In a traditional pharmaceutical batch process, its settings are validated and fixed, the quality is tested at the end of the process, compared with specifications, resulting in a pass or fail result. Hence, varying input materials and environmental conditions may lead to varying output quality. In a continuous process, material is constantly charged, processed and discharged. The ability to acquire information from the process during manufacturing enables tuning of the process in real time and obtaining the desired quality requirement through adaptation to varying input quality. Integral to this is having a deep understanding of materials and the manufacturing process, which can be achieved by mechanistic modelling and rapid analysis in or close to the process, i.e. with process analytical technology (PAT). In addition to trending and control, PAT also offers the opportunity for real-time release, and is often enabled with optical spectroscopic techniques, such as near-infrared spectroscopy (NIR).

1.1.1 Aim of the Project

This master thesis aimed at developing in-line measurements for the continuous manufacturing of pharmaceutical solid dosage formulations, with an emphasis on the continuous direct compression (CDC) process. The in-line measurements were be performed by evaluating probe holders that present the powder blend to the probe for real-time monitoring of the powder blend homogeneity after mixing. Analytical techniques such as near-infrared spectroscopy (NIR) were investigated, as well as investigation of the possibility to use an off-line calibration for predicting in-line measurements. However, the focus of the project was on sample presentation and data evaluation using multivariate statistics.

Chapter 2

Background

2.1 From Batch to Continuous Manufacturing of Pharmaceuticals

Pharmaceutics have traditionally been manufactured through a series of batch-wise unit operations. The industry has controlled the manufacturing based on a regulatory framework that protects the quality of the drug by assessing the manufacturing operations, characterising the raw material and the end-product, and testing the process conditions and intermediate products. This quality by testing has limitations which have been broadly recognised for both small molecules and biopharmaceutics [1, 2].

Similar processing fields, like chemical manufacturing, have implemented continuous manufacturing decades back. However, the pharmaceutical industries have been hesitant to implement new technologies due to not knowing how these new innovations would be perceived by the regulators. Many companies did not prioritise to solve these technical problems and as a result high degree of waste related to batch-wise processing has been observed. Reported waste levels could reach up to 50 % of the manufactured product [2]. It also seemed to be hard to predict the effect of scale-up on the quality of the end-product, along with an inability to understand the underlying causes of manufacturing failures. All these, together with the FDA scrutiny of the manufacturing process and difficulties implementing changes to it gave high manufacturing related costs [2]. Also, the pharmaceutical industry has had high margins of profit compared to other industries, which gave small incentive as long as new products were launched.

2.1.1 Continuous Manufacturing Opportunities

Continuous manufacturing shows many advantages compared to traditional batch manufacturing in terms of efficiency, control of product quality and flexibility. Using batch manufacturing, the industry is inflexible in the aspect of scale-up and possesses limited ability to rapidly increase the production during pandemics or other emergencies. To bring up a new batch manufacturing facility could take months to years, whilst continuous manufacturing scale-up is achieved by longer processing times or increased flow rate and can be built into the process design and validation.

Supply chains for many APIs can span over several countries due to financial reasons, which makes it vulnerable. In contrast to continuous manufacturing, intermediates in batch manufacturing need to be stored between unit operations and

TABLE 2.1: Attributes and corresponding possible advantages of continuous manufacturing

Attribute	Advantage
Small equipment and space required	Efficient. High throughput.
Short supply chain	No storage or shipping for intermediates. Reduced costs. Fast response to market demand. Less degradation for sensitive intermediates
No batch handling	Increased operator safety
Production flow continuous	Easy scale-up through longer running time or increased mass flow
High product and manufacturing understanding	Product quality inherent. Reduced batch-to-batch variations

shipped to the next manufacturing facility. Shorter supply chains can directly improve both the manufacturing footprint and the product quality when APIs or intermediates are unstable or sensitive to environmental conditions.

Unit operations in continuous manufacturing often show higher efficiency compared to the batch manufacturing equivalent, making the required size of the production equipment smaller [3]. Since intermediates do not move between unit operations and hence neither require suites nor dedicated modules for holding, the footprint can be reduced further. Nonetheless, new production facilities and generation of process knowledge need an initial investment, and transitioning the current batch manufacturing facilities into continuous manufacturing could be a financial obstacle [4]. Thus, candidates to implement continuous manufacturing are likely new therapeutics or already approved therapeutics with a large market that require expansion of the manufacturing [5]. Some continuous manufacturing attributes and possible advantages are summarised in Table 2.1 [5].

A growing interest has emerged during the last years in increasing drug quality and safety, and at the same time implement more structured methods in pharmaceutical development and manufacturing and increasing the manufacturing cost efficiency. Examples of these approaches are the QbD approach by ICH and the PAT guidance by FDA [6]. Both tools seem necessary to implement as the pharmaceutical industry moves to continuous processing.

2.1.2 Pharmaceutical Quality by Design

Implementing QbD could facilitate the pharmaceutical industry and drug authorities transition into a more scientific, holistic and proactive approach to development. The approach facilitates and promotes the understanding of the product and its manufacturing through the whole chain from product development, basically making quality inherent. This is a contrast to the traditional approach, which is highly empirical and assures product quality by testing. With QbD, a product is designed in a way that it meets the desired clinical functioning, and that the manufacturing consistently meets the desired quality attributes of the product [6]. Figure 2.1 illustrates the different steps a pharmaceutical process goes through during the life cycle, i.e. define, design, characterise, validate, monitor and control. The dashed
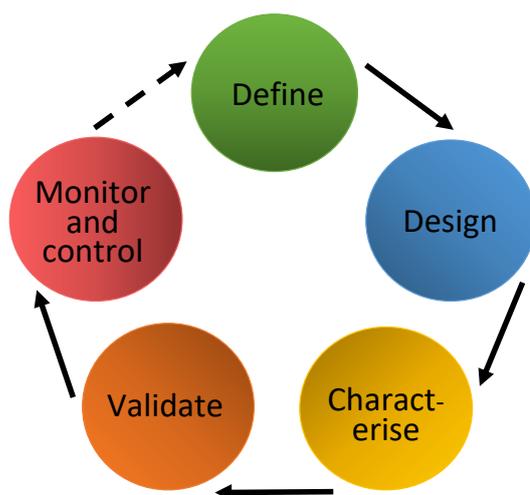
FIGURE 2.1: An illustration of the phases in development of pharma-
ceutics. The dashed arrow represents possible process changes.

arrow represents the possible process changes due to process optimisation or improvements in robustness or performance. Above mentioned makes it necessary to understand how raw material and process parameters could impact the final product quality and requires the process to be continually monitored and updated, i.e. using PAT.

2.1.3 Process Analytical Technology

PAT is an adaption of process analytical chemistry (PAC) that existed outside of the pharmaceutical industry before the FDA PAT initiative [7]. As the pharmaceutical industry moves into a new phase of advanced technology and the use of continuous manufacturing, PAT was created to facilitate the implementation of more sophisticated manufacturing techniques with an emphasis on process monitoring and control. Figure 2.2 illustrates how PAT can support this transition by [8]:

- Encourage the pharmaceutical industry to implement new modern technology

- Aid the pharmaceutical industry to adopt quality system approaches and modern quality management to all aspects of manufacturing and quality assurance

- Encourage the pharmaceutical industry and agencies to adopt risk-based approaches to critical areas

- Improve the consistency and coordination of the FDA drug quality programmes, partly by adopting improved quality system approaches regarding review and inspection activities into the agency business processes

- Make sure that state-of-the-art pharmaceutical science form the basis of regulatory review and inspection policies

The technical use of PAT is to analyse and control quality attributes of raw materials and in-process materials during processing, to ensure final product quality [8]. As
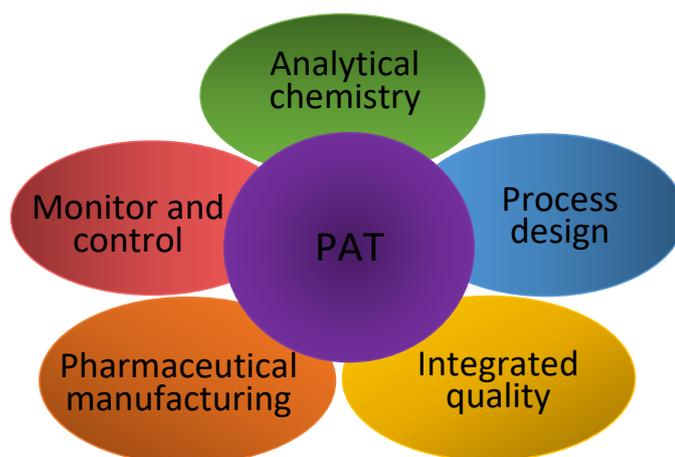
FIGURE 2.2: An illustration of how PAT can support the transition to
more sophisticated pharmaceutical manufacturing technology.

opposed to batch-wise manufacturing, continuous manufacturing lacks isolated intermediates and hence require real-time monitoring of process parameters and quality attributes.

However, the sampling interface for continuous manufacturing systems, i.e. where the sample is presented to the PAT instrument/probe, can be a technical challenge. Experience from the industry indicates that poor measurements often can be ascribed to sampling system issues rather than the analytical instrument itself [9]. Sampling errors could be reduced by in-line monitoring, but do not necessarily solve all sampling issues [10]. Therefore, sampling considerations should be evaluated, e.g. location of the probe for representable sampling, disturbance on the process of the probe should be minimised, sample size, penetration depth and the number of scans of the spectroscopic method. Also sampling frequency should be considered, using high enough resolution for detection of a pulse variability as a result of process disturbance.

PAT can also serve as a tool for process understanding, by using multivariate models to extract process knowledge, like blend homogeneity, from the data provided by the analytical instruments. Furthermore, type of sensor should be carefully selected for successful process monitoring. Spectroscopic methods like NIR are widely used [11, 12]. NIR allows rapid and non-destructive measurements with little or no sample preparations and provides both chemical and physical information. The probes can be integrated to the manufacturing system and are coupled to the spectrometer by fibre optics, making it possible to monitor in-process.

Near-Infrared Spectroscopy

NIR is a molecular vibrational spectroscopic technique studying vibrational transitions in molecules and studies the absorption of electromagnetic radiation in the near-infrared region (700-2500 nm). The principles and theory of NIR has been described in several books and papers [12–18].
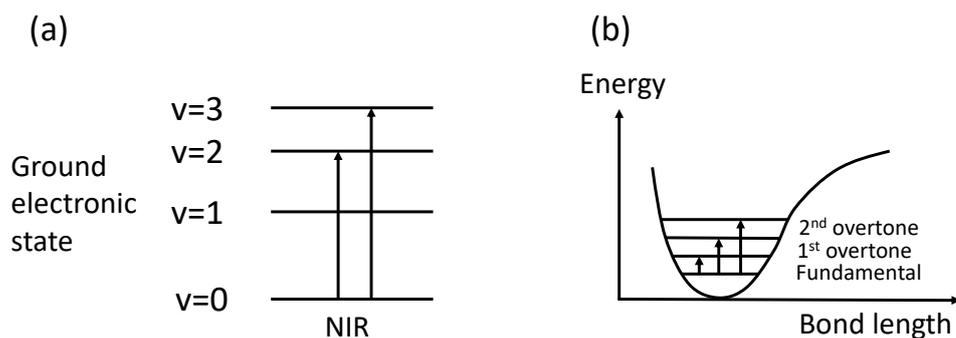
FIGURE 2.3: (a) NIR absorption and (b) The anharmonic vibration model.
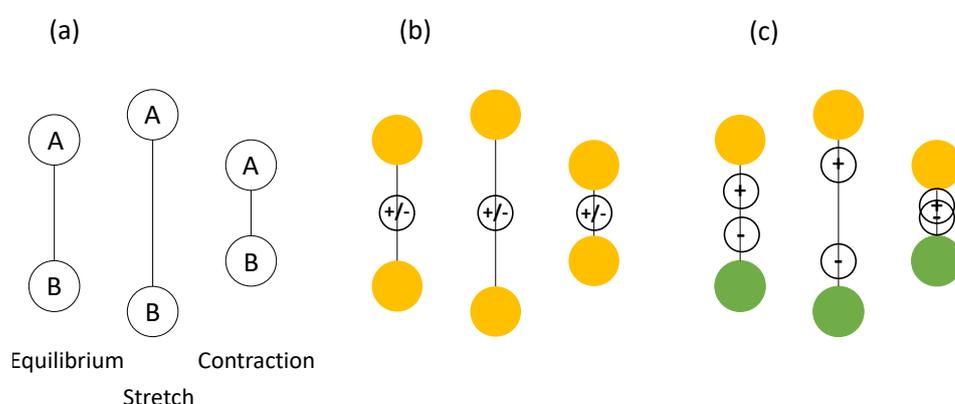
FIGURE 2.4: (a) The vibration states of diatomic molecules, (b) An X_2 molecule experience no change in dipole moment during stretch vibration and (c) An XY experience change of dipole moment during stretch vibration.

When analysing using NIR, the sample is irradiated with near-infrared light. Common lights sources include incandescent or quartz halogen light bulbs and light-emitting diodes. Light at some wavelengths of the near-infrared region will be absorbed by the material, bringing the molecules to a higher vibrational state. This is illustrated in Figure 2.3 a. Vibrations which result in changes in molecular dipole moment, i.e. the product of distance and charge, are the only near-infrared light that can be absorbed. As can be seen in Figure 2.4 b, no change in dipole moment occurs for an X_2 molecule during stretch vibration, e.g. H_2. However, an XY molecule show a change in dipole moment during stretch vibration, as can be seen in Figure 2.4 c [12]. The vibration states of a diatomic molecule can be seen in Figure 2.4 a. Diatomic molecules require a permanent dipole to be infrared active, while multiatomic molecules only need an induced dipole by the vibration. R-H groups are strong near-infrared absorbers, since the dipole moment is high. O-H, N-H, C-H and S-H bonds show strong absorption as well.

Molecules that absorb near-infrared light vibrate in two modes, stretching and bending. Stretching is when the interatomic distance along the bond axis continuously change. Bending is when the bond angle changes. Figure 2.4 a illustrates vibrational states of a diatomic molecule, and the potential energy of these vibrations varies with the bond length. The potential energy is low at equilibrium. Repulsion is induced as the atoms come closer together, which will increase the potential energy. The atoms experience attraction as they start to pull apart, resulting in increased potential energy as well. By keep adding distance between the atoms will eventually make them dissociate. However, quantum theory describes that only specific vibrational energy levels, corresponding to specific wavelengths, are allowed [12]. See the horizontal lines in Figure 2.3 b. The energy levels do not have the same distance in an anharmonic vibration model. An NIR spectrum has both overtones and combinations. It is possible to operate in diffuce reflectance mode using NIR due to the low molar absorptivity of the absorption band, making it possible to analyse samples with little or no sample preparation. The reflected light, i.e. the light not absorbed by the sample, is measured in reflection mode [19].

Due to the amount of overtones and possible combinations, NIR spectra are often highly overlapping with poorly defined bands containing chemical information of all sample components. Overtones and combination bands are less defined than the primary absorption band, and additionally overlap, thus the NIR spectrum become difficult to interpret. NIR is also sensitive to physical properties, like density and particle size, which imposes baseline shifts. The acquired analytical information is inherently multivariate. To interpret the spectra, mathematical and statistical methods (MVA and chemometrics) are required to extract relevant information and to reduce the irrelevant information. It is also possible to reduce the effect of interfering variance in which one is not interested by pretreating the data [20].

NIR is suitable as a PAT tool since it performs measurements rapidly (seconds) and non-destructively. However, it generates a massive amount of data used both offline or in-line. Multivariate statistics (MVA) can be used for data handling and interpretation to extract useful information leading to process and material understanding.

Multivariate data analysis and chemometrics

MVA and chemometrics are terms used for describing statistical methods associated to establishing relationship between the complex analytical signal (e.g. NIR spectra) and quality attributes. It is used in several sectors, the pharmaceutical industry beeing one of them for e.g. classifying materials (qualitative work) and e.g. water content measurements (quantitative work). However, an NIR analyser must be trained, i.e. calibrated, before it can perform quantitative analysis. In short, the calibration process includes the following steps [18]:

1. Select representative samples in a calibration set.

2. Acquire spectra and determine reference values.

3. Mulivariate modelling to relate the spectral variations to the reference values of the analytical target property.

4. Validation of the model.

Light scattering, path length variations and random noise from variable physical sample properties or instrumental effect could be possible interfering spectral parameters that can be corrected through pretreatment of the data. Pretreatment prior to MVA reduces the impact on the spectra and makes standardisation possible. The robustness of a calibration model can be improved by carefully choosing pretreatment.

When performing quantitative analysis, sample properties that have to be related to spectral variations have discrete values. These values represent a sample identity or a sample quality. Multivariate classification methods are used to solve issues related to selectivity and interference of NIR spectra for grouping samples with similar characteristics. One fundamental purpose of these classification methods is to establish mathematical criteria for parameterisation of spectral similarity. This allows to identify similarities between samples or a sample and a class to be expressed quantitatively.

Design of Experiments

DoE, or statistical experimental design, is a common tool to utilise for increased process understanding and can be used for optimisation and robustness testing of operation variables in a manufacturing process. It can also be used for, among others [21]:

- Construct a representative set of calibration samples

- Develop new products or processes

- Improve current products or processes

- Screen important factors

- Minimising costs or pollution related to manufacturing

It is a way of reducing the number of experiments in a systematic way. The number of variables (factors) and levels of the factor, dictate the number of experiments performed. E.g., the investigation of two variables to vary at two levels would generate four experiments. An equation that describes the general number of experiments when applying a full factorial design at two levels is 2^k, where k is the number of variables. Going back to the simple example, four experiments are seldom sufficient during an investigation and the number of variables can easily be four, five or more, giving for example $2^5 = 32$ experiments. It is possible to investigate both main and interaction effects using full factorial design, but at the cost of time and material since the experimental load increases exponentially [22]. However, utilising fractional factorial design (DoE) the number of activities can be systematically reduced to 2^{k-p} experiments, where 1/p is the size of the fraction.

By using DoE, one can construct a reduced set of experiments where all relevant factors are varied simultaneously. A DoE set usually does not exceed 10-20 experiments but can be altered to meet certain requirements. The experiments are distributed in a rectangular design space, making it possible to identify direction which will generate better results. Analysis of the data will identify which factors influence the results and may be used for optimisation. To put it simply, DoE offers a reliable
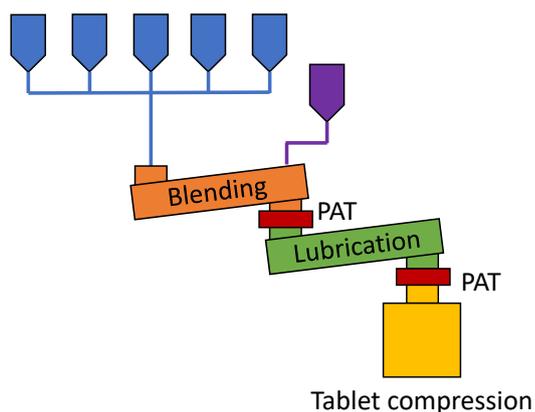
FIGURE 2.5: A flowsheet of continuous dry powder mixing and continuous direct compression.

foundation for decision-making, offering a structure for changing all the critical factors in a systematic manner, but requiring a reduced number of experimental actions [21].

2.1.4 Continuous Direct Compression

The most common dosage form for marketed drug products is tablets, and the most straightforward example of continuous tablet manufacturing is the integration of continuous dry powder mixing and tablet compression [23]. It combines material handling, feeders, two consecutive blenders and tablet compression. The process is illustrated in Figure 2.5. The individual ingredients are transferred to dedicated top up systems. Feeders can be integrated on the system, positioned before the inlet of the two continuous dry powder mixers. The first mixer is used for intensive mixing, while materials which are shear-sensitive, e.g. lubricants, are introduced in the second mixer. The powder is discharged and guided to the feed frame of the tablet press. PAT instruments can be placed between the two mixers and prior to the feed frame for monitoring the powder blend uniformity. In continuous manufacturing, the powder feeders play a critical role for the overall performance of the manufacturing line and hence the product quality. If the inflow composition shows high variability, so can the tablet quality, even if the mixer and tablet press perform properly [24–26].

2.2 Formulation of Oral Solid Dosage Forms

In addition to the API, medicines also contain excipients to enhance stability, processability and performance of an oral solid dosage form. An excipient can serve more than one function in a dosage form. The main functions are fillers that bulk up at dosage form when the API content is too small for pressing a tablet; disintegrants that make the tablet break apart after administration; lubricants that are added to reduce friction between metal parts of the manufacturing system and the powder blend; and finally glidants that are added to improve flowability of the powder blend. This section will describe physical properties of excipients and properties that can influence the performance. The emphasis is on tablets produced by direct compression.

2.2.1 Fillers

Fillers are added to an oral solid dosage form when the API content is so small that it would not be possible to compress it into a tablet. Fillers can also help to bind the tablet when manufactured through direct compression due to the increased strength as a result of enhanced binding properties, as well as bulking up the tablet. Fillers also play an important role in regards to manufacturability and processability by influencing both flow, compactibility and compressibility. In regards to performance of the dosage form, fillers play an important role by impacting friability, overall homogeneity, dissolution and stability [27]. One or many fillers can be used in a formulation to parry complications that can emerge when using only one filler, such as sharp granulation endpoint or high expenses. One can categorise fillers as cellulosic materials and sugars, e.g. MCC and mannitol respectively, that will be described below, and inorganic salts that not will be included in this thesis.

Filler Performance

Important to consider is the influence an API will experience of the fillers used in the formulation. It is therefore important to know about the physicochemical compatibility between the drug substance and the fillers. There are many properties of the filler that need to be considered. Based on the United States Pharmacopeia National Formulary, these properties include particle size, particle size distribution, particle shape, moist content, polymorphic form, crystallinity, density, specific surface area, flow characteristics, solubility, degree of polymerisation and compaction characteristics. These characteristics affect both the manufacturability and the performance and quality of a dosage form. Some are also co-dependent, for example the crystallinity that can influence the compactibility, disintegration and dissolution of a dosage form [28–30]. The compactibility is affected by the material being more plastic in the amorphous state, whilst being more brittle in the crystalline state. Another example is increased dissolution rate of dosage forms containing less degree of crystallinity versus standard degree of crystallinity of MCC.

Particle shape has also proven to be a critical factor in the aspect of performance of a dosage form. Granulated powdered mannitol with less transparency and more irregular morphology showed higher tensile strength after exposure to the same compaction pressure compared to crystal powders with smoother surface [31]. Tablets with MCC have showed higher tensile strength with increased width-to-length ratio [32]. In this case, changed dimensions may also influence both the specific surface area and bulk density, where decreased bulk density further improves compactibility [33, 34]. Lastly, since the filler content in a dosage form vary over a wide range, the concentration of filler, and properties and interactions of the other excipients will ultimately determine how the quality will be affected.

Microcrystalline cellulose

Microcrystalline cellulose is a commonly used filler that derives from α-cellulose that has been purified and partly depolymerised. The chemical structure is depicted to the left in Figure 2.6. MCC is often applied in the range of 20 to 90 w/w-%. It shows good compactibility even at relatively low pressures, and undergoes plastic deformation when compressed [27]. However, selecting a grade with larger particle size generates tablets with decreased compactibility. In return larger particle sizes enhances the flow properties of a blend. MCC is often used in combination with
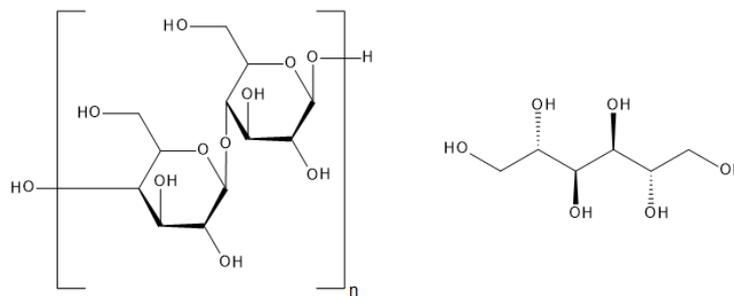
FIGURE 2.6: The chemical structure of microcrystalline cellulose (left)
and mannitol (right).

other fillers in direct compression processes. The reason binary fillers are used is because MCC is sensitive to scale-up (dwell time), and mixing it with a brittle filler decreases that sensitivity. Another characteristic of MCC that needs to be considered is its affinity for water [35]. MCC is hygroscopic, making it essential to control the water content when used in the formulation of a dosage form containing a drug substance sensitive to moist. In addition, having either low or high moisture content can have a negative effect on the compaction properties.

Mannitol

Mannitol is another common filler used in both the pharmaceutical and food sector, and the chemical structur can be seen to the right in Figure 2.6. It is not hygroscopic, hence being suitable for moisture-sensitive drug substances. When using mannitol as a filler, also the compression characteristics need to be considered and a suitable polymorphic form chosen depending on requirements [31]. Spray-dried grades are commonly used for direct compression processes because of the poor flow and/or binding characteristics of the other grades.

2.2.2 Disintegrants

Disintegrants are excipients that are added to a formulation for the finished tablet to disintegrate, i.e. break apart, after swallowing. The breakup works by the disintegrant rapidly taking up water upon entering the aqueous environment in the stomach. The disintegration can include one or more mechanisms: swelling, wicking or structure recovery [27]. When smaller fragments form from disintegrating, the API dissolution rate increases by the increased interface between the fragments and the aqueous environment. The disintegrant is normally added prior to lubrication in direct compression manufacturing of tablets to promote the break apart.

Disintegrant Performance

The performance of the disintegrant is dependent on several factors, one being compression force. Both increased and decreased disintegration times have been reported in previous studies, depending on disintegrant [36]. This indicates that the disintegrant performance varies depending on the mechanism of disintegrant action and the deformation behaviour. This is due to the influence of compression force on tablet porosity, where increased compression leads to decreased porosity. Tablets with very low porosity can have decreased ability of water uptake, especially for
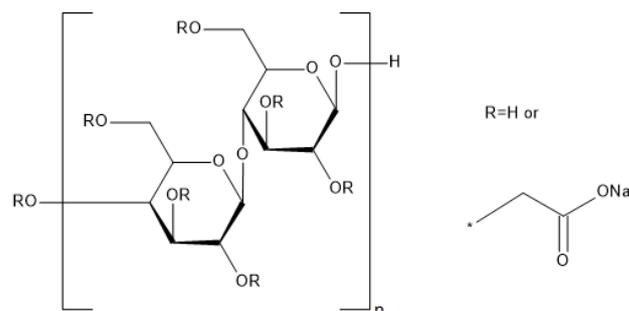
FIGURE 2.7: The chemical structure sodium carboxymethyl cellulose.

disintegrants with wicking as main mechanism. In contrast, too high porosity can lead to poor disintegration due to insufficient disintegrating force that is needed for disintegrant action [27].

Another factor that can influence the performance is the solubility of other excipients. Disintegrants show higher efficiency when used in formulations with insoluble excipients [27]. pH can also influence the efficiency of the disintegrant, for example decreased swelling capacity in acidic environments as a result of lower liquid holding capacity [37]. Lubricants can also negatively decrease the efficiency by coating particles and hence interfere with the wetting of tablets. Disintegrants with higher swellability are affected in less extent compared with disintegrant that show lower swellability [27].

Also moisture can influence the efficiency of a disintegrant [38, 39]. The natural tendency of disintegrants to take up water can lead to swelling of tablets, which may make them soft and friable. Additionally, the dissolution efficiency decreases upon ageing as moisture uptake results in reduced ability to absorb water and swell. Generally, disintegtants that more readily absorb water also show a higher tendency to disintegrate with less efficiency. When tablets contain water soluble excipients, this effect is even higher.

Sodium Carboxymethylcellulose

NaCMC is a polymer derived from cellulose where hydroxyl groups have been substituted with carboxymethyl groups. The chemical structure is depicted in Figure 2.7. Being hydrophilic, the polymer rapidly swells as a consequence of taking up water upon entering an aqueous environment. The swelling ability is negatively influenced in acidic environments due to carboxymethyl sodium converting to the free form, which is less hydrophilic [27]. The disintegration can be impacted by the particle size of CMC, where the tendency to swell increases with particle size. Additionally, higher weight CMC shows somewhat higher capacity of taking up water compared to CMC with lower molecular weight. Finally, the physical properties of the CMC vary depending on what source of cellulose it derives from - wood pulp or cotton linters. CMC from wood pulp tend to have lower molecular weight, increased water solubility, somewhat lower pH, lower water capacity and swelling rate compared to CMC derived from cotton linters [27]. CMC is used as a disintegrant at a concentration of 0.5-5 % w/w and is commonly used in direct compression manufacturing [36, 38].

2.2.3 Lubricants

Lubricants are added to a formulation to reduce friction between metal parts of the manufacturing system and the blend. There are several proposals of their mode of action [40]. One with more experimental evidence is that lubricants deposit on the metal surfaces upon contact with the powder blend during e.g. tableting. This reduces the friction between the blend and metal. Materials commonly used as lubricants include fatty acids, metallic salts of fatty acids, fatty acid esters and inorganic materials [41].

Lubricant Performance

Lubricants are also added in low levels, from under one percent to a few percents depending on which lubricant is being used [27]. The lubricant is often screened through a sieve prior to addition to break apart possible lumps. The addition to the rest of the formulation is often performed by first mixing the lubricant with a small amount of the blend, before adding and distributing to the entire blend. Except to lubricate blends, the lubricants can influence the tablet or capsule formulation in an unintentional way. Some lubricants are hydrophobic and insoluble in water, which can lead to a "water-proofing" effect and decrease the dissolution as the lubricant coats the powder blend. The extent of this effect depends on the solubility of API, where the effect increases with decreased water solubility [42]. Several process parameters during blending operation can increase the deleterious effects of lubricant, namely blending time, speed and scale [43]. Softer tablets can be a result of overmixing due to prevention of bonding of powder blend during tableting. More hydrophilic API or formulations containing high-swelling superdisintegrant tend to be less sensible to overmixing.

Sodium stearyl fumarate

Different materials can be used as lubricants within the pharmaceutical industry, fatty acid esters being one of them. NaSF is a fatty acid ester commonly used for tablet compression when other lubricants fail to provide proper tablet strength and show a negative effect on tablet dissolution [40]. The molecular structure of NaSF is shown in Figure 2.8.

2.2.4 Glidants

Glidants are added to a formulation to improve powder flowability. A uniform powder flow is essential for providing a consistent product dosage, whether it is a tablet or other oral dosage form. Free flowing powder can reduce the amount of material that stick to the walls of the transfer system, tabletting and other equipment. Silicon dioxide can be used as a glidant in a dosage form [44]. It us usually added at around
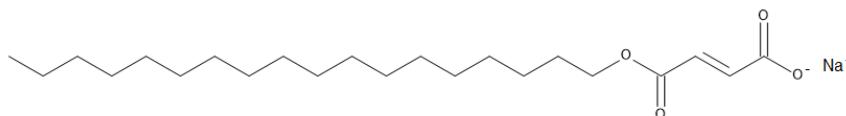
FIGURE 2.8: The chemical structure sodium stearyl fumarate.

1 % or less. It can also improve structural stability and tensile strength, and reduce the friability of a tablet.

Chapter 3

Methods

3.1 Probe holders

3.1.1 Development of the in-house made probe holder

A probe holder called the Revolver was developed. A visual prototype is depicted in Figure 3.1. The probe holder consists of a tube that will be placed between the two powder blenders in the CDC. A wheel with five compartments was mounted inside the tube, where the powder could fall, be collected and presented to the NIR probe. The probe was mounted from the outside of the tube, through the upper hole of the tube in the upper left corner in Figure 3.1. The wheel was manually rotated from the outside of the tube using a ratchet wrench. Since this was the first prototype, developed with the aim of evaluating whether the principle works, it had a simple construction with no automatisation or electronics. The Revolver was developed and manufactured by Bönhult Industriteknik AB.
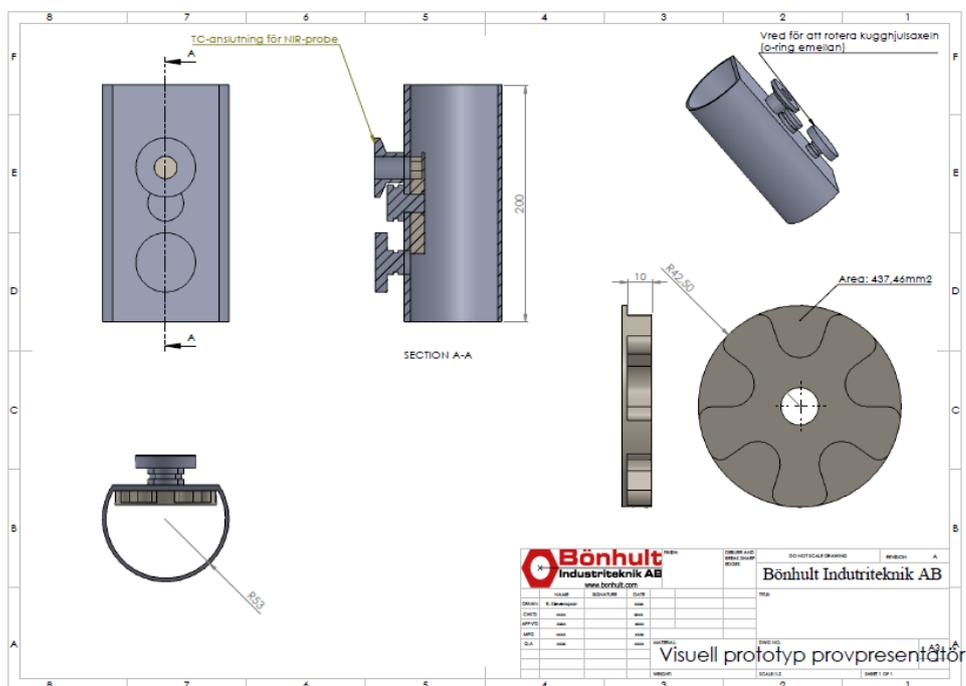
FIGURE 3.1: A visual prototype of the in-house made near-infrared spectroscopy probe holder called the Revolver, (courtesy of Anders Klevensparr).

FIGURE 3.2: The probe holder rented from ExpoPharma. The probe
is mounted from the back.

3.1.2   Probe holder from ExpoPharma

A probe holder from ExpoPharma was rented to compare it with the in-house made
Revolver. It is depicted in Figure 3.2. The probe holder works by temporarily col-
lecting the falling powder in a sampling spoon and presenting the sample to the
NIR probe in a reproducible way. The optical probe is mounted from the back of
the probe holder, which is mounted to a tube similar to the one used for the Re-
volver. The set-up can be seen in Figure 3.5. A rotary pneumatic actuator drives the
spoon $180°$ to discharge the sample, and then rotates back to the original position to
collect the next sample. The probe holder was connected to a controller unit. The
purpose of the controller unit was: 1) to control the rotary pneumatic actuator in the
probe holder; 2) to get the feedback of the spoon position, i.e. charge and discharge
positions; 3) to provide the interface for external connections.

3.2   Preparations and pre-experiments

Powder blends were produced prior to evaluating the probe holders. One set used
for the construction of the calibration model (calibration set) and one set for evalu-
ating the calibration models (the test set). Below follows a description of the DoE,
mixing methods, NIR measurements and calibration models.

3.2.1   Experimental design of the calibration set and test set

The following formulation is a typical one developed at AstraZeneca at this date.
Paracetamol was chosen as API to avoid issues related to publication of this thesis
and because it has low toxicity. The experimental design had five factors: concen-
tration of API, mannitol, MCC, NaCMC and NaSF. Apart from the mentioned in-
gredients, the powder blends also contained fixed concentration of SiO_2 at 1 %. It
was a full factorial design with randomised runs, i.e. randomised mixing order of
the powder blends. The API was varied at four levels plus centre point, while all
other factors were varied at two levels plus centre point. The parameters are listed
in Table 3.1, where the calibration set and test set consisted of N1-N13 and N14-N20,
respectively. N19 and N20 were identical, but using different batches of mannitol

to evaluate whether the calibration model could identify batch-to-batch variations. This DoE was first used by Josefsson, 2017 [45]. The DoE was done using MODDE 12 (Sartorius Stedim Biotech, Umeå, Sweden).

TABLE 3.1: The experimental design of the calibration set (N1-N13)
and the test set (N14-N20) .

Blend name	Run order	API (%)	Mannitol (%)	MCC (%)	NaCMC (%)	NaSF (%)
N1	2	12	61,5	22	2	1,5
N2	9	18	54,5	22	2	2,5
N3	1	12	54,5	28	2	2,5
N4	5	18	49,5	28	2	1,5
N5	7	12	58,5	22	4	2,5
N6	10	18	53,5	22	4	1,5
N7	6	12	53,5	28	4	1,5
N8	3	18	46,5	28	4	2,5
N9	4	15	54	25	3	2
N10	11	15	54	25	3	2
N11	8	15	54	25	3	2
N12	12	10,5	8,5	25	3	2
N13	13	19,5	49,5	25	3	2
N14	16	12	59	22	4	2
N15	20	18	55	22	2	2
N16	18	12	55	28	2	2
N17	19	18	47	28	4	2
N18	15	15	54	25	3	2
N19	17	15	54	25	3	2
N20	14	15	54	25	3	2

3.2.2 Materials used and mixing method of the powder blends

The API used in this project was standard grade paracetamol (Hebei Jiheng Group, China). The excipients used in the formulations were mannitol (Pearlitol 100 SD, Roquette, France), MCC (Avicel PH-102, FMC BioPolymer, Ireland), NaCMC (Ac-Di-Sol SD-711, FMC BioPolymer, Ireland), NaSF (PRUV, Moehs, Spain) and SiO_2 (Syloid 244FP, Grace, USA).

The following mixing method was first used by Savolainen, 2018 [46]. API, mannitol, MCC, NaCMC and SiO_2 were put in a 2 L stainless-steel container. A lid closed the container and was put in a Turbula T2C mixer (Willy A Bachofen AG Machinenfabrik, Basel, Switzerland) for 15 minutes at 32 rpm. The powder blend was milled in a Quadro Comill U5 (Quadro Engineering Inc., Ontario, Canada) operating at 1500 rpm through an 813 µm sieve to dry coat the SiO_2 onto the paracetamol and reduce potential lumps. The blend was mixed in the Turbula mixer for another five minutes after milling. NaSF was sieved through a 500 µm sieve and added to a vessel containing a small portion of the powder blend, approximately the same volume of powder blend as the NaSF. This portion of powder and NaSF was mixed using a spatula before distributing in the 2 L stainless-steel container with the rest of the powder. The powder blend was mixed one final time in the Turbula mixer for ten minutes. The total amount of material was 500 g per blend. A block diagram of the procedure can be seen in Figure 3.3.
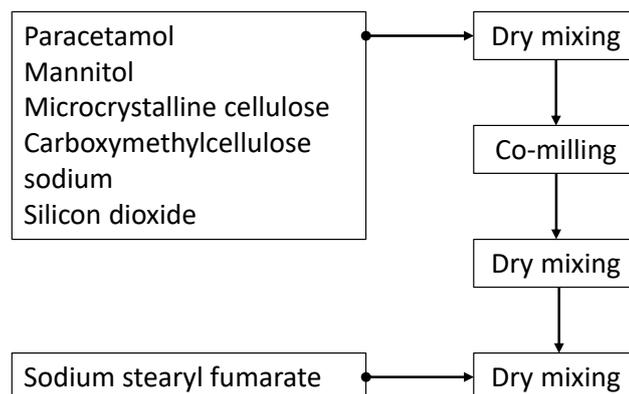
FIGURE 3.3: A flow scheme of the mixing method.

3.2.3   NIR measurements

NIR measurements were performed on a SentroPAT FO diode-array equipped with a SentroProbe DR LS (Sentronic, Dresden, Germany). Spectra were collected in the spectral region from 1100 to 2100 nm. The integration time was 8 ms and each spectrum was an average of 100 scans. As long as nothing else is stated, these were the NIR settings.

Off-line calibration models

Calibration models were constructed in SIMCA 15 (Sartorius Stedim Biotech, Umeå, Sweden), a multivariate data analysis software package. For the off-line calibration model, two samples were taken from every powder blend in the calibration set and put in glass vials. The measurements were performed by placing the vials on the probe. Every sample was measured once, turned upside-down and back again to expose a new portion of material and measured a second time. The probe is depicted in Figure 3.4. No sample preparation was done prior to the measurements. The calibration model was constructed as an OPLS [47], pretreated with first derivative [48] and SNV [49] filters.

The real concentration of the samples from the off-line calibration was determined using ultraviolet-visible spectroscopy, a modified variant of the method used by Johansson et al, 2007 [50], according to Savolainen, 2018 [46]. The results were used in all calibration models. The measurements were conducted on a Cary 60 UV-Vis spectrophotometer (Agilent Technologies, USA) using a 1 mm flow-through cuvette at 243 nm. The powder samples were weighed and dissolved in 500 mL 0.1 M HCl and placed on a mechanical shaker for one hour. The samples were left to sediment overnight. After sedimentation, the samples were then diluted to proper concentration, i.e. concentration giving absorbance withing the linear range from 0,1 AU to 1 AU and measured with the UV spectrometer. All samples were measured twice. The concentration of API was determined using standard calibration using solutions with API in 0.1 M HCl.
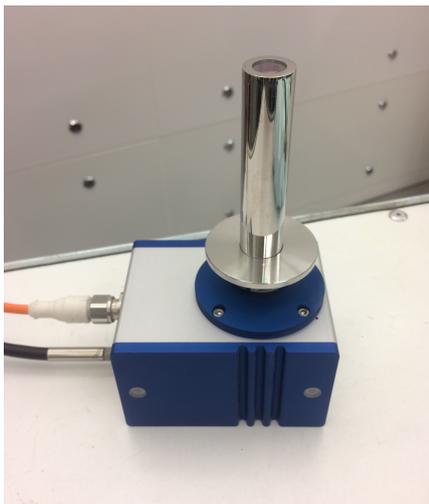
FIGURE 3.4: NIR probe used for both off-line and in-line measurements.

Local centring

The off-line calibration was transferred to predict in-line measurements using local centring, previously done by Lorber et al [51]. Transferring calibrations between different NIR instruments using local centring has been done before by e.g Leion et al, 2005 [52], and Bergman et al, 2005 [53]. The use of an off-line NIR calibration to use for in-line measurements at a tablet feed frame was conducted by Hetrick et al, 2017 [54]. For the local centring, samples were taken from the calibration set, two samples from 12, 15 and 18 % API each. Off-line NIR analysis were conducted using the Revolver for sample presentation to perform measurement directly on the powder ($\mathbf{X}_{revolver}$). The samples were collected and put in glass vials to analyse in the same manner as the off-line calibration, i.e. by putting the vial on the probe and analyse the powder through the glass vial ($\mathbf{X}_{vial}$). The vial spectra ($\mathbf{X}_{vial}$) were transferred to be similar to revolver spectra ($\mathbf{X}_{revolver}$) using local centring according to

$$\mathbf{X}^{*}_{vial} = \mathbf{X}_{vial} - \bar{\mathbf{x}}_{vial} + \bar{\mathbf{x}}_{revolver}$$

Where $\mathbf{X}^{*}_{vial}$ is the matrix with transferred vial spectra similar to revolver spectra, and $\bar{\mathbf{x}}_{vial}$ and $\bar{\mathbf{x}}_{revolver}$ are the mean spectra of $\mathbf{X}_{vial}$ and $\mathbf{X}_{revolver}$, respectively. The local centring was performed on the off-line calibration using Matlab R2017b (Math-Works, USA).

In-line calibration models

Two in-line calibration models were constructed as well, one using each probe holder. The discharge of the first blender in the CDC was simulated using a K-Tron Soder feeder (Coperion K-Tron, Germany). It was automatically calibrated prior to every experiment to keep an even flow at 10 kg/h. Every measurement series were conducted for approximately two minutes, rotating the Revolver wheel or ExpoPharma spoon every 10 s. Spectra corresponding to the five first seconds of every rotation were not included in the model, since the compartments or spoon were not completely filled with powder. The calibration models were constructed as OPLS, pretreated with first derivative and SNV filters.
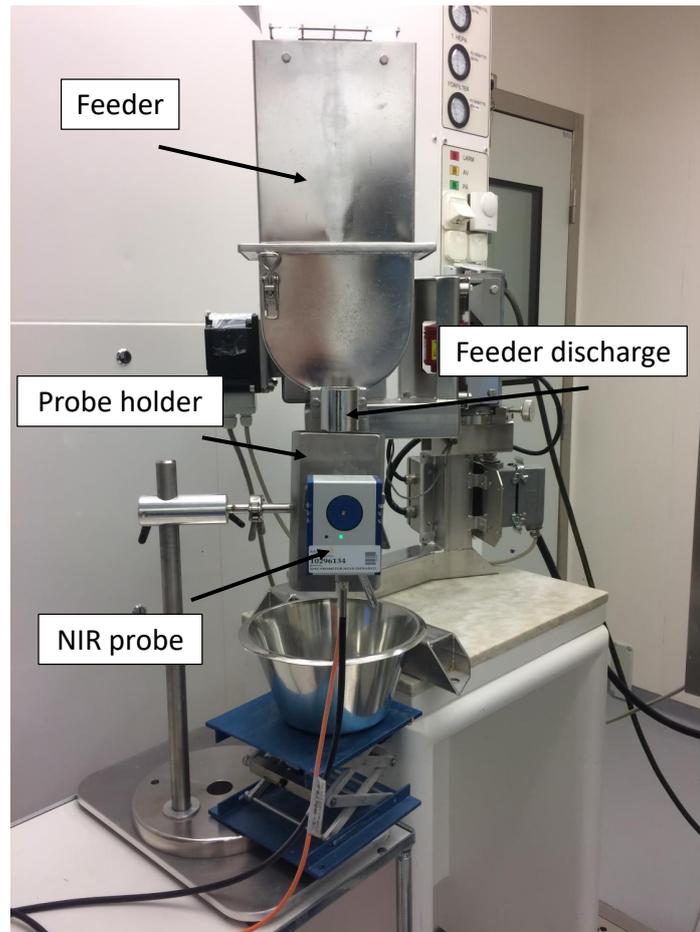
FIGURE 3.5: The experimental set-up during the in-line measurements using both the Revolver (depicted) and the probe holder from ExpoPharma. It simulated the powder discharge from the blender in the continuous direct compression set-up.

Figure 3.5 shows the experimental set-up for the simulation of the powder discharge from the first blender in the CDC set-up. The powder was charged from the top of the feeder. Two screws regulated the feeder flow. The powder was discharged right above the tube of the probe holder. The powder was collected in the Revolver compartment or ExpoPharma spoon and discharged periodically every 10 s. The powder was collected in a container underneath the probe holder.

Chapter 4

Results and Discussion

4.1 Powder blend composition

The DoE contained thirteen powder blends in the calibration set. Samples were taken from all powder blends from the calibration set and analysed with NIR for constructing the off-line and in-line calibration models. The same samples that were used for the off-line measurements were analysed for API composition using UV-Vis spectroscopy, i.e. reference analysis, twice for every sample and averaged. The two samples from every powder blend were averaged as well. Table 4.1 presents the real concentration of the powder blends. The API concentration was somewhat lower than the nominal values. This is probably a result of material loss after weighing the ingredients in separate plastic bags prior to combining in the same vessel for mixing.

TABLE 4.1: The real and nominal concentrations of the calibration set,
determined using UV-Vis spectroscopy

Blend name	Real API concentration (%)	Nominal API concentration (%)
N1	11,7	12
N2	17,3	18
N3	11,5	12
N4	17,4	18
N5	11,7	12
N6	17,5	18
N7	11,6	12
N8	17,5	18
N9	14,6	15
N10	14,5	15
N11	14,5	15
N12	10,1	10,5
N13	18,9	19,5

4.2 Calibration models

4.2.1 Off-line calibration model

Spectra for the off-line calibration models were generated by measuring samples from the calibration set using NIR. The measurements were done directly on the powder through the bottom of the glass vial in which the powder were contained.

The spectra were used for generating a calibration data set to be used for building the calibration models. Two spectra for every measurement were used. Figure 4.1 displays raw spectra and SNV pretreated spectra collected from the calibration set and pure paracetamol, used to identify corresponding peaks. The formulation and paracetamol are presented in mulicolors and red, respectively. Paracetamol has two characteristic peaks at 1640 nm and 1670 nm, and two more at 2020 nm and 2040 nm.
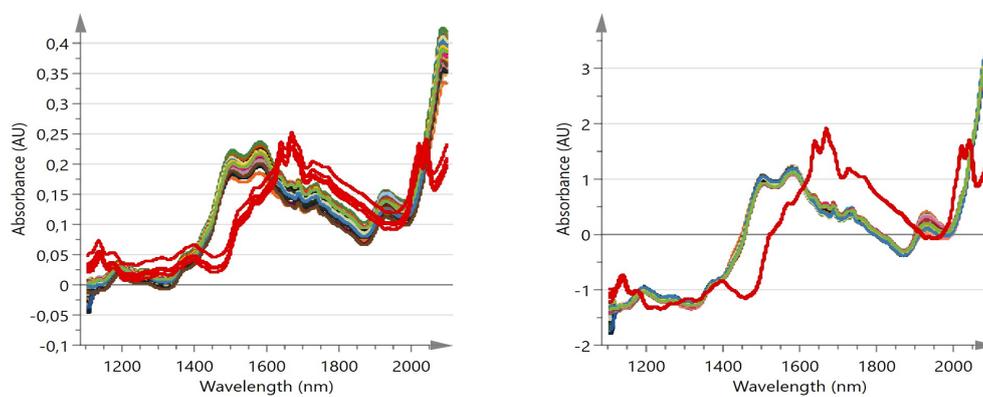

FIGURE 4.1: Raw spectra (left) and SNV pretreated spectra (right) for the calibration set and pure paracetamol measured off-line. The formulation is displayed in multicolors and paracetamol in red.

An OPLS calibration model was developed by pretreating the off-line calibration data set with first derivative followed by SNV filters. The first and last 50 nm were excluded from the models due to poor signal in the flower and upper wavelengths, i.e. the wavelength region included was 1150 nm to 2050 nm,. DmodX and Hotelling's T2 were evaluated, however, no outliers were identified. A score plot is displayed in Figure 4.2. It is coloured according to nominal API concentration (%). The scores that lie closest together are NIR spectra from the same sample. As can be seen, the results show some overlapping, which may be due to compositional variations in the individual samples.

TABLE 4.2: The averaged off-line prediction for every blend

Blend name	Predicted API concentration (%)	Diff. nominal and predicted
N14	15,9	+3,9
N15	18,7	+0,7
N16	14,6	+2,6
N17	20,1	+2,1
N18	17,0	+2,0
N19	17,8	+2,8
N20*	15,1	+0,1

*Different batch of mannitol.

The prediction of the test set can be seen in Figure 4.3, where the predicted API concentration (%) is plotted versus powder blend, and the averaged prediction for every blend is presented in Table 4.2. As can be seen, the off-line calibration model overpredicts the concentration with approximately 2 %. It is likely that the overprediction is a systematic error caused from the measurements of the calibration set and test set being performed differently. The calibration set was analysed off-line
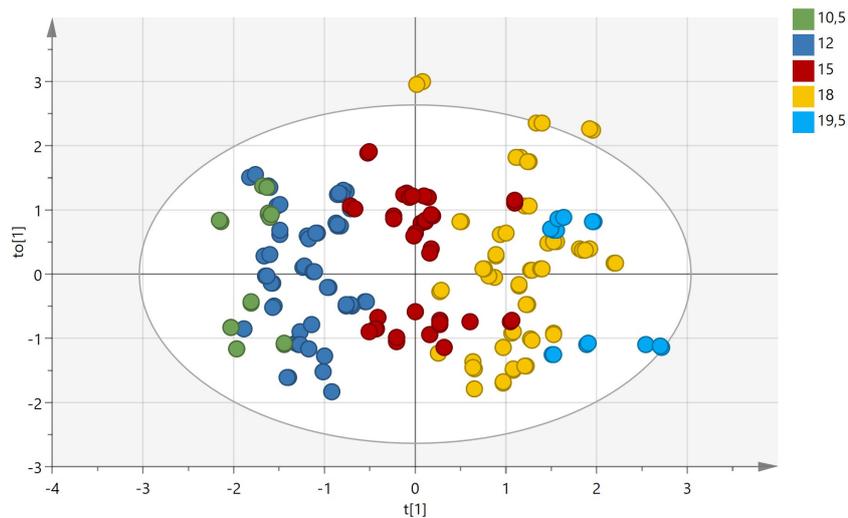
FIGURE 4.2: Score plot for the off-line calibration model. Coloured according to nominal API concentration (%)

through the glass vial, whereas the test set was analysed in-line directly on the powder using the Revolver.
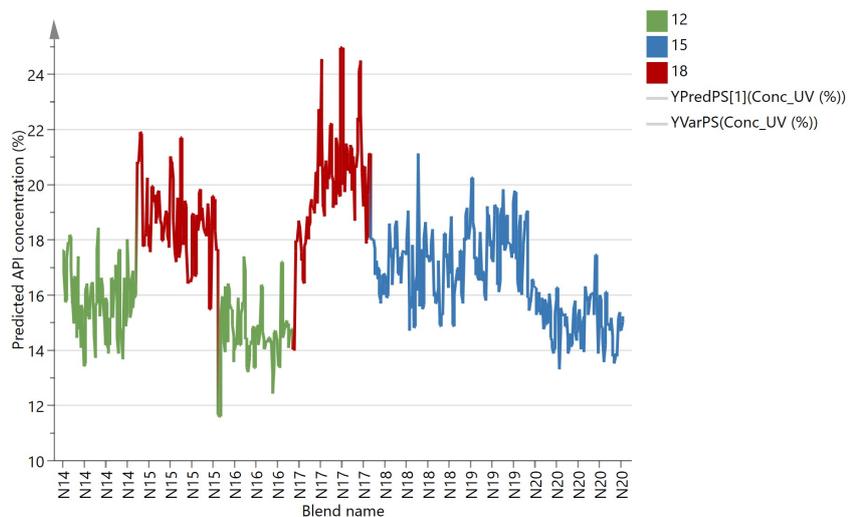
FIGURE 4.3: Off-line prediction of the test set. The test set is measured in-line using the Revolver. Coloured according to nominal API concentration (%)

4.2.2 Local centring

Since the overprediction likely originates from a systematic difference on how the measurements were performed, one might circumvent the issue by pretreating the calibration data set. Transferring calibration models from one instrument to be used at another has successfully been done before by applying local centring [52, 53]. The overprediction was a similar issue, so local centring was performed on the off-line

prediction set. Local centring can subtract the effect of the glass vial without having to re-measure all samples. This approach could save both time and resources. The local centring was conducted by taking samples from the powder blends and analysing them directly on the powder using the Revolver, and later collected and put them in glass vials to be analysed in the same manner as the off-line calibration set. This was firstly done using only one sample at 12 %. The results were transferred to be used for the off-line calibration model. However, the calibration model still overpredicted the test set. To solve this, two additional samples were analysed giving in total three powder blends at 12 %, 15 % and 18 % to include the whole concentration range. Though, the appearance of the newly obtained spectra did not look like spectra from previous analysis. The deviating spectra showed similarities with paracetamol. Figure 4.4 shows a representative spectrum of the powder blends (black), a spectrum that deviates (blue) and a spectrum from pure paracetamol (red). It would be interesting to investigate the approach of local centring further by re-mixing the powder blends and perform new analysis, however it was not possible to do it in this project due to limited time. Constructing an off-line calibration model only required small amount of materials, only a few millilitres per powder blend. All 13 samples in the calibration set were analysed within 30 minutes. Generating spectra in-line required 500 g of material per blend and took one full work day to complete.
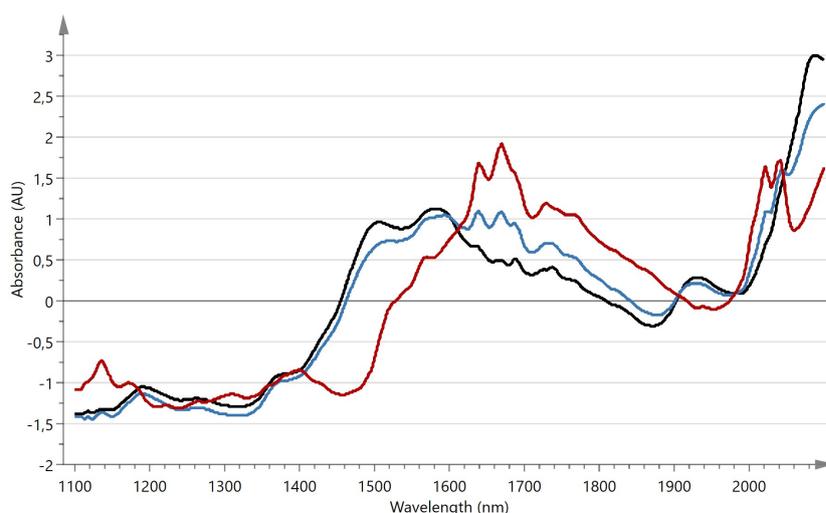
FIGURE 4.4: Possible segregation of powder blends. The black line is a representative spectrum, and the blue line suggests higher concentration of paracetamol due to similarities to spectra of pure paracetamol (red).

4.2.3 In-line calibration model using the Revolver

Since the off-line calibration model overpredicted the concentration of the test set, another calibration model was developed from measurements performed on the calibration set in-line using the Revolver. The measurements were performed in-line directly on the powder. The Revolver wheel was rotated every 10 s. The obtained NIR spectra were used for generating a calibration data set to be used for developing

the in-line calibration model. The real API concentrations obtained from the reference analysis were used as Y-values in this calibration model as well.

FIGURE 4.5: Score plot for the Revolver in-line calibration model. Coloured according to nominal API concentration (%)

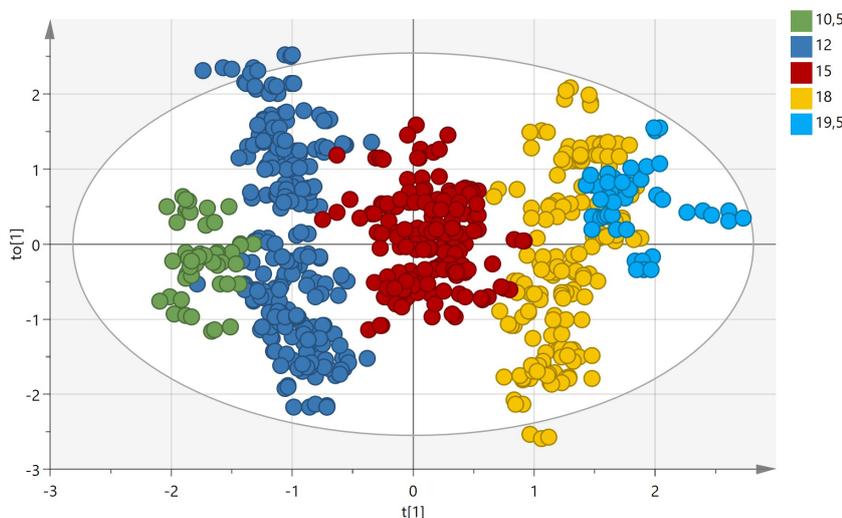The in-line calibration data set was constructed by the obtained spectra. The spectra corresponding to the filling of the compartment were excluded, leaving three spectra from every compartment included in the data set. An OPLS calibration model was constructed by pretreating the calibration data set with first derivative followed by SNV filters. The first and last 50 nm were excluded from this model as well, i.e. the wavelength region included was 1150 nm to 2050 nm. DmodX and Hotelling's T2 were evaluated but no outliers were identified. The score plot of the calibration model is displayed in Figure 4.5. It is coloured according to nominal API concentration (%). Again, the results show some overlapping due to compositional variations.

A prediction of the test set can be seen in Figure 4.6, where the predicted API concentration (%) is plotted versus powder blend, and the averaged prediction for every blend is presented in Table 4.3. In contrast to the off-line calibration model, the Revolver in-line calibration model preforms in accordance with the results from the calibration set reference analysis. Some slight variations can be seen, e.g. N17 at 17,8 % which lay close to the nominal API concentration of 18 % compared to e.g. N14 at 12,3 % which correspond better to the materials loss observed after reference analysis.

4.2.4 In-line calibration model using ExpoPharma probe holder

An in-line calibration model was constructed based on in-line measurements performed using the ExpoPharma probe holder. The analysis were performed directly on the powder similarly to the previously described in-line measurements. The ExpoPharma sample spoon was rotated every 10 s. The obtained spectra were used for generating a calibration data set to be used for constructing an in-line calibration model. The real API concentration obtained from the reference analysis were used
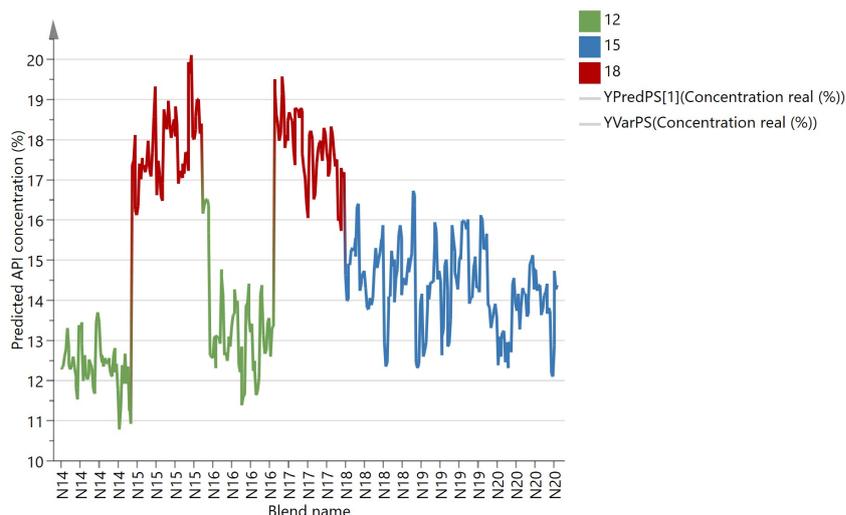
FIGURE 4.6: In-line prediction of the test set. The test set is measured in-line using the Revolver. Coloured according to nominal API concentration (%)

TABLE 4.3: The averaged in-line prediction for every blend. Measurements performed using the Revolver.

Blend name	Predicted API concentration (%)	Diff. nominal and predicted
N14	12,3	+0,3
N15	17,9	-0,1
N16	13,4	+1,4
N17	17,8	-0,2
N18	14,8	-0,2
N19	14,5	-0,5
N20*	13,8	-1,2

*Different batch of mannitol.

as Y-values in this calibration model as well. Again, the spectra were similar to the off-line analysed samples presented in Figure 4.1.

The in-line calibration data set was constructed by the obtained spectra. The spectra corresponding to the filling of the compartment were excluded, leaving three spectra from every compartment included in the data set. An OPLS calibration model was developed by pretreating the calibration data set with first derivative followed by SNV filters. The first and last 50 nm were excluded from this model as well, i.e. the wavelength region included was 1150 nm to 2050 nm. DmodX and Hotelling's T2 were evaluated. One sample was identified as an outlier and hence excluded. The score plot of the calibration model is displayed in Figure 4.7. It is coloured according to nominal API concentration (%).

A prediction of the test set can be seen in Figure 4.8, where the predicted API concentration (%) is plotted versus powder blend, and the averaged prediction for every blend is presented in Table 4.4. Similarly to the Revolver in-line calibration model, this calibration model corresponds better to the results from the reference analysis. This can probably confirm that a systematic error is introduced by analysing the
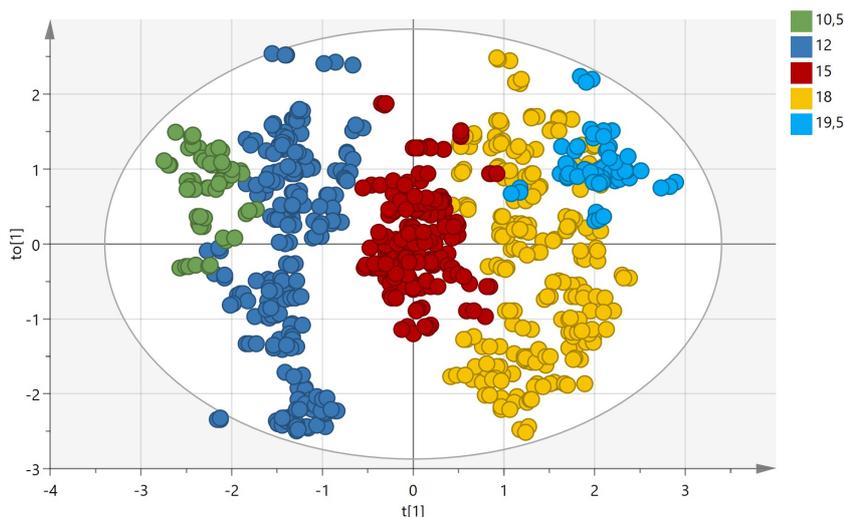
FIGURE 4.7: Score plot for the ExpoPharma in-line calibration model. Coloured according to nominal API concentration (%)

samples through glass vials.
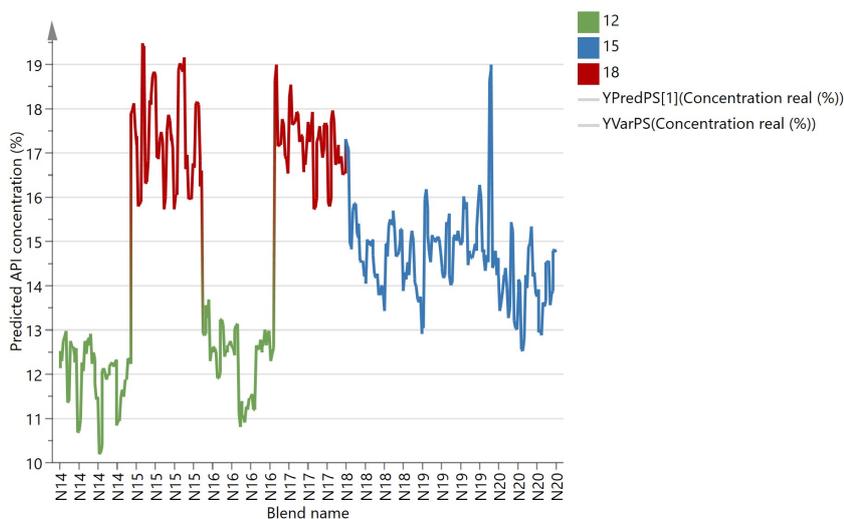
FIGURE 4.8: In-line prediction of the test set. The test set is measured in-line using the ExpoPharma probe holder. Coloured according to nominal API concentration (%)

4.3 Comparison of the probe holders

The calibration models developed from measurements performed by the Revolver and the ExpoPharma probe holder show similar results. This indicates that they function equally well according to the results of this project in terms of presenting the sample to the NIR probe. The principle behind both probe holders is the same: (a) collecting the falling sample; (b) temporarily holding the sample still while

TABLE 4.4: The averaged in-line prediction for every blend. Measurements performed using ExpoPharma.

Blend name	Predicted API concentration (%)	Diff. nominal and predicted
N14	12,0	0
N15	17,4	-0,6
N16	12,3	0,3
N17	17,3	-0,7
N18	14,8	-0,2
N19	14,8	-0,2
N20*	14,3	-0,7

*Different batch of mannitol.

analysing it, and lastly; (c) discharging the sample before starting another cycle. Disadvantages with the ExpoPharma probe holder are its large size and heavy weight, but most importantly the fact that it lacks a back wall. With a very flowing powder, it might flow off the spoon and leave improper amount of material to analyse. The supplier's solution is to tilt the probe to create an angel, however this might be difficult to do giving the limited available space between the two blenders.

Before AstraZeneca decides on which approach to use, they should consider for example costs and validation requirements for the two probe holders. If AstraZeneca decide to move forward with developing the next generation of the Revolver probe holder, the type of driving system should be considered. The ExpoPharma probe holder is driven by compressed air, however an electrical driving system could also be implemented for the Revolver. It is also crucial to synchronise the sampling and monitoring in order to derive spectra to a certain point of time during manufacturing. It might also be beneficial to have a sample thief if it would be necessary to perform further analysis.

Chapter 5

Conclusion and future work

5.1 Conclusion

The in-house made Revolver probe holder and the commercial Expopharma probe holders evaluated in this project show promise to be used for supporting the NIR probe by collecting and presenting the powder blend in a simulated continuous mixing process. If AstraZeneca decides to move forward with the in-house made probe holder, aspects like type of driving system and synchronising the rotation of the wheel with the collected spectra should be considered.

An off-line prediction model was constructed to be used for real-time monitoring the API concentration. However, a systematic error was introduced by measuring the off-line calibration set though glass vials and not directly on the powder, which is how the sample will be presented in CDC. Local centring was applied to remove the effect off the glass vial, but did not solve the problem. Deviating spectra suggest that segregation of some of the powder blends has occurred. Local centring can save both time and resources.

The in-line prediction models show promising results, giving predictions similar to the reference analysis. The Revolver and ExpoPharma in-line calibrations gave similar results, indicating that the principle of the sample presentations works equally well. On that basis, it would be interesting to predict the test set measured using ExpoPharma on the Revolver calibration, or vice versa.

5.2 Future work

If continuing with this work, the next step could be to further investigate the possibility of using an off-line calibration. This could save a lot of time and resources. To do so, the powder blends would have to be re-mixed to solve the issue of segregated powder blends before continuing with the local centring. It would also be necessary to investigate the origin of the segregation, whether it was caused by the probe holders, the handing of the powder or something else.

If moving forward with the Revolver, the next step could be automating the wheel. In that case, suitable turning frequency of the wheel ought to be investigated. Regarding sample presentation, other principles could be possible as well. Instead of momentarily holding the sample still, one could use a chute to slow the sample down. In that case, the probe should be introduced with an angle, e.g. perpendicular to the chute. This would be a simpler construction compared to the Revolver or ExpoPharma.

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