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Development and Start-up of an Automated Continuous Tablet Manufacturing Line

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Table of Contents

Table of Contents ..... *i*

List of Tables ..... *iii*

List of Figures ..... *iv*

Abstract ..... *v*

Zusammenfassung ..... *vi*

1.Theoretical Background *1*

1.1Continuous Manufacturing **1**

1.2 Process Analytical Technologies (PAT) **4**

1.3 Control Strategies **7**

1.4 Hot Melt Extrusion **10**

1.4.1 PAT in Hot Melt Extrusion 15

2.Problem Statement *18*

3.Methodology *19*

3.1 Description of the manufacturing process **19**

3.1 Materials **22**

3.2 Line Devices **23**

3.2.1 In-line Measurement Devices 27

3.2.2. Off-line Measurements Devices 30

3.3 In-line Measurements **33**

3.3.1 RTD measurement **33**

3.3.2 Chemometric Model Development 35

3.4 Control Strategy **36**

3.5 Off-line measurements **36**

3.5.1 Off-line Tablets Analysis 36

3.5.2 Off-line pellet analysis 37

3.5.3 Analysis of NIR calibration blends for Vitamin B1 pellets 37
3.5.4 Analysis of Strands with Different API concentration 38

4.Results and Discussion 39

4.1 In-line Measurement 39

4.1.1 NIR Measurements 39
4.1.2 Chemometric Model Development 40
4.1.3 Result and Discussion of Control Experiments 41

4.2 Off-line Measurement 43

4.2.1 Off-line Pellet Measurement 43
4.2.2 Off-line Tablet Testing 44
4.2.3 Analysis of Vitamin B1 Strands 48

6.Summary and Conclusions 49

7.References 51

List of Tables

Table 1:Extrusion Line 22
Table 2:Premix for Continuous Line 22
Table 3:Premix for DC Line 23
Table 4:Temperature of barrels 24
Table 5:Experimental Design for RTD measurements 33
Table 6:Change in Pelletizer Speed and Time of Colored Pellets 34
Table 7:Calibration Experiments for NIR 35
Table 8: Concentrations of calibration blends with Vitamin B1 pellets 38
Table 9:Sieving Results of the Pellets 43
Table 10:The Mean values of the Samples 45
Table 11: Results of HPLC Experiment 48

List of Figures

Figure 1:Process Analytical Technology setup (PAT)[31] 5
Figure 2: Hot Melt Extrusion.....11
Figure 3:Block Diagram of the Complete Continuous Line.....21
Figure 4:Feeders.....24
Figure 5:Extruder 25
Figure 6:Pelletizer 26
Figure 7:Tableting Press.....27
Figure 8:ColVisTech Probe 28
Figure 9:Diameter Scanner 29
Figure 10:Pressure Sensor 30
Figure 11:UV/VIS Spectrophotometer.....31
Figure 12:ERWEKA hardness tester.....32
Figure 13:Box Diagram of the speed and times.....34
Figure 14:RTD curve of the melt.....39
Figure 15:API prediction chemometric model 40
Figure 16:Control Experiment results of the entire line.....41
Figure 17:Mean weight values of the samples.....45
Figure 18:Mean Thickness values of the Samples.....46
Figure 19:Mean Strength of the Samples 46
Figure 20:Mean Diameter of the Samples.....47

Abstract

This thesis investigates an automated continuous manufacturing line, which is preferred more than batch manufacturing in the pharmaceutical industry nowadays. To obtain an automated continuous line with uniform product, it is important to develope accurate processes and have good process understanding. To achieve this, PAT is applied and also control a concept is developed and implemented. NIR is used for the in-line measurement. The line consists of two parts; extrusion and direct compression (DC)line. NIR is implemented at the end of the extruder and also in the DC Line to obtain data to develop chemometric model. Residence Time Distribution (RTD) is also identified for the process as a part of the control concept. For automation, control strategy is developed by applying a model predictive approach.

The aim of this thesis is to install a continuous line and implement in-line measurement devices and control strategies. Therefore, the test runs are performed with PAT tools and control strategy. The continuous tableting line was run with model materials Vitamin B1 and Tablettose 70 and the DC line with acetylsalicylic acid and a premix of Kollidon, Avicel and Magnesium stearate. NIR data is used for the chemometric model development to predict API content and RTD determination. The chemometric model is created by using *Multivariate Data Analysis* on SIMCA with NIR data from the line. RTD measurement is done on the extrusion line with iron dioxide and the NIR measurements are again evaluated on SIMCA. In this thesis, the control concept that the extruder is the master is experimented. To test it, the mass flows of the extrusion line feeders are kept constant and mass flows of the DC line are changed and response of the system is observed. The expectation is to obtain the tablets with desired specifications even though there is change in the system.

The produced tablets and pellets from the continuous line are also tested off-line. The tablets are tested for their physical properties and also their API content. The pellets are tested for their API content in order to help to develop the chemometric model. The results are evaluated to compare if the products meet the specifications when the production method is the continuous manufacturing with Hot Melt Extrusion.

Zusammenfassung

In dieser Arbeit wird eine automatisierte kontinuierliche Fertigungslinie untersucht, der heutzutage in der Pharmaindustrie zur Serienfertigung der Vorzug gegeben wird. Um eine automatisierte kontinuierliche Linie mit einheitlichem Produkt zu erhalten, ist es wichtig, genaue Prozesse zu bestimmen und ein gutes Prozessverständnis zu haben. Dazu wird PAT auf den Prozess angewendet und auch ein Steuerungskonzept entwickelt und umgesetzt. NIR wird für die Inline-Messung verwendet. Die Linie besteht aus zwei Teilen; Extrusions- und Direktkompressionslinie (DC). NIR wird am Ende des Extruders und auch der DC-Leitung implementiert, um Daten zur Entwicklung eines chemometrischen Modells zu erhalten. Die Verweilzeitverteilung wird für den Prozess auch als Teil des PAT-Konzepts identifiziert. Für die Automatisierung wird die Steuerungsstrategie durch einen modellprediktiven Ansatz entwickelt.

Ziel dieser Arbeit ist die Installation einer durchgehenden Linie und die Implementierung von Inline-Messgeräten und Regelstrategien. Daher werden die Testläufe mit PAT-Tools und Kontrollstrategie mit kontinuierlicher Tablettierungslinie mit den Materialien Vitamin B1 und Tablettose 70 durchgeführt und für die DC-Linie enthält Acetylsalicylsäure und Premix Kollidon-, Avicel- und Magnesiumstearat. NIR-Daten werden für die chemometrische Modellentwicklung verwendet, um den API-Gehalt und die Residence Time Distribution(RTD) vorherzusagen. Das chemometrische Modell wird mit Hilfe der multivariaten Datenanalyse für SIMCA NIR-Daten aus der Linie erstellt. Die RTD-Messung erfolgt auf der Extrusionslinie mit Eisendioxid und die NIR-Messungen werden erneut auf SIMCA ausgewertet. In dieser Arbeit wird das Steuerungskonzept, dass der Extruder der Master ist, getestet. Um dies zu testen, werden die Massenströme der Dosierer in den Extruder konstant gehalten und die Massenströme der Tablettierlinie werden geändert und das Verhalten des Systems wird beobachtet. Es wird erwartet, die Tabletten mit den gewünschten Spezifikationen zu erhalten, obwohl sich die Parameter im System ändern.

Die hergestellten Tabletten und Pellets aus der kontinuierlichen Linie werden auch off-line getestet. Die Tabletten werden auf ihre physikalischen Eigenschaften und auch auf ihren API-Gehalt getestet. Die Pellets werden auf ihren API-Gehalt getestet, um das chemometrische Modell zu entwickeln. Die Ergebnisse werden ausgewertet, um zu vergleichen, ob die

Produkte die Spezifikationen erfüllen, wenn das Herstellungsverfahren die kontinuierliche Herstellung mit Hot Melt Extrusion ist.

1.Theoretical Background

1.1Continuous Manufacturing

In pharmaceutical industry, the processes have been mainly batch manufacturing processes. However, recently continuous manufacturing has taken interest since it allows economical, cleaner and faster manufacturing [1]. Even though the batch processes are still used in the pharma industry, it cannot be said that they are the most efficient method for pharmaceutical processes due to scale-up issues. Furthermore, since there is a need of implementing the Quality by Design (QbD) and Process Analytical Technology (PAT) in the pharma industry, to transition from batch manufacturing to continuous manufacturing for the drug products has become more important. Continuous manufacturing eliminates scale-up problems and ensures the product quality by obtaining more process knowledge. Moreover, continuous manufacturing makes processes function in almost steady state and this situation allows the critical product quality attributes to be kept constant by manipulations in the process [2].

Continuous manufacturing has been chosen for pharmaceutical manufacturing processes over traditional batch processes since it offers many advantages. The continuous manufacturing allows to produce the same quality product and 24-h automatic production for desired amount with less material. Also, there are less produced out-of-specification material in continuous line since it needs real-time quality control [3]. Furthermore, automation enables to monitor and control product quality by Process Analytical Technologies [4]. Moreover, it shortens the product development time and time-to-market. It also decreases capital investment and labor costs. Since it is continuous production, there is no transfer of intermediate products or storage of intermediate products. The continuous manufacturing needs less floor space because of elimination intermediate products and less energy [5].

Despite many benefits of continuous manufacturing, there are also many problems. The main problems that is encountered by the companies that decide to implement continuous manufacturing are initial cost of the implementation, maintaining the continuous manufacturing development, difficulty with current PAT and process control tools to control the processes. These challenges lead to other problems related to manufacturing. One of these problems is material traceability. Since there is no batch, it is hard to determine problems in

the material or end product. Therefore, residence time distribution is used to determine time of the material passing in each unit operation. Depending on the material, adhesion also can be big problem since the material is passing through several surfaces through line. It can cause clog or change in the residence time [2]. The continuous manufacturing is not suitable for small manufacturing. The continuous manufacturing needs robustness and for fast steady state. Also, the method still has regulatory issues [5].

On the other hand, continuous manufacturing is very difficult implement since it has many challenges. Because it is continuous operation, failure related to process equipment and raw material can happen any time and can lead to out-of-specification material [2]. Therefore, it requires an integrated process with all unit operations are connected, real time monitoring and PAT and control with PAT, and a control system to diminish effect on the final product that caused by process and materials [6]. These strategies can be used various scenario that could go wrong during process such as deviations in active pharmaceutical ingredient (API) concentrations [2].

There are several companies that invest to change from batch manufacturing to continuous manufacturing [38]. These companies are Lilly[7,8], Pharmatech, Vertex [9], Pfizer [10], Novartis [11], Johnson &Johnson[12,13], Amgen[14],and GSK[15].

Nowadays, the interest in the pharma industry regarding to continuous manufacturing and integrating the monitoring tools and more effective control system increases. Besides many advantages of the continuous manufacturing, it is more steady operation and this quality makes it more suitable for the model predictive control and optimization [16]. The implementation and operation of the control systems is still new for the pharma industry, but it is open research area to develop for academics and industry [17].

The unit operations in the continuous tablet manufacturing line is not fully automated and they are controlled manually and separately via their own operating user interface and this means that most of the pharmaceutical production facilities operate as manual or semiautomatic. Since the automation has not been implemented in the manufacturing processes, it is hard to integrate control systems. Implementing the control hardware, software and sensors in the process equipment is a difficult goal to achieve because there is no standardization for the pharmaceutical equipment to develop control strategies. Therefore,

there is big interest in the systematic framework to be able to use in the pharmaceutical plants to automate the process [17].

The process understanding is an important term in the control strategies and defined by the FDA “A process is generally considered to be well understood when all critical sources of variability are identified and explained, variability is managed by the process, and product quality attributes can be accurately and reliably predicted over the design space established for the materials used, process parameters, manufacturing, environmental and other conditions.” [43] Another important concept in control is open and close loop control systems. Open loop systems can be defined as the systems that considers the input and give no response on the feedback to get the output. It works on fix conditions and with no disturbances. The closed loop systems are the systems that work with feedback. The output is considered in these systems and can make changes according feedback. It can modify the output to desired condition. The appropriate transition from open loop to closed loop control starts with process understanding. Then, the next steps are design, hardware/software and sensor integration and implementation of control system [16]. Barrasso et al.,2013, Barraso and Ramanchandran, 2012and Sen and Ramanchandran, 2012 have model-based studies to understand the continuous manufacturing process. Also, several experimental studies have been conducted by Vanarase et al.,2011, Vanarase and Muzzio,2011. In the studies of the Singh et al.,2010, Ramanchandran and Chandhury,2011 and Ramanchandran et al., 2012, the attempts to design a control system for tablet manufacturing process can be seen. Nevertheless, there are very little attention is given to implement the control hardware/software and sensors in the existing continuous manufacturing line and to automate the whole line.

The continuous tablet manufacturing line has been developed by the Singh et al., 2012b placed in ERC-SOPS, Rutgers University. It is possible to develop fully automated line if it runs through centralized control platform. The automation provides opportunity to collect data from the sensors that is measured throughout the process [16].

1.2 Process Analytical Technologies (PAT)

Process Analytical Technologies (PAT) is defined by FDA as “a system for designing, analyzing and controlling manufacturing through timely measurements of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality” [27].

Another important definition for PAT concept is critical quality attributes to determine the product quality. The critical quality attributes (CQAs), as defined, “should be the relevant performance indicators for pharmaceutical finished products, which are basically the desired in vitro / in vivo performance and targeted clinical response, as well as the required physical and chemical stability shelf-life of the product." All the CQAs of the process materials including intermediates and in-process materials should be agreeable to PAT application, so that it shows the performance qualities of the products [27].

According to definition by FDA, it can be seen that PAT can be used in designing stage of a new process, and also analyzing the current processes and improve the control over processes. To be able to achieve that, measurements that are done by time is necessary. Moreover, all the information about process and materials that are used should be obtained to have more control over the quality of the end product [27]. The main task of the PAT is to feed information to a control system to observe the critical quality attributes of the product that is produced by continuous manufacturing [2].

In general, PAT detects variations in the process. The conditions that is used in the pharmaceutical processes are usually predetermined and fixed. Due to this circumstance, any variation in the process or in the material can cause variation in output material. This situation can be tested at the end with the product and the product quality is determined accordingly. On the other hand, being able to obtain information from inside the process allows to control running process and produce desired products even if there is input material variations. However, it is important to know the process and materials very well in order to adapt this technique [27].

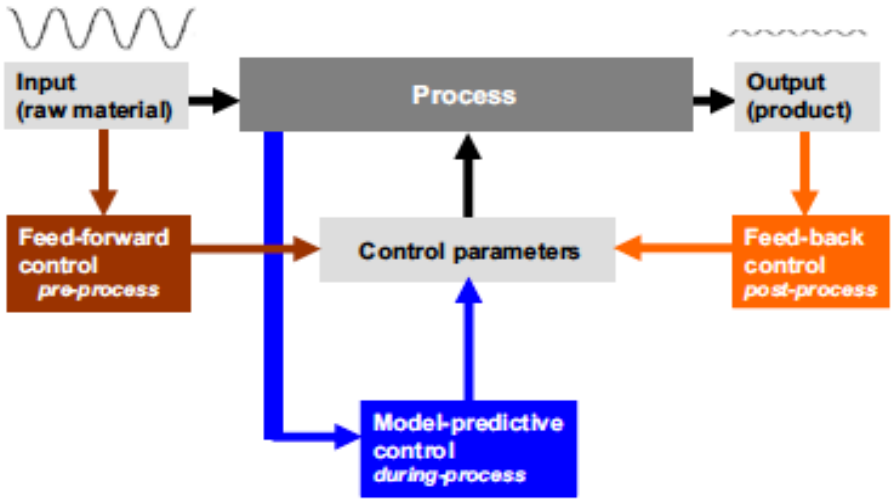

Figure 1:Process Analytical Technology setup (PAT)[31]

The Figure 1 above shows the setup for PAT in the manufacturing process. Model-predictive control slows the predict variations in the system and adapt process accordingly so that the end products meet the specifications.

Since the manufacturing processes are changing from batch process to continuous process, PAT becomes even more important to understand the processes. It should also be considered that materials are constantly charged and processed in the continuous processes and the continuous processes should be monitored to stay in the predefined limits of the process. To keep the quality of the process, the real- time measurements and analysis, and appropriate control strategy must be done [27].

There are several methods used as PAT in pharmaceutical manufacturing, but most common techniques are Raman and NIR spectroscopy [30].NIR is generally used to monitor the mixing of API and excipients in the manufacture of the solid oral dosage forms with continuous manufacturing. Since the mixing is the crucial step in the manufacturing process, there must be the implantation of control strategies for powder blending. NIR method and the results of this method become important in order to determine the concentration of the drug and decide if it is acceptable to be compressed or rejected. In the continuous manufacturing, NIR serves to monitor the blending in real time and determine the quality of the blend and if it meets the specifications [6].

There are 2 sampling methods that are used in pharmaceutical industry.

1. Off-line sampling: the sampling is simply done by removing of the samples from the process and analyzed in the laboratory. The method is slow and invasive, however has the flexibility in determining the measurement method.
2. At-line sampling: a specific device is placed to the line. Sampling is performed by removal of the samples occasionally or continuously. The devices are robust and worked with fixed parameters and standard procedures.

There are two measurement techniques that are used in the industry.

1. On-line measurement: In this measurement samples are taken continuously from the stream and passes through the analyzer and then is sent back to the stream. This eliminates many preparation possibilities; however, large portion of the stream can be measured.
2. In-line measurement: In this type of measurement, samples are measured in the unmodified product stream and therefore there is no effect on the process. Nonetheless, it may be difficult to get sample and calibration is comprehensive [27].

The data analysis for data collected are conducted by tools. These tools allow to structure the data such as reduce redundant data and obtain the relevant data. These tools include process monitoring and multivariate data analysis tools to determine the process in the design space. Principal component analysis (PCA) is the mostly used method for process data evaluation [27].

1.3 Control Strategies

There are many challenges that pharmaceutical companies encounter such as high cost and length of time of drug development, patent life and regulatory issues, and ineffective quality measurement with Quality by testing (QbT) in the batch manufacturing. In order to address these problems and deal with them in a more effective way, automation has become the direction in the industry. The continuous manufacturing becomes more appealing to use classical process control methods since it runs at steady state. This situation can make the manufacturing processes more robust and reliable. The steady state can be achieved in minutes and this situation allows to apply Quality by Design based manufacturing. Despite the advantages of the implementation control methods in pharmaceutical industries, it is new and unknown research area. Because batch manufacturing is established in the industry and process understanding is available, it is still most common production root despite its many disadvantages [26].

Batch processes mainly uses the off-line analysis to check the quality of the intermediate and the end product. Nevertheless, off-line analysis cannot be applied to continuous processes. The should be investigated in real time means that at-line, on-line and in-line analysis as defined in the PAT guideline for industry [5]. Therefore, it is important to implement a sophisticated process analytical technology (PAT) concept in order to overcome the challenges of the continuous manufacturing in the industry. The PAT concept gives advantages for in-line and off-line measurement for the critical process parameters and critical quality attributes. The aim of the process control is to ensure to produce the product with desired quality. To obtain this, it is important to develop a process with a robust process [27]. Moreover, it is important to have advanced control strategies to keep the critical process parameters at the given set point and to obtain intermediates and products at desired quality. To achieve this situation, model-based control concepts are favorable techniques. There are many industries that are using the model- based control such as robotics, heating, air conditioning. To design model-based controller, it is necessary to have suitable dynamic process model [28].

In a pharmaceutical plant, to implement real time inline/online process monitoring and closed loop feed-back and feed forward control systems can achieve Quality by Design. Implementing of the control systems increases efficiency since it provides several advantages such as optimal use of time, space and resources. Furthermore, this approach satisfies the market demands, complexities of the operations and economic limitations. Even though the model predictive control is expensive to implement comparing to PID (proportional-integral-derivative), the better performance of the closed loop process can be obtained. The main problems of selection between PID and model predictive control are integration of the available software and hardware, availability of the data, implementation of the control loop [26].

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To achieve automation, the companies should have electronic PAT tools that is integrated with process control in order to obtain continuous quality and verification. The important aspect of the continuous manufacturing is the real-time product release. Data-driven verification of the quality can be provided by PAT to achieve real-time release and assurance with inline measurements [27].

The data that collected by PAT tools is evaluated by data regression models by using chemometrics software from CAMO, Matlab, Umetrics. A value of the critical quality attribute is obtained as a result. The values of the critical attributes of the unit operations of the entire process lead to advanced process control in order to have closed loop model predictive control by control the critical process parameters in the process. The aim of the advance process control is to have a closed-looped control to check critical process parameters and maintain the products to be produced within the specifications at all times [27].

To understand to continuous process, it is important to understand the interaction between critical process parameters and the critical quality attributes. Any changes such as adjusting a parameter to quality attribute can affect another critical attribute. Therefore, the process model and interactions may be non-linear. Due to this situation, the better solution is provided by model predictive control. In this method, predictive loop controller can foresee the values that are controlled and keep them under control to meet specifications of critical quality attributes [27].

The control concept is very new area of research in the pharma industry, therefore there are many challenges in its applications. The control methods that are usually used are not consider many parameters in the continuous manufacturing. There are many problems in terms data, communication and connection between control platform and equipment. For example, real -time measurements of critical quality attributes of tablets are still not developed properly [26].

In order to implement continuous manufacturing, dynamic simulation and tools for optimization becomes very important. They can be used to increase yield and productivity and decrease wastes costs and energy consumption. Modeling is another important aspect for efficiency, robustness, and well-understood processes [29].

1.4 Hot Melt Extrusion

Hot melt extrusion (HME) is a continuous process that has been recently used in pharmaceutical manufacturing that forces polymer by using a rotating screw at temperatures above their glass transition temperature (Tg) in order to executes molecular level mixing of the compounds [30].

One of the reasons that HME is used in pharmaceutical industry is to increase bioavailability of poorly soluble drugs due to dispersion of the API at molecular level [32]. Also, HME is very stable system to achieve higher bioavailability [27]. On the other hand, HME has other advantages such as modification of the release of the drug and conceal the bitter taste of API [33].

Hot melt extrusion is a continuous line and involves several steps such as dosing, melting blending, cooling, shaping. In the HME line, there are usually feeders, extruder, and shaping step such as pelletizing.

In pharmaceutical industry, extruders have been improved to mix drugs with carriers for different dosage forms. There are two types of extrusion process which are ram extrusion and screw extrusion. The screw extruder has a rotating screw and heated barrel, whereas ram extruder consists of a positive displacement ram that can generate high pressure to move the materials through the die. The screw extruder operates with shear stress and intense mixing. This type of extruder includes three parts: the conveying unit for transporting of material and mixing, the die system for shaping and auxiliary equipment for further processes such as cooling or collecting the final product [34]. A typical extruder includes a drive unit, processing unit that has several temperatures controlled, screws with different configuration, a die plate and a measurement and control unit [27]. In the screw extruder, there are standard process control and monitoring devices that are controlling temperature and speed of screw, drive amperage and pressure and viscosity. The temperature at the barrel are controlled by electrical heating bands [34].

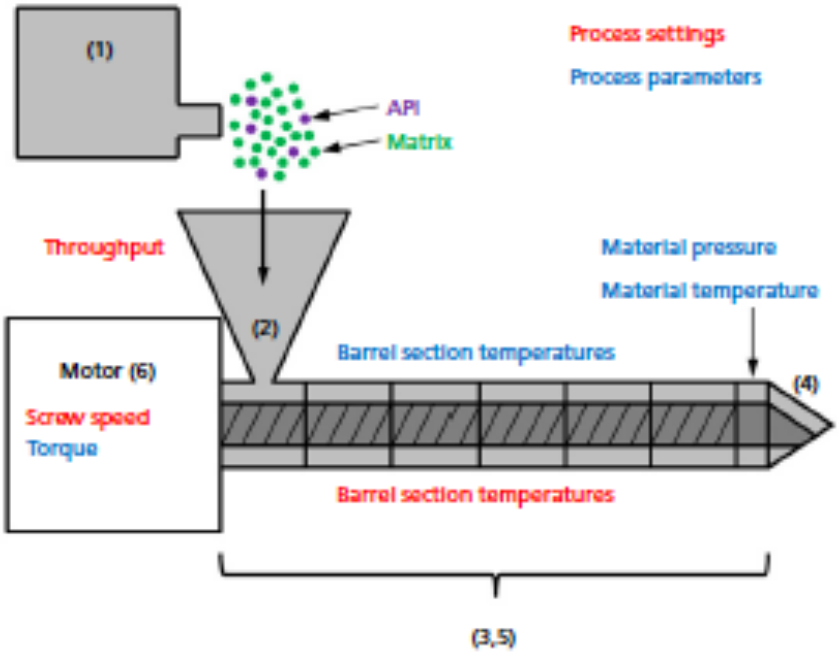

Figure 2: Hot Melt Extrusion

This figure above shows that the sections of the extrusion device. The parts are 1: Feeder, 2: Hopper, 3: Barrels with one or two screws, 4: Die, 5: Heating and cooling device, 6: Screw-driving unit respectively [32].

The polymer industry is the industry, in which the extrusion equipment was used originally. In the pharma industry hot melt extrusion is used lately [27]. HME operates with either single-screw or twin-screw instruments. In single screw extruder, there is one screw that is placed to the barrel as much as possible to produce sufficient shear. Feeding, melting, devolatilizing, and pumping is the processes that are accomplished by single screw extruder. The material is taken from the feed section in the single screw extruder and transferred to screw in the barrel. This type of extruders has three basic operations: solids conveying, melting, and pumping. (Pharmaceutical Applications of Hot-Melt Extrusion: Part I) In twin-screw extruder, there are two screws that are enabling to create numerous design and configurations that allow to optimize formulations and the end products. Twin-screws produce highest shear energy and it leads to excellent mixing in the barrel. According to rotation of the screw, there are two types of twin screw extruder; co-rotating extruder that the screws rotate in the same direction and counter-rotating extruder that the screws rotates the opposite sides. High shear stress is mostly achieved by counter -rotating extruder designs. Moreover, the layout is also beneficial for dispersing particle in the mix. There are several disadvantages including potential air entrapment, high-pressure generation, and low

maximum screw speeds and output. On the other hand, co-rotating extruder are more important in the industry. They can operate at high speeds and obtain high outputs, and also accomplish good mixing and conveying attributes. Twin-screw extruders are more advantageous than single screw extruders including easier material feeding, high kneading, and shorter transit time. Mechanical simplicity and reasonable cost are the areas where single screw has more advantage over twin screw extruder [34].

The screws consist of several sections, that operate with different functions which are feeding, mixing, compression, and metering. They are mainly stainless steel in order to decrease friction and chance of chemical reactions. These sections help the material to transfer in feeding section, soften and melt in the compression section and the polymer is in molten state when it enters to metering section. This zone is responsible for reducing the pulsating flow and obtaining a uniform delivery rate in the die. The die is the part that is at the end of the barrel. It determines to shape of the extrudate [34].

In the pharmaceutical process, the important processes are to obtain suitable melt and the downstream process. There are many downstream processes for extrusion process. After the polymer out of thee die, cooling is the first downstream process. It can be achieved by air, nitrogen, on stainless steel rolls, or water. Then, the next step is pelletizer. (Pharmaceutical Applications of Hot-Melt Extrusion: Part I) The pelletizer that are used in extrusion process is originally used in the plastic industry and generally revolves around two principles which are die-face and strand palletization. Die-face is the pelletization which the strand is cut by moving knives right after it leaves the extruder. Since the melt is at the molten state, the round shape pellets can be obtained more easily. In the second case, the strand is led to certain distances which it gets cold and then into pelletizer to be cut. The temperature is the most important parameter for the both cases to obtain uniform pellets. The rheological properties of the material and the mechanical properties of the strand is the important parameters in order to choose the right palletization [27].

In the HME process, the polymer properties and the design of the extruder are the two factors that are used to determine the efficiency of the melting process. The materials with low melt viscosities and high thermal conductivities are better choice for polymer to obtain an effective melting process. Alterations in the screws can affect melting process in a positive way and also mass flow through the extruder. The material of the polymer is important since solidified

polymer components can cause a blockage in the channel and end up as a surge of the material around the blockage.

The conditions of the process depend on chemical stability and physical properties of the material. There are several characteristics to be considered in order to set appropriate process parameters. These are melt viscosity, molecular weight, glass transition temperature, and melting point. The melt encounters mechanical shear stress due to rotating screw, and thermal stress due to high temperature and pressure. These conditions may cause depolymerization, thermal degradation and chain scission.

In the pharmaceutical processes by HME, the materials that are used should melt easily and then solidify before the exit form die. The levels of purity and safety of the materials must be the same as traditional methods. The important prerequisite of the compounds is the thermal stability for the processes, even though the short process time may not lead to limit all thermolabile compounds.

The drugs that are produced with hot-melt extrusion are the mixture of active pharmaceutical ingredients and excipients. These excipients can be categorized as matrix carriers, release modifying agents, bulking agents, antioxidants, thermal lubricants, and miscellaneous additives.

The active ingredient is embedded in a one or more type of carrier mixture in hot-melt extrusion produced drugs. The choice of a suitable carrier is important in the formulation and design of drugs that are produced with hot-melt extrusion. The carriers have different effects on process conditions [34].

There are many advantages of HME. Using this method eliminates solvents, decreases processing steps and manufacturing costs in comparison to other tablet processing methods.
All these benefits are more useful combined with benefits of continuous manufacturing if process analytical technology (PAT) is used. PAT allows quality by design and real time release of the product. HME is one of the best methods for the continuous manufacturing since it does not require the solvents, it is economical and scale-up is easy to achieve.

Even though hot melt extrusion is a very good method to use in continuous manufacturing, there are several disadvantages of this method. The high temperature can cause degradation in some thermolabile materials due to selected polymers. There are also reported cases that recrystallization occurs in active substances during storage even though dosage forms that produced with hot melt extrusion have long-term stability [35].

There are two important aims to implement PAT in the HME. One of that is to improve the understanding of the process monitoring and visualizing the material behavior while process is running, and the other aim is to monitor and analyze the critical parameters of the product and process for process control to achieve a desired process state and ensure the quality of the final product. To achieve these goals in HME, NIR spectroscopy is mainly used to determine concentration of the melt component [32].

Another technique that is used in HME as a PAT tool is UV-VIS spectroscopy. It has been used recently in pharmaceutical processes to monitor residence times of the melt, determine polymer degradation, determine impurities in the melt, and analyzing the melt quantitively [32].This spectroscopy can be implemented simply by using the fiber-optic cables. It has much lower detection limit than other techniques such as Raman and NIR spectroscopy. The disadvantage of this technique is overlapping spectral bands. Hence, suitable preprocessing of the spectra data and chemometric analysis is necessary [32]. The paper of Wesholowski et al. is shown the use UV/VIS spectroscopy to check whether it can be used in a Hot Melt Extrusion (HME) as a PAT tool for in-line measurement to determine the Residence Time Distribution (RTD). In the paper, it is also mentioned that using an effective PAT is necessary for continuous processes like HME in order to determine the process parameters or quality attributes of the product [37].

To determine formulation composition quantitively and to measure degree of interaction between the API and polymer, NIR spectroscopy is commonly used. The obtained spectra from NIR is very complex. To analyze this data, chemometric (PLS and PCA) is applied for calibration of measured spectra against a set of concentration known materials [27].

1.4.1 PAT in Hot Melt Extrusion

Hot met extrusion line is a continuous line itself and consist of several operation steps that are dosing, melting, blending, solidification and etc. The main benefit of HME is the ability to achieve stable amorphous system with increased bioavailability. The extrusion is mainly used in polymer industry and has many different options. Also, recently it has been used in pharma industry, and the types that are used in this industry includes co-rotating screws since they can clean themselves, provides shorter residence time distribution. The extrusions have a drive unit, a processing unit and a die at the end and also measurement and control unit. After die plate, the melt is transferred to pelletizer unit. The palletization is also used in plastic industry and have two types that die- face palletization and strand pelletization.

The important detail for the both technologies is to keep the thermal state under control and stable since the uniformity of the pellets are determined by the uniformity of the strand velocity at the die.

The most important step in any continuous manufacturing line is feeding. Even if there is back -mixing at the certain degree in the extruder to lessen the perturbations, still a controlled feeding process is necessary to obtain uniform products. The one or more feed rates, composition and are the process parameters to determine uniformity of the product. These parameters are the ones to consider in PAT strategy. The extrusion process can be explained by the certain throughput and the screw speed. These parameters can be used in the measurement for scaling and comparing in the extrusion process that are the specific mechanical energy consumption (SMEC) and the residence time distribution (RTD).

In the recent studies, the review for PAT tools for HME can be found includes in-line, on-line, univariate and multivariate methods which are applied in the pharmaceutical and plastic industries. Even though there are many documents about NIR spectroscopy, Raman spectroscopy, and UV/VIS spectroscopy, there are still very little information about constant feeder monitoring.

The most important difficulty to be considered for the PAT tools is the spatial and time sampling. The spectral data has to be revised because of screw and non-uniform sample on the probe and univariate data can be obtained on the wall. One of the challenges is to measure

the melt temperature throughout the process. The sensors that are usually used are thermocouple sensors with slow response time. Because of the slow response time, the data becomes irrelevant to control process. Moreover, these sensors may be easily influenced by the temperature changes in the barrels if the insulation is done poorly. The other type sensors are the Infrared (IR) sensors and they are better to detect variations, however they are relied on the qualities of the material which affect the signal. Therefore, the sample size uniformity is important to monitor temperature and may lead changes in the signal [27].

NIR spectroscopy is one of the commonly used PAT techniques especially HME. It is used to monitor concentration of API in the polymer and quantify the composition. It is also used to observe the interaction between the API and polymer. The probe of NIR is generally placed at the end of the extruder. In NIR, the light from the probe passes via optical fiber through sapphire window into the melt. Since the measurement in the barrel is too difficult due to its shape and material on twin screw during the process, it is hard to be sure the coverage of the sampling window [27].

Analysis of NIR data is complex and needed to be process in order to use it for future references. The data is treated with application of chemometric (mostly PLS and PCA) to calibrate measured data with known concentrations. This chemometric model is used to obtain real-time indication of the specific parameter. Furthermore, the spectra form NIR are averaged to decrease noise, however this situation affects the sampling frequency. In HME, NIR is also used to determine residence time distribution (RTD) with a tracer material that is added in feeders [31].

Another method that is used in HME is Raman spectroscopy and placed in the die or barrel. The spectra from Raman spectroscopy is evaluated with PLS models to correlate with known API concentrations. Raman spectroscopy also can be used in determining the degree of hydrogen bonding between API and polymer and to conclude the state of crystalline of the API.

Another application of the Raman probe is to obtain measurements from different locations throughout the barrel during the extrusion process. The parameters that are measured are the temperature setting, speed of screw and drug content and their effect on the API are determined.

According to recent studies, when these two methods are compared, it is shown that these two methods give the same type of information about content of the API and the interaction between polymer and API. Besides these two spectroscopic methods, UV/VIS spectroscopy that is used ultraviolet and visible wavelength is also used in the Hot Melt Extrusion in order to measurement of degradation. This method is also used in the extrusion process to determine residence time distribution, with colored tracers and temperature of the melt by using the temperature sensitive colored tracers.

One of the process control strategy is to create flow sheet models of the process line, by using RTDs. This modelling is used to study start-up and control strategies to identify the failures in the system and increases the efficiency of the manufacturing [27].

2.Problem Statement

The section 1 theoretical background gives an overview about continuous manufacturing in the pharmaceutical industry. Any of the papers mentioned in the theoretical background hardly mentions work related to complete continuous direct compaction line with hot melt extrusion. Even though there are studies that has been mentioned in the continuous manufacturing chapter, there is no work with fully automated DC line with HME. This works develops PAT and control strategy.

The aim of this project is the installation of the continuous line and implementation of in-line measurement devices and process control strategies. In this thesis, the installation of the pelletization step with Hot Melt Extrusion unit and auxiliary equipment into an existing tableting line will be performed. Therefore, to develop an automated continuous line, the PAT tools that are selected by the research team are implemented. The tools are NIR and various sensors. The sensors are for pressure, temperature, hopper level sensor and melt diameter senor. The temperature sensors are connected to extruder. The pressure sensors control the pressure in the system. There is also the sensor for the measuring the diameter of the melt and hopper level sensors to monitor material level in the hoppers. These tools provide the necessary process and material data to control the line or robust continuous operation. NIR probe is mounted at the end of the extruder to monitor API concentration of the melt produced by hot melt extrusion and also another probe is placed to the blender to observe API concentration of the mixture of pellets and premixed that goes into tableting machine. Sensors are used to control pressure and temperature. The chemometric model is designed by using NIR data and *Multivariate Data Analysis (MVDA)*. For the investigation of the tablets, UV/VIS spectrophotometer and hardness tablet tester are used to test tablets. Additionally, to test strands and mixture of the DC Line, sieving and NIR measurement are performed to support data from in-line measurement.

To develop control strategy to achieve fully automated line, model predictive approach is used by the research team. Three concepts are determined to create controlled line. First one is that the master in the line is extrusion which the set points are kept constant, the second concept is to make the tablet press master and change the set points of the extrusion and the last is the to run the line without master. In this work only the first concept is tested experimentally.

3.Methodology

3.1 Description of the manufacturing process

The manufacturing line consists of feeders, extruder, cooling track, pelletizer, feeders, blenders and tableting machine. The line also has sensors to control and implement control concepts. These sensors are temperature and pressure sensor. Diameter scanner (Zumbach 13Trio) is also used. The aim of the project is to implement HME as granulation step and also to implement PAT technology and test if it is fits to the continuous manufacturing line. All system is automated. PAT tool is tested by using spectroscopy methods, firstly ColVisTec (UV/VIS) and later NIR. Also, Residence Time Distribution of the polymer is considered to create chemometric model for the process. For the test runs, Vitamin B1 and Eudragit EPO is used for the granulation. For tableting, the pellets from the granulation process and Premixes with Avicel, Kollidon CL and Magnesium Straete are used. Moreover, to test the DC Line another formulation with Acetysalicyclic acid (ASS) and premix with Tablettose 70 and Magnesium Straete is used. NIR measurements is also used for DC Line experiments. The measurements are performed for two different formulation.

Furthermore, a hopper is designed to transfer suitable pellets to feeders for tableting and separates the unfit pellets. The hopper is designed for flow rate of 4 kg/h. For the design of the hopper, firstly the density of the pellets is necessary. To calculate the density, the pellets are collected in Becher glass and weighed. According to its weight and volume, it is calculated. Then, the angles for good flow are tested with pellets and it is determined to be 45^{o}. The hopper is combination of conical and cylindrical shape. After height is calculated, the hopper is produced in the facilities. After manufacturing, it is mounted at the end of the pelletizer with valve for the separation of the pellets that are produced.

In the block diagram below, it can be seen entire continuous line. Feeder1 and feeder 2 is fed with API and Eudragit EPO as powders. They are fed to extruder and then continue to cooling track. The strand enters pelletizer to obtain pellets and sent to Feeder 3 and there it is blend with and premix from Feeder 4 and goes to Tableting machine to form tablet at desired qualities. The system is monitored with NIR at the end of the extruder and after blending step. Implementing control concepts allow to monitor quality of pellets and discharge the undesired

quality pellets and also after blending step, if the mixture has not desired level of concentration, again discharge of the powder will take a place.

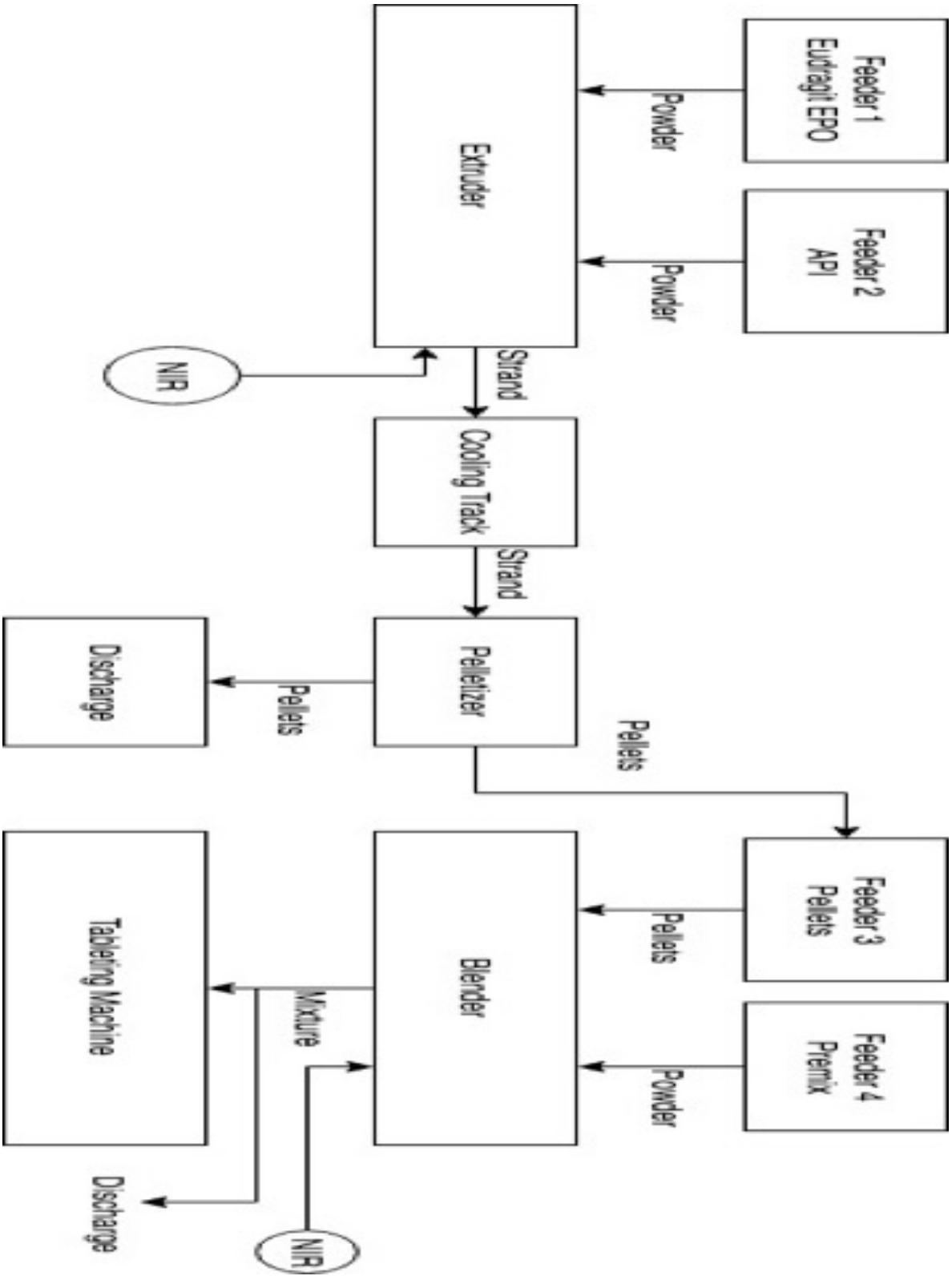

Figure 3:Block Diagram of the Complete Continuous Line

3.1 Materials

Continuous Line Experiments

API:

Vitamin B1 (Thiamine)

Polymer:

Eudragit EPO

Table 1:Extrusion Line

	Flow rate	Concentration
API Vit B1	0.8 kg/h	0.4
Eudragit EPO	1.2 kg/h	0.6
Total	2.0 kg/h	

Premix:

Avicel PH 102

Kollidon CL

Magnesium Stearate

Table 2:Premix for Continuous Line

	Percentage
Avicel PH 102	74,35%
Kollidon CL	24,40%
MgSt	1,25%
Total	100%

DC Line experiments

API:

Acetylsalicyclic acid (ASA)

Excipient:

Premix: Tabletttose70

Magnesium Stearate

Table 3:Premix for DC Line

	Percentage
Tablettose	99%
MgSt	1%
Total	100%

3.2 Line Devices

Feeders:

In the line, the feeder that is used for feeding matrix substance Eudragit EPO is a twin-screw loss-in-weight Coperian K-tron (Switzerland) feeder using a powder screw with small pitch size. The feeder for feeing API Vitamin B1 is also a twin-screw loos-in-weight Brabender (Germany) feeder for small feed rates and powder screws with large pitch. The both feeder is placed on the beginning of the barrels and conveys material into the same downpipe as shown Figure 4.

Figure 4:Feeders

Extruder:

Cooperion is an extruder with co-rotating twin screws. It is designed for continuous manufacturing pharmaceutical products in pharma industry. It can be used in lab scale, also can be used for continuous pharmaceutical production systems. [39]

In the extrusion process in the Master thesis, there are 11 barrels and die. The barrels have individual heating and cooling systems except the inlet barrel. The temperature and screw speed are set at the beginning of the process and it is set according to Table 4 below and they are kept constant throughout the experiments. The barrels 2,3 and 9 are kept open for venting. The torque is set to 200 1/min for the process.

Table 4:Temperature of barrels

Barrel	1	2	3	4	5	6	7	8	9	10	Die
^{o}C	22	70	110	115	115	115	115	115	115	115	110

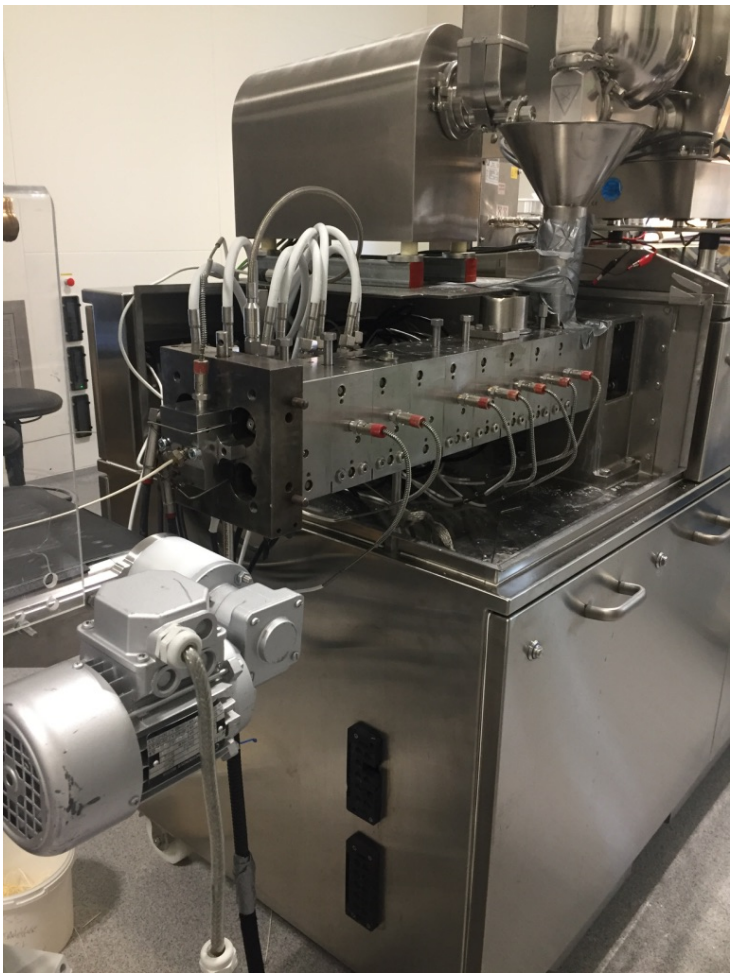

Figure 5:Extruder

Pelletizer:

Pelletizer are used for cutting the melted polymer to spherical, dry and easy to handle pellets.

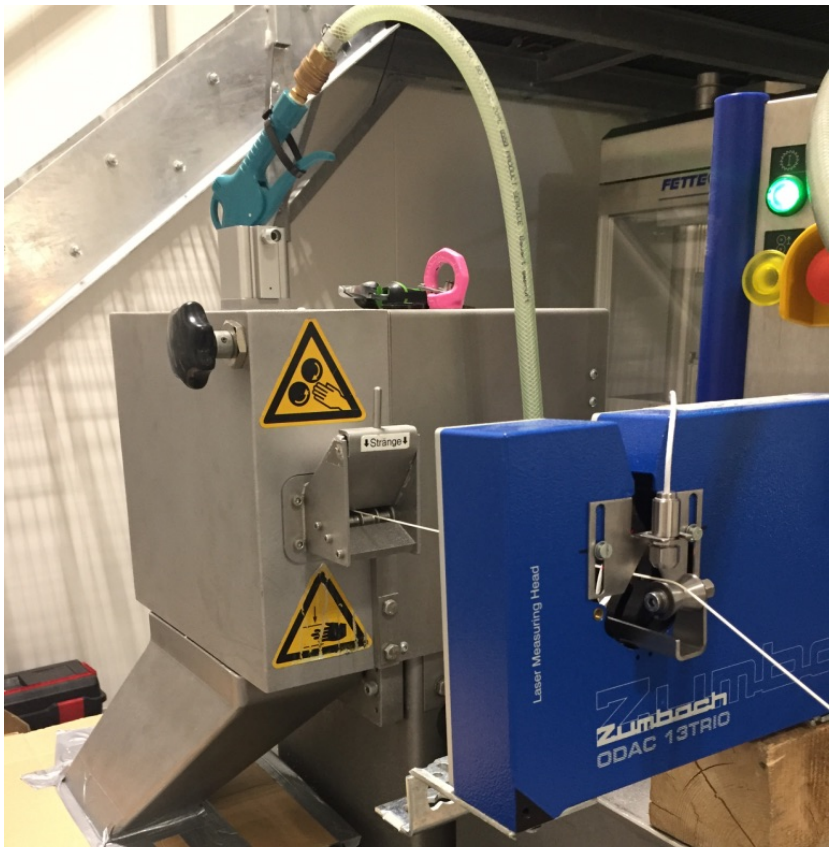

Figure 6:Pelletizer

Tableting Press (FETTE 102i):

Fette compacting 102 is a process-oriented laboratory scale tableting press that compacts with 8 pairs of punches. It can save all production data and used for clinical samples and small batches. It allows to direct scale-up and decrease the scale-up costs. It has wide range of applications.

Figure 7:Tableting Press

3.2.1 In-line Measurement Devices

ColVisTec:

ColVisTec is inline UV/Vis spectrophotometry-based that measures continuously the manufactured material directly in the process in real-time. Since it is inline measurement, there is no need for sampling and production line is not disturbed. This advantage increases the efficiency of the production and minimize the costs. It has many advantages such as continuous monitoring, no sampling, automated, minimization of errors, fast correction, early detection of dosage problems, etc.

Figure 8:ColVisTech Probe

Near-Infrared Spectroscopy (NIR):

NIR is one of the spectroscopic method that uses detection of molecular vibration method. It uses the near-infrared region of electromagnetic spectrum from 780 nm to 2500 nm. It can be used in many areas such as medical, pharmaceutical, food etc. The method is based on molecular overtone and combination vibrations. Even though NIR is not very sensitive techniques, it can be useful in probing bulk material without sample preparation. Since molecular overtone and combination bands are very complex, it is hard to determine specific chemical components. Therefore, multivariate calibration techniques are used to analyze the spectra to extract the desired information. It makes the application of multivariate calibration very important for NIR application.

Zumbach Odac 13Trio:

Zumbach Odac 13 Trio is on-line measurement device that measure the diameter. The device uses three axis and displays ovality, coverage, and diameter; also has flaw detection capabilities in one device. The Zumbach Odac 13 Trio uses 3-Axis laser measurement. The measurement with this model is obtained from three different viewpoints. These three axes are coplayer and placed 60 degree separately from each other. The measured material should be perpendicular to measurement field. To measure diameter, ovality and position of the product, the micrometer is used. [40]

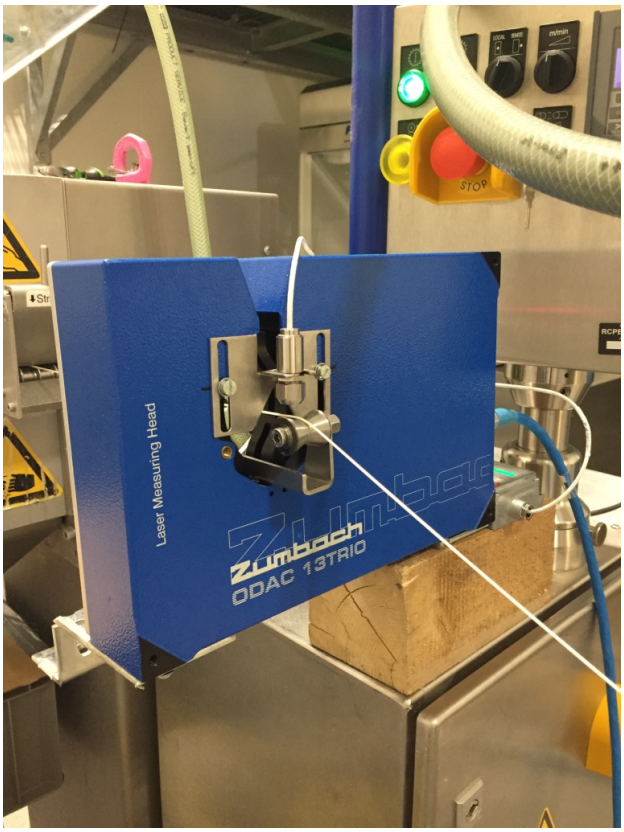

Figure 9:Diameter Scanner

Temperature sensor:

The temperature sensor is a device that allows to monitor and detect hotness and coolness and presents it as electrical signal. Temperature sensors in the test runs are on the barrels. Each barrel has its own temperature sensor and also at the die to detect the temperature changes on the barrels.

Pressure valve (Festo):

Festo VPPE is a pressure valve that controls the pressure proportionally to a desired setpoint value.

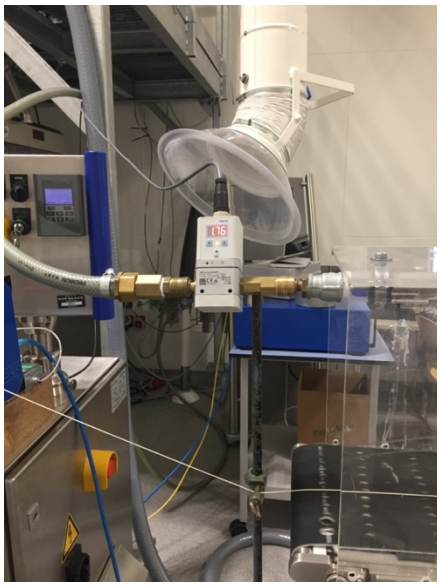

Figure 10:Pressure Sensor

3.2.2. Off-line Measurements Devices

UV/VIS Spectrophotometer:

UV/VIS spectroscopy is mainly used for quantitative analysis of the concentrations in the solutions of transition ions or conjugated organic compounds. It is generally used for solids. The basic principle behind the spectroscopy can be explained with Beer-Lambert Law. It is used with software in the connected computer.

Figure 11:UV/VIS Spectrophotometer

ERWEKA:

EWREKA combination hardness tester is designed to analyze properties of the tablets. It is fully automated and operates with MC.NET software. It can analyze large number of tablets. At the end of analysis, weight, diameter, hardness, length and thickness can be recorded. It is compatible with all pharmacopoeias. [41]

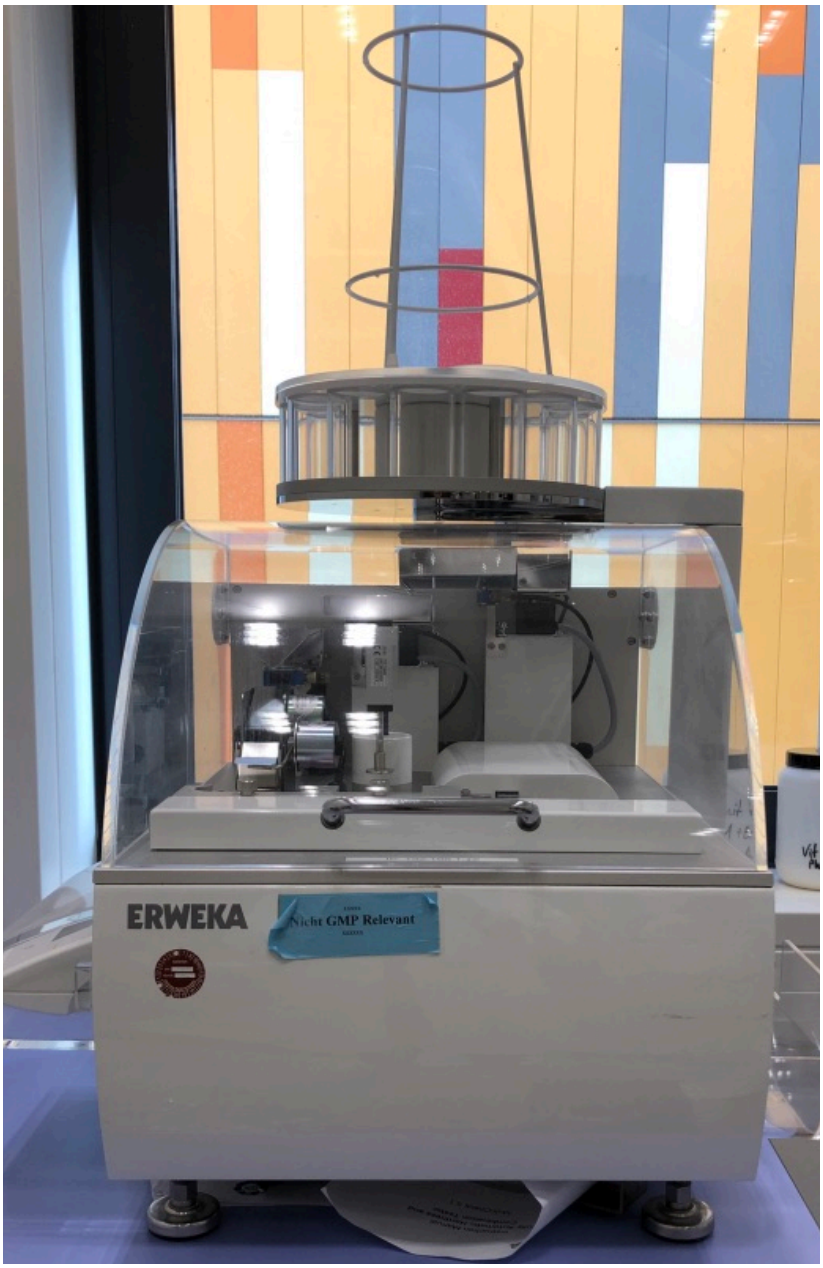

Figure 12:ERWEKA hardness tester

Sieving:

Sieving is a process to determine particle size of the material. In the project, sieving is performed to see is the desired number of pellets are in the mixture after blending step. As a size 355 µm is used.

3.3 In-line Measurements

3.3.1 RTD measurement

The experimental design begins with RTD measurement. RTD measurements are important since. To determine RTD, both NIR measurement and addition of color tracer are used. The experiments that are for RTD measurements are conducted with 3 test runs and start up experiment. The materials are fed as pure substances from two different feeders. The API percentage in the test runs are chosen to be 40%. The feeders are set to be 2 kg/h for the first 3 experiment and 3 kg/h for the last test run. In this test runs, iron dioxide is added as color tracer for the experiment. The tests run for 25 min except for the start-up experiment which runs for 15 min. The table below shows the planning of the test runs.

Table 5:Experimental Design for RTD measurements

Runs	**Total (kg/h)**	**Eudragit(kg/h) 60%**	**Vitamin B (kg/h) 40%**	**Time (min)**
Start up	2	1,2	0,8	15
1	2	1,2	0,8	25
2	2	1,2	0,8	25
3	3	1,8	1,2	25
Run time per run: 25 min			Total:	90

ColVisTec is the UV/VIS spectroscopy and firstly used for the concentration measurements in the test runs. ColVisTec is calibrated with black and white balances at the beginning of every experiment. Then, it is mounted at the end of the extruder, under the die and data is recorded. Since the melt is red because of Iron dioxide, the color is reflected different in the spectra and show the RTD. However, after analyzing of the data after several test runs, it is seen that the spectra interval is not appropriate for the material. Therefore, it is changed to NIR spectrometer. The calibration is done with white balance and the probe is mounted at the same place and test runs analysis is done according to NIR data in the SIMCA program. The data is pretreated and imported to SIMCA and *Principal Component Analysis* (PCA) is applied to data to identify RTD graphics of the spectra. Principal component analysis is a chemometric analysis method for spectral data analysis. It compresses the data and define the data as a

small number of principal components. SIMCA has many PCA models in the program itself. All the data from NIR is imported to SIMCA and the spectra interval is chosen according to color of the strand. Since it is colored with Iron Dioxide, the spectra interval for red is chosen and PCA analysis is performed between time and spectra. Furthermore, to observe better the RTD curve, three point from the beginning, peak point and at the end is selected. Spectra vs. absorbance graph of these three points is drawn.

Another in-line test is done for the control concepts modelling. The speed of the pelletizer is changed, and the strand is marked with marker. Then the time between the strand is entering the pelletizer and the colored pellets are stop coming from pelletizer is recorded. The experiment is repeated for 3 times for each change. The average and standard deviation and average of these data is calculated, and Box-Whisker diagram is drawn in Excel. The Table 6 below shows the recorded times at different speeds.

Table 6:Change in Pelletizer Speed and Time of Colored Pellets

Speed	Sample 1(sec)	Sample 2(sec)	Sample 3(sec)	Standard Deviation	Average
45%	9,55	8,6	8,54	0,57	8,90
57,50%	7,08	7,22	6,65	0,30	6,98
70%	6,67	6,74	5,67	0,60	6,36

The diagram below is the Box-Whisker diagram of the recorded times for 3 times repeated at the same speed of the pelletizer.

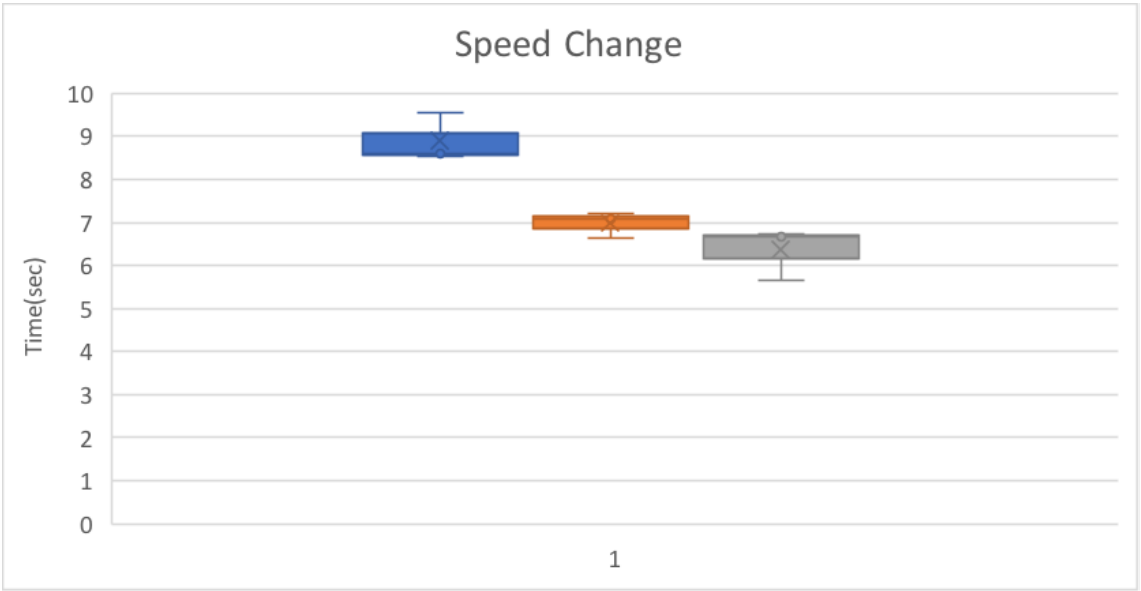

Figure 13:Box Diagram of the speed and times

3.3.2 Chemometric Model Development

The chemometric model is developed to predict API concentration from the data. The table below shows the calibration experiments for the chemometric model. The model is calibrated with the concentrations from the Table 7. The model can be created with the known API concentration and measured spectra data.

Table 7:Calibration Experiments for NIR

Experiment No	API (%)	Feeder API	Feeder EPO
1	30	0,60	1,40
2	34	0,68	1,32
3	37	0,74	1,26
4	40	0,80	1,20
5	43	0,86	1,14
6	46	0,92	1,08
7	50	1,00	1,00
8	40	0,80	1,20
9	30	0,60	1,40

Since the off-line samples are difficult to be used in the calibration of the model due to effect of sample presentation, melt properties and temperature, in-line experimental data is used for the calibration. For in-line experimental data, 9 different concentration for the API level is chosen. The data is computed with Principal Component Analysis at first to identify principal components of the observed data. Since the observed data is too many variables, PCA reduces to number of the variable by producing linear combination of the original variables, that can describe the variance in the original data.

3.4 Control Strategy

To be able to have automated line, the control concept should be developed and implemented. In this work, three situations are identified to experimented. The continuous line consists of two main line, extrusion line and direct compaction (DC) Line. The control concept is developed according to three scenarios. The first scenario is to make extrusion master and keep the set points of the feeders constant and changed the set points of the feeders of the DC line to observe changes. The second situation is to make DC line the master and the change set points of the feeders of the extrusion line and the last scenario is to make no master and make changes in the both lines. The control concept is done by the results according to experiments that are conducted by the research team. Model predictive control approach is used to develop the control strategy in order to achieve fully automated continuous tableting line.

3.5 Off-line measurements

The standards of the products of the continuous line, extrusion line and tableting line is also tested with off-lines samples. The different concentration of the API for the NIR calibration is also collected for the off-line analysis as pellets and strands. The tablets that produced as different speed in the tableting machine also are collected for testing. The tests are done to observe if the concentration of the API is really as desired and the tablets that are produced has the right concentration and standards in terms of weight, hardness, length and strength. Also, the results of the off-line tests are used for the reference measurement for the chemometric model development.

3.5.1 Off-line Tablets Analysis

As a part of control concepts, different speeds are tested for tableting machine and samples are collected in containers. The 13 containers of samples are collected for 5 minutes from different speeds of the tableting machine. Even though speeds are different, the concentration of the samples is expected to be 20% for each sample. To analyze concentration, UV/VIS spectrophotometer is used. 5 tablets from each sample are taken and weighed. They are placed in 500 ml flasks and dissolved in 0.1M HCl. Then, 4 ml of solution are taken from each flask and put into glass tubes and incubated for 20 min. Then the samples are poured into cuvette of the spectrophotometer and the absorption is measured at 760 nm. The

corresponding values are recorded, and the concentration is calculated according to these values. This procedure is applied to all 13 samples.

Also, tablet of 11 samples that are produced by the whole continuous line are tested for their weight, hardness, strength, length, and diameter. The ERWEKA analyzer is used for testing. 20 tablets from each sample are placed in the tester and results are recorded and compared with specifications of the tablets according to Pharmacopoeia.

3.5.2 Off-line pellet analysis

One of the control concept tests is to see if the level in feeders stays at set point even if there is change in the tableting line. To test this situation, the mixture with pellets with 40% API and premix that contains Avicel, Kollidon and MgSt are blend at the tableting line and collected in the containers at 20 different time intervals for 5 minutes. To test the weight percentage of pellets, the sieving is chosen as a test method. The chosen sieve tray is 355 μm. The bottom part and sieve with 355 μm is weighed and recorded. The sample is weighed with container. Then it is poured on the sieve and the bottom tray is weighed with fine powder. Also, empty container of sample is weighed and then it is weighed with pellets inside it again. The all this data is recorded. The weight of pellets in each sample are calculated. According to this data, percentage of pellets are calculated.

3.5.3 Analysis of NIR calibration blends for Vitamin B1 pellets

To create calibration line with Vitamin B1 in the tableting line, mixture of pellets and premix is used. Premix is prepared beforehand with Avicel, Kollidon and MgSt. The samples are prepared according to Table 8 below. The Vitamin B1 pellets includes 40% of API are chosen for the experiment. The samples are filled with desired amount of both Vitamin B1 and premix and mixed in Turbula mixer for 10 min at 700 rpm.

Table 8: Concentrations of calibration blends with Vitamin B1 pellets

Sample No	VitaminB1 Pellets(g)	Premix(g)	API (%)
1	20	80	8
2	28	72	11,2
3	33	67	13,2
4	37	63	14,8
5	40	60	16
6	43	57	17,2
7	47	53	18,8
8	52	48	20,8
9	60	40	24
10	40	60	26
Sum	400	600	

The samples are measured with NIR. The samples are poured through NIR and data recorded to be used in the calibration line that leads to develop the chemometric model.

3.5.4 Analysis of Strands with Different API concentration

The extrusion line and control concept are tested to observe if the different concentration inputs of API produce the strands with the desired concentrations or not. To test this situation, the strands with different concentrations of API are produced in the extrusion line. The strands hat the same different concentration as Table 7 above. The experiment is conducted with the same procedure for each concentration. The experiments are carried out for 11 minutes. At the beginning, the line is run for 8 min and the samples of the pellets are collected from 8^{th} min to 11^{th} min. These samples are milled with planetary ball mill for 5 minutes at 700 rpm and are split into half and one half is sent to Merck for the analysis of the concentration of the API in the polymer. The other half is melted and then cooled. Then the samples are melted again, and the concentration of the samples is measured with NIR again to determine to API content.

4.Results and Discussion

In this section, the results of the experiments are explained. In-line measurement includes the data process of the NIR in the different experiments and development of control concept for the whole line to control if there is change in the system and the system can still work properly. Off-line testing is done to tablets, pellets and strands to support the results of the NIR data. Also, the results are interpreted in this section.

4.1 In-line Measurement

4.1.1 NIR Measurements

The data that are obtained by NIR is used to develop the chemometric model for the API prediction for the continuous production line. To create the model, the data is evaluated by SIMCA. The data is used to define Residence Time Distribution (RTD) of the melt. Since there are too many variables to evaluate the data, Multivariate Data Analysis is used. Principal Component Analysis (PCA) is applied to data from the test runs. The principal components are identified, and curves are drawn to distinguish RTD curve of the melt. Since Iron dioxide is used, the interval for the red is chosen from the spectra. Residence Time Distribution also evaluated by MATLAB by the research team.

Figure 14:RTD curve of the melt

The Figure 15 above shows the NIR data analysis in SIMCA with PCA analysis. The iron dioxide is used as color tracer to determine the RTD of the melt. Since it paints the melt red, range of 590-650 nm is chosen for the analysis from the NIR data. The peak point is where the red color is seen by the NIR and then again going down because the color of the melt turns to white again.

4.1.2 Chemometric Model Development

The data that is obtained from the calibration experiments are evaluated in SIMCA. After the data is evaluated by Principal component analysis, Partial Least Square (PLS) method is used to create chemometric model to predict API concentration in the line. The developing of the chemometric model is done by the research team.

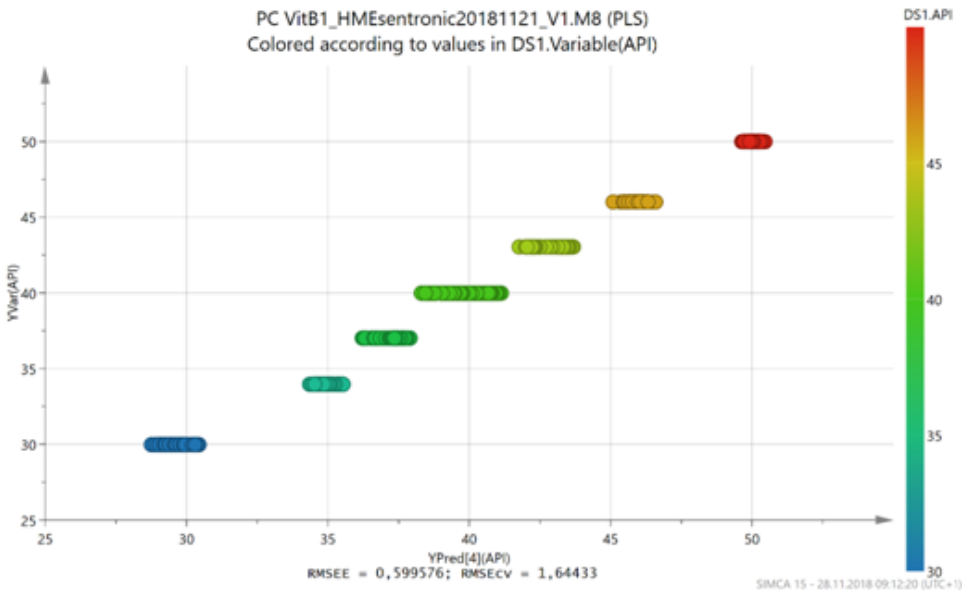

Figure 15:API prediction chemometric model

The Figure above shows the chemometric model with PLS analysis from the data NIR. In the graph, the x-axis shows the predict values and y-axis is the actual API content. According to Figure, it can be seen that the model can predict the API content very closely and works properly.

4.1.3 Result and Discussion of Control Experiments

The control experiments and simulations were conducted by the research team. The diagrams below show on whole line with keeping extrusion line master.

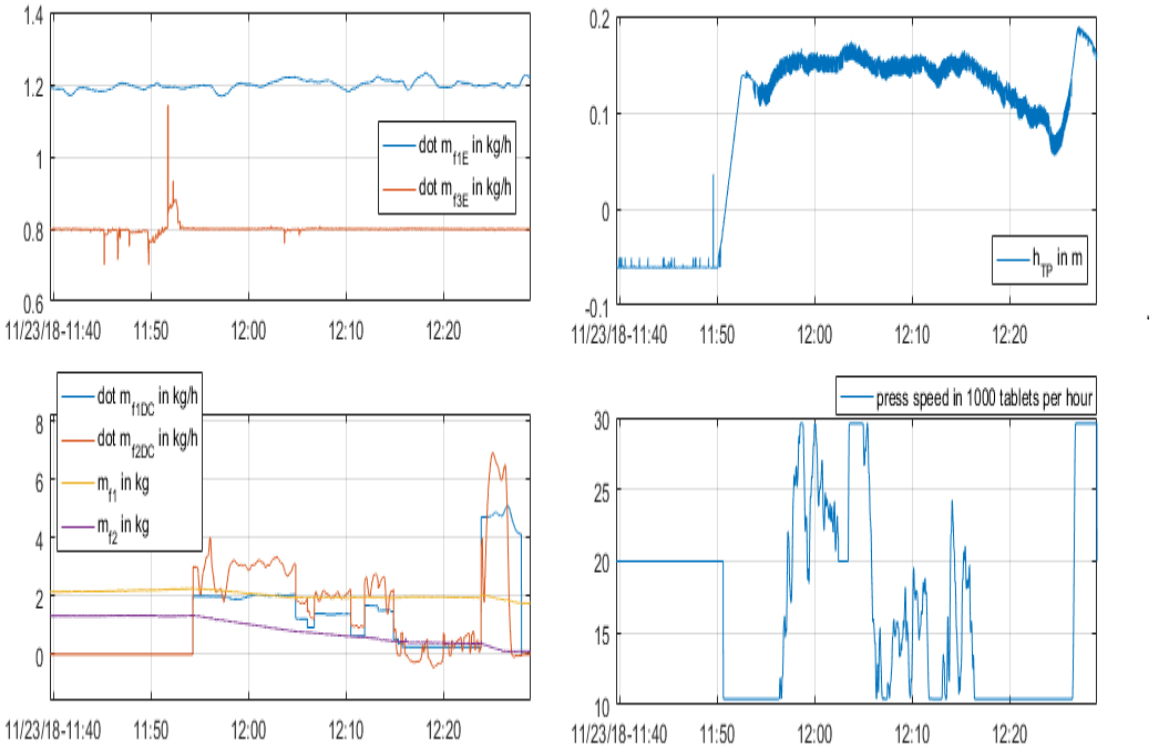

Figure 16:Control Experiment results of the entire line

The diagram placed at the left top corner shows the mass flow of the materials (the blue line for polymer and orange line for API) in the extrusion line, the top right diagram is the hopper level in the DC Line. The diagrams on the bottom are mass flow and mass hold up of the materials (blue line is for pellets, orange line for premix, purple line for mass of premix in the feeder hopper and yellow line for mass of the pellets in the feeder hopper) in DC Line (left) and tablet press speed (right).

According to control concept that is tried, the extrusion line was the master and therefore, the material level was set to 1.2 kg/h and 0.8 kg/h and kept constant. The pellets that are produced in the extrusion line were sent to DC Line. The bottom left diagram shows the mass flow changes in the DC line. For the premix and the pellets a sudden increase can be seen in the diagram. According to this change the material level is decreases since there is no material adding to premix, on the other hand, the material level for pellets is not changing as much due

to constant feeding from the extrusion line. After the process start, hopper under the feeders of the DC line starts to fill. When the set point of 0.15 m is reached it starts to keep constant to control tablet quality. The fluctuations at the hopper can be caused from the noises but still have a constant profile. After the mass flow is reached at the zero at the DC line, another change in the DC Line was done at around 12:25 and mass flow of the pellets are set to increase accordingly. The change again can be seen at the hopper level diagram around the same time. The hopper level diagram changes can be used to explain the diagram at the bottom right. The tablet press speed went to zero to wait for level of the hopper to its set point. After it reached its level, the tablet press speed increases and produces the tablets at the same quality.

4.2 Off-line Measurement

4.2.1 Off-line Pellet Measurement

Pellets were produced with Hot Melt Extrusion to have 40% API in them and premix are mixed in the tableting line. The samples are collected after blending step at specified seconds that are shown in the Table 11 below. The samples are expected to have 40% pellets in weight. The samples were analyzed with sieving. The data was recorded and the percentage of the pellets in each sample was calculated. The table below shows the results for each sample. The sieving tray was 355 μm.

Table 9:Sieving Results of the Pellets

Sample (second)	Total weight(g)	Empty container(g)	Pellets with container(g)	Pellets (g)	Weight of Samples(g)	%of pellets
0	22,1746	13,3095	15,8292	2,5197	8,8651	28,42
5	20,2338	12,9066	15,0026	2,096	7,3272	28,61
10	26,0793	13,2436	16,5831	3,3395	12,8357	26,02
15	21,099	13,1226	15,1576	2,035	7,9764	25,51
20	19,2599	12,8845	14,4773	1,5928	6,3754	24,98
25	20,4001	13,1227	14,8461	1,7234	7,2774	23,68
30	20,6961	13,1579	14,99	1,8321	7,5382	24,30
35	19,0341	12,96	14,4252	1,4652	6,0741	24,12
40	19,8864	12,9486	14,7055	1,7569	6,9378	25,32
45	19,0028	12,9564	14,4547	1,4983	6,0464	24,78
50	22,3818	13,0354	15,3068	2,2714	9,3464	24,30
60	22,3888	13,1038	15,4481	2,3443	9,285	25,25
70	21,7068	13,2395	15,3363	2,0968	8,4673	24,76
80	24,9498	13,1872	15,8985	2,7113	11,7626	23,05
90	27,1399	13,2984	16,6487	3,3503	13,8415	24,20
120	25,6534	13,1747	16,0902	2,9155	12,4787	23,36
150	21,3258	13,1429	15,0126	1,8697	8,1829	22,85
180	19,6731	13,1687	14,6404	1,4717	6,5044	22,63
240	20,3012	13,2675	14,9249	1,6574	7,0337	23,56
300	21,7	13,201	15,1646	1,9636	8,499	23,10

This experiment is conducted to given supportive result to NIR measurement at the DC Line to develop chemometric model. The table shows the percentage of the pellets in each sample. Even though it is expected to have 40% pellets in each sample, the sieving experiments showed that the content of the API in the samples are less 30% for each sample. WHY?

4.2.2 Off-line Tablet Testing

A total of 65 tablets with ASA and Tablettose 70 are analyzed in order to calculate their API content with spectrophotometer. The tablets are supposed to have 20% API in them. The solutions are 1/5 diluted. The spectrum is chosen 760 nm. According to calculations of the experiment, the concentration should be in the 20% range with ±5%.

According to results of the spectrophotometer, the tablets are in acceptable range. Therefore, it can be said that the tablets that are produced in the tableting line are met the specification, even there is change in the speed of the tableting machine. Therefore, it can be said that the system is controlled and response to changes very fast to keep tablets within specifications.

Not only the tablet from DC Line is tested, but also tablets that produced from entire line is examined. These tablets are tested if they meet the physical parameters according to pharmacopoeia. The whole line tablets that are produced in complete line are tested for their weight, hardness, strength, length, and diameter. The 20 tablets form 11 different batch is tested. The data is recorded on the software. The software provides a data for all the tablet for each sample. These values are individually evaluated, and mean values are calculated. The tablets are produced at different speed of the tablet presser to control if the tablets can be produced uniformly and, in the specification, even there is change in the line during the process. Therefore, the tablets are expected to meet certain parameters. The table below shows the results of the hardness tester. The mean values are calculated for all the parameter and for each sample. As shown in the table 10, the mean values for each parameter are close to each other in every samples. Also, the values are in the range for the uncoated tablets according to International Pharmacopoeia [42].

Table 10:The Mean values of the Samples

Probe No	Time	Mean Weight(mg)	Thickness(mm)	Diameter(mm)	Crushing strength(N)
1	14:38:57	242,6	3,38	8,18	79
2	14:41:00	243,5	3,41	7,95	77
3	14:43:00	243,4	3,4	8,12	84
4	14:44:15	243,9	3,39	8,07	93
5	14:47:00	242,7	3,4	8,02	85
6	14:50:00	243,6	3,4	8,04	83
7	14:51:30	242,7	3,4	7,98	80
8	15:01:30	242,4	3,39	7,95	79
9	15:05:03	242,7	3,4	8,03	85
10	15:07:24	243,3	3,39	8,09	80
11	15:12:00	242,6	3,39	8,08	86

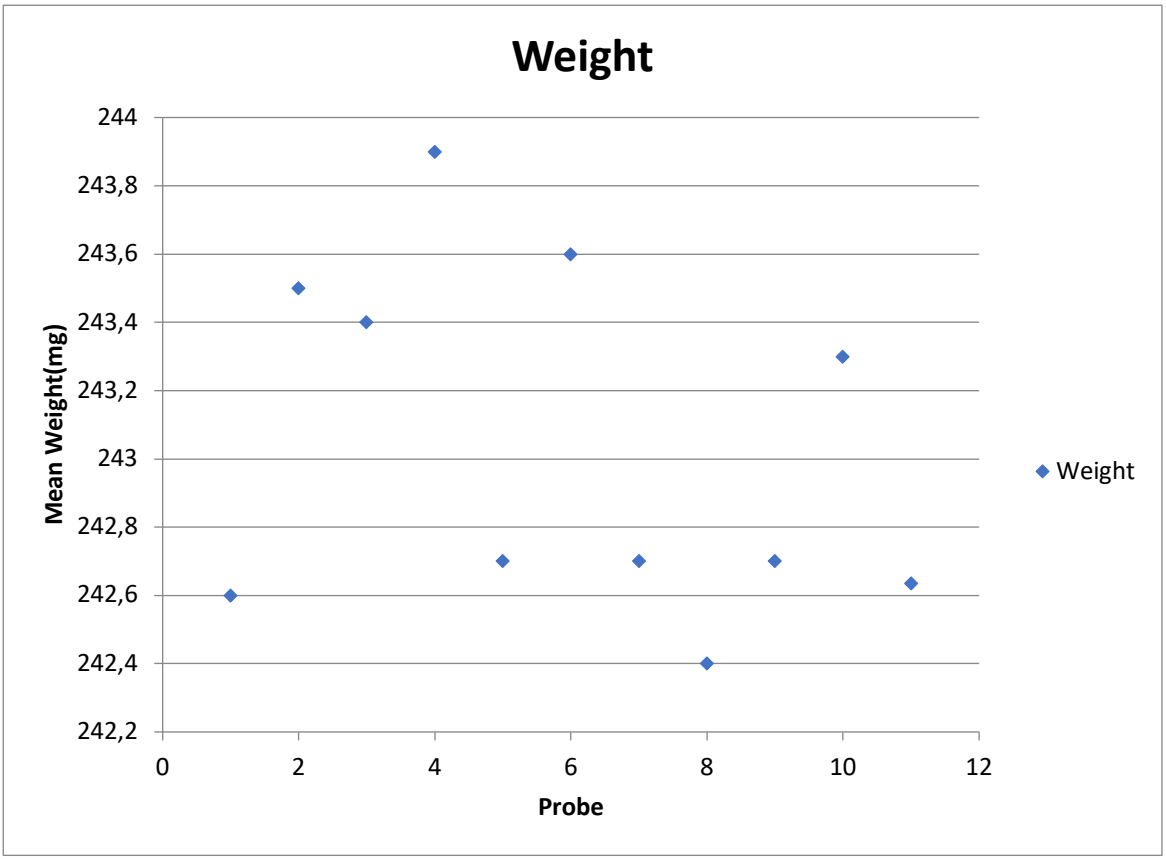

Figure 17:Mean weight values of the samples

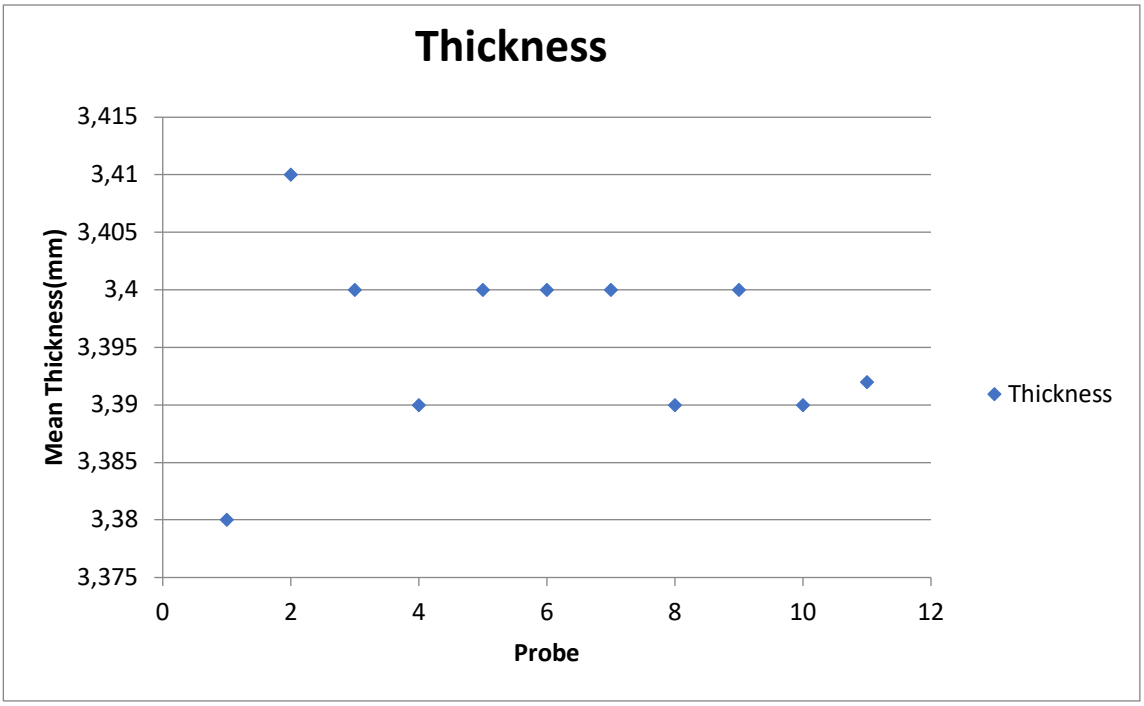

Figure 18:Mean Thickness values of the Samples

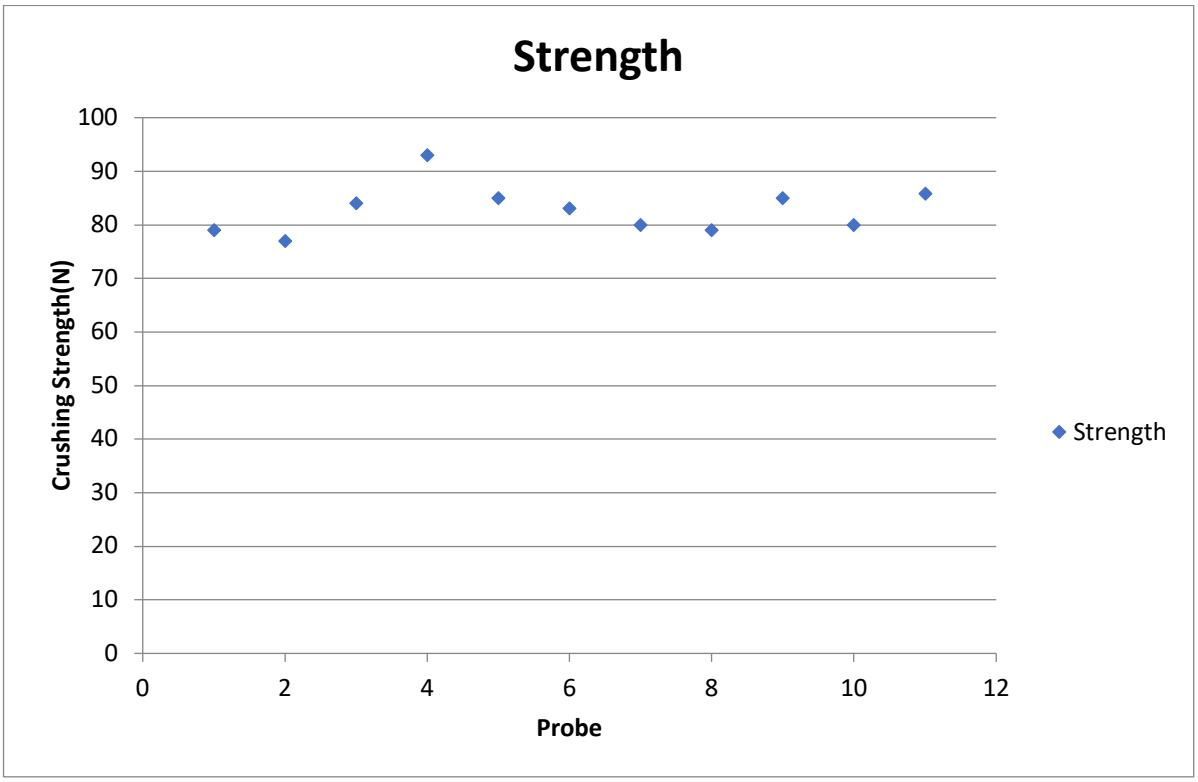

Figure 19:Mean Strength of the Samples

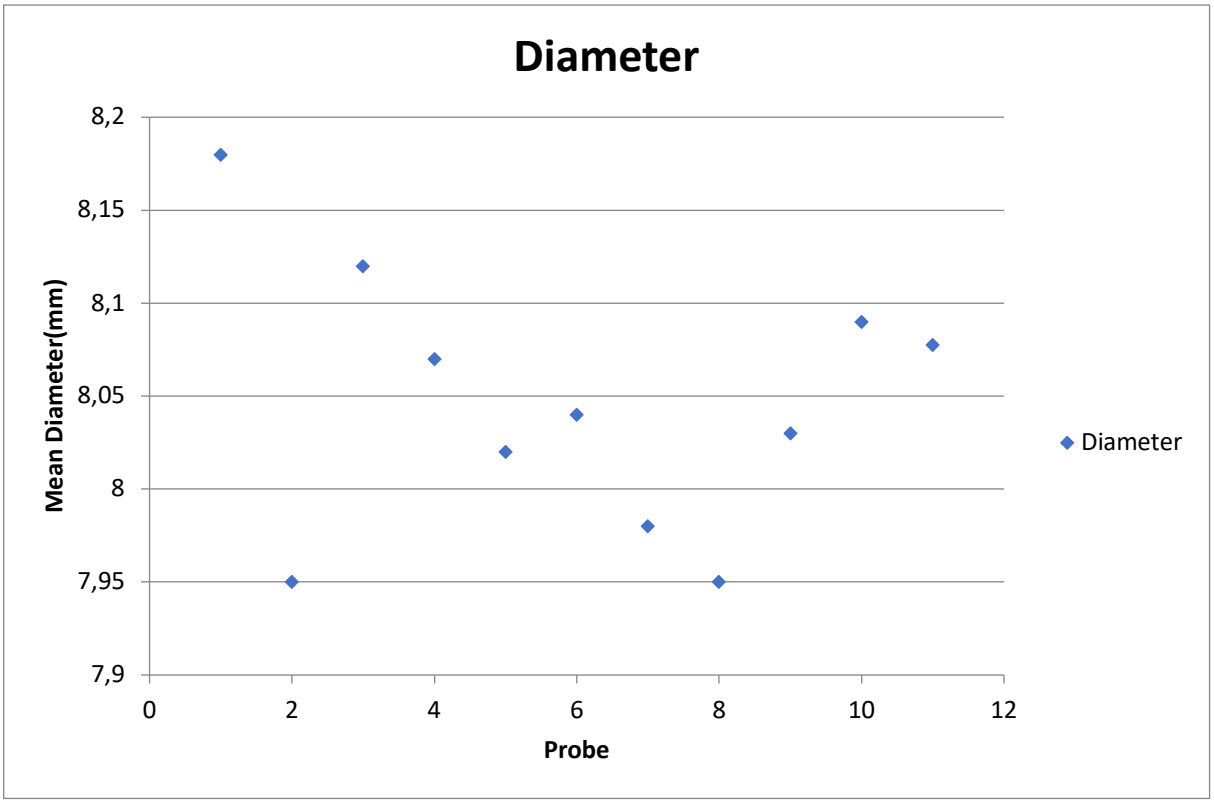

Figure 20:Mean Diameter of the Samples

The Figure 16,17,18,19,20 show the mean value representation for each sample. It can be interpreted as the mean values are very close to each other in each sample, this shows the uniformity of the tablets. Therefore, it can be said that a change in the line is not affect the end-product quality due to PAT. Also, the values are in the right range according to pharmacopoeia so that it can be said that the process is controlled properly and can maintain the product quality. All tablets are in the expected range; therefore, it can be said that the control concept works.

4.2.3 Analysis of Vitamin B1 Strands

The strands from calibration run for NIR are collected and they were milled at planetary ball mill and the samples were divided into two halves. The one set of samples were sent to Merck and analyzed with HPLC in order to determine if their API content is at the desired level. The table below shows the results of HPLC at Merck. The other half of the samples are melted and cooled to create solid one piece for each sample and then melted again and NIR was used to determine the concentration of the NIR. This part is performed by the research team.

Table 11: Results of HPLC Experiment

Sample name	Result
V1_Vit B1 30%	24,685 %
V2_Vit B1 34%	33,572 %
V3_Vit B1 37%	37,026 %
V4_Vit B1 40%	39,410 %
V5_Vit B1 43%	37,653 %
V6_Vit B1 46%	42,419 %
V7_Vit B1 50%	46,652 %
V8_Vit B1 40%	37,505 %
V9_Vit B1 30%	24,161 %
tablets	34,428 mg/tablet

According to the Table above, it can be seen that the content of the API in the samples from the calibration experiments and even though there are samples with the less concentration of the API than they should have, most of the samples have the concentration of the API as desired level by being produced in Hot Melt Extrusion. This experiments also contributes to support NIR results and develop the chemometric model. The other half of the samples also give good results in terms of concentration of the API.

6.Summary and Conclusions

In this thesis, it was investigated how to install the hot melt extrusion as pelletization step and control the whole continuous line to keep the quality of the products constant. In order to find this, in-line and off-line experiments are conducted. As in-line measurement devices NIR and sensors for both temperature and pressure is selected. For off-line measurements, tablets, pellets and strands are tested to prove the quality of the products.

The in-line measurements were done by NIR and the data from NIR was evaluated by SIMCA for the Residence Time Distribution of the melt that is produced by Hot Melt Extrusion and development of the chemometric model for API prediction in the continuous production line. The *Multivariate Data Analysis* was applied to NIR data and Principal Component Analysis method was used to obtain Residence Time Distribution. The control concept is simulated to create feed-forward control in the whole system to ensure end product quality in case of a problem in the steps of the continuous line. The system is considered as two main lines: extrusion and tableting line. The experiments were conducted to observe the changes in the system if the main part is extrusion line, tableting line or no main part at all.

The off-line tests were studied by using various instruments such as UV/VIS spectrophotometer, ERWEKA tablet analyzer, planetary ball mill and sieving. The aim of off-line tests was to provide supportive information about the products that were produced in extrusion line or tableting line or the whole line. It was observed that the information gives strong support to in-line measurements and the continuous line is controlled and respond to changes in time to protect the quality of the end-product.

The main aim of this thesis was to obtain automated continuous tableting line with using HME as granulating step. The experiments were conducted to observe the responses of the line to any problem that may occur in the system and fix it without and affecting the end product quality. The in-line and off-line measurements showed that the line had promising results for the automated continuous manufacturing in the pharma industry.

PAT is used to control the continuous system and the results can be used to develop the automated continuous system. In this work, only the control concept that is the extruder is master is experimented and it seen that the concept is working, and the product can keep the same quality even with a disturbance in the system. The chemometric model to predict API works with control concept. This control concept can be enhanced more stable, robust and also less out-of-spec material automated production.

Furthermore, the study can be done with other control concept which is the tablet pressing is the master or no master at all and results can be compared to develop stable and automated continuous systems. Moreover, by integrating this concepts and PAT in the industrial application, the pharmaceutical production can be turned to long term production. With this approach, the production can be continuous and material quality can be assured.

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