Bernhard Wagner, M.Sc.

Process development on a continuous production system for direct filling of hard gelatin capsules

DOCTORAL THESIS

to achieve the university degree of
“Doktor der technischen Wissenschaften”
submitted to

Graz University of Technology

Supervisor

Univ.-Prof. Dipl.-Ing. Dr. techn. Johannes G. Khinast
Institute for Process and Particle Engineering, University of Technology, Graz

Dr. Thomas Brinz
Robert Bosch Packaging Technology GmbH, Waiblingen

Graz, August 2019

First assessor and supervisor

Univ.-Prof. Dipl.-Ing. Dr. techn. Johannes G. Khinast

Institute for Process and Particle Engineering, University of Technology, Graz

Research Center Pharmaceutical Engineering GmbH, Graz

Second assessor

Univ.-Prof. Dr. Dr.h.c. Stanko Srčič, M.Sc. Pharm.

Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Ljubljana

EIDESSTATTLICHE ERKLÄRUNG

Ich erkläre an Eides statt, dass ich die vorliegende Arbeit selbstständig verfasst, andere als die angegebenen Quellen/Hilfsmittel nicht benutzt, und die den benutzten Quellen wörtlich und inhaltlich entnommenen Stellen als solche kenntlich gemacht habe. Das in TUGRAZonline hochgeladene Textdokument ist mit der vorliegenden Dissertation identisch.

....

Datum Unterschrift

„Ich kann freilich nicht sagen, ob es besser werden wird wenn es anders wird; aber so viel kann ich sagen, es muss anders werden, wenn es gut werden soll.“

Georg Christoph Lichtenberg

Acknowledgements

An erster Stelle möchte ich mich bei Prof. Johannes Khinast bedanken. Er ermöglichte es mir, diese Arbeit an der Doctoral School zu verfassen. Besonders schätzte ich seine Unterstützung, Führung in der Wissenschaft, Erfahrung in der pharmazeutischen Prozesstechnik, sowie seine Geduld und Offenheit gegenüber den vorgebrachten Entwürfen und Ideen.

Ein besonderer Dank gilt Dr. Thomas Brinz von der Firma Bosch. Er übernahm die Betreuung dieser Arbeit, stützte und förderte sie. Danke für die vielen wertvollen Diskussionen, Besprechungen und Anregungen. Hierbei habe ich viel gelernt.

Vor allem die Kollegen Gerhard Schultz, Philipp Stirm und Sebastian Rühle standen mir zur Seite, wenn es um den Prozess des Kapselfüllens ging. Stephanie Otterbach möchte ich für ihre Unterstützung im Bereich Pharmatechnik und für ihre Beiträge bei der Untersuchung und Charakterisierung von Materialeigenschaften danken. Mein Dank gilt Stefan Manz, der mich in der Diskussion oft auf neue Ideen und Ansätze gebracht hat. Danke an das gesamte Team, das es mir ermöglichte, die Zeit in einer sehr angenehmen und positiven Arbeitsumgebung zu verbringen. Dank gilt auch den Kollegen aus der Entwicklung. Hier unterstützten mich die Kollegen Werner Runft, Martin Sigle, Martin Vogt und Jens Schlipf im besonderen Maße, sei es bezüglich Hardware, Software oder Prozessthemen. Außerdem möchte ich mich bei den vielen weiteren Kollegen bedanken, die ich hier aus Platzgründen nicht alle aufführen kann. Darüber hinaus der Firma Bosch, die diese Arbeit ermöglicht und finanziert hat.

Ein Dankeschön den Studenten, die ich während dieser Zeit betreut habe und die mit ihrer Arbeit dazu beigetragen haben dieses Thema voranzutreiben.

Einen indirekten, aber wichtigen Beitrag haben meine Freunde bei dieser Arbeit geleistet. Danke für jedes offene Ohr, die Abwechslung und Motivation, die ihr mir gegeben habt.

Zu guter Letzt möchte ich mich bei meiner Familie bedanken. Ohne eure Unterstützung, euren Rückhalt und eure Ermutigung wäre diese Arbeit nicht möglich gewesen. Vielen Dank.

Abstract

The process development of a continuous system can be a challenging task. *Quality by Design* demands an overall understanding of the process. This is challenging because there are many effects and interactions which can influence the process. In order to investigate development methods and to find a development strategy, this thesis explored a continuous production system for hard gelatin capsules.

The first step explored the automation of a capsule filler. Using an automated capsule filler makes it possible to adjust the process parameters quickly. Along with the automation, a modified control loop was applied to the powder bed height, which allowed a precise control of the same. This led to stable output, even when a small powder bed height was used. A transfer force sensor helped to enhance the machine safety. This investigation showed that the capsule filler could be fully automated. Thus, when the capsule filler is integrated in the continuous process, every critical process parameter could be adjusted or controlled.

The rapid automated process development was introduced in the second step. This innovative technique uses most widely automated process parameters and automated measurement of the target quality attributes. In combination with statistical optimized experiments a process model is generated. This technique was successfully applied to the continuous capsule filling system. The created model allowed the investigation of the process. Effects and interactions were documented and got transparent. The process was understood as a whole. Coincidently, it was developed in a very short time (two days). The formulation composition was optimized as well as the process parameters. In consequence, an option of how to develop a continuous process efficiently was presented.

Content and content uniformity are important targets when a dosage form is produced. By the help of an X-ray system, the benefits of an online content measurement were revealed when used in the combination with the rapid automated process development. With the help of an online content measurement, it was possible to understand and to optimize the process in an enhanced way. The model showed that the standard deviation of the mean weight and the content uniformity had different optimization goals. Therefore, including the content measurement into the rapid automated process development is a valuable opportunity.

Moreover, the control of the capsule weight was investigated in the last chapter. By controlling the capsule weight, it is possible to correct the amount of active pharmaceutical ingredient content inside the capsule. Hence, the capsule weight control is an important control instrument. Different process parameters of the capsule filler can be used to control the weight. The parameters of the controller, however, have to match the specific material. An experiment

showed that unmatched process parameters lead to a bad behaviour of the weight control. With the models generated by the rapid automated process development, the controller parameters were successfully established. Therefore, a very efficient method was presented to develop a control for a continuous process.

This thesis presents new methods and procedures. Valuable data was generated by experiments, executed by a capsule filler integrated into continuous production system. It helps to face challenges in the process development and to implement capsule filling into continuous manufacturing.

Abstract (German)

Die Prozessentwicklung für eine kontinuierlich produzierende Anlage ist eine anspruchsvolle Aufgabe. Der Ansatz *Quality by Design* verlangt ein umfassendes Prozessverständnis. Dies zu erfüllen ist eine Herausforderung, weil es viele Effekte und Wechselwirkungen gibt, die den Prozess beeinflussen können. Um Methoden für eine Prozessentwicklung zu erforschen und um eine Prozessentwicklungsstrategie zu entwickeln, wurde in dieser Arbeit ein System zur kontinuierlichen Produktion von Hartgelatinekapseln untersucht.

Im ersten Schritt wurde die Automatisierung eines Kapselfüllers untersucht. Mit Hilfe eines automatisierten Kapselfüllers ist es möglich die Prozessparameter schnell einzustellen. Im Zuge der Automatisierung wurde eine angepasste Pulverbetthöhenregelung aufgebaut, welche eine genaue Einstellung des Pulverbetts ermöglicht. Dies führte zu einer stabilen Produktion selbst bei niedrigem Pulverbett. Ein Übergabekraftsensor erweiterte die Maschinensicherheit. Dementsprechend können nun alle kritischen Prozessparameter eingestellt oder geregelt werden, wenn der Kapselfüller in einem kontinuierlichen Prozess eingebunden ist.

Darauffolgend wurde die Methode der „schnellen automatischen Prozessentwicklung“ (Rapid Automated Process Development) eingeführt. Diese neuartige Technik verwendet weitestgehend automatisierte Prozessparameter und eine automatische Erfassung der Zielgrößen. In Verbindung mit statistisch optimierten Versuchen wird ein Prozessmodell erzeugt. Diese Technik wurde erfolgreich auf das Kapselfüllsystem übertragen. Das erstellte Modell erlaubte eine Untersuchung des Prozesses. Effekte und Wechselwirkungen wurden erkannt und aufgezeichnet. Der Prozess wurde im Ganzen verstanden. Gleichzeitig wurde der Prozess in sehr kurzer Zeit entwickelt (zwei Tage). Sowohl die Formulierung als auch die Prozessparameter wurden optimiert. Folglich wurde eine Möglichkeit vorgestellt, wie man effizient einen kontinuierlichen Prozess entwickeln kann.

Der Wirkstoffgehalt und die Gleichförmigkeit des Wirkstoffgehalts sind bei der Entwicklung eines Medikaments entscheidend. Anhand eines Röntgensystems wurden die Vorteile einer Online-Gehaltsbestimmung aufgezeigt, wenn sie mit der schnellen automatisierten Prozessinbetriebnahme verbunden ist. Mit Hilfe der Gehaltsbestimmung war es möglich, den Prozess noch besser zu verstehen und weiter zu optimieren. Das Prozessmodell zeigte, dass die Standardabweichung des mittleren dosierten Gewichts und die Gleichförmigkeit des Wirkstoffs unterschiedliche Optimierungsziele hatten. In Folge dessen ist die Gehaltsbestimmung eine wertvolle Option, wenn sie in Kombination mit der schnellen automatischen Prozessinbetriebnahme eingesetzt wird.

Weiterführend wurde die Regelung des Kapselfüllgewichts im letzten Kapitel untersucht. Durch die Regelung des Kapselfüllgewichts ist es möglich, die Wirkstoffmenge in der Kapsel zu korrigieren. Aus diesem Grund ist die Regelung ein wichtiges Element in der kontinuierlichen Produktion. Unterschiedliche Prozessparameter können dazu verwendet werden, das Füllgewicht zu verändern. Die Parameter des Reglers müssen jedoch dem jeweiligen Material angepasst werden. In einem Beispiel wurde untersucht was passiert, wenn die Regelparameter nicht dem Produkt angepasst sind. Das Ergebnis war eine schlechte Regelung des Gewichts. Mithilfe der erstellten Prozessmodelle konnten die Regelparameter auf das jeweilige Produkt angepasst werden. Dadurch entstand eine sehr effiziente Methode, wie die Regelung für kontinuierliche Prozesse entwickelt werden kann.

Diese Arbeit präsentiert neue Methoden und Vorgehensweisen. Mit Versuchen auf dem Kapselfüller, eingebunden in die kontinuierliche Produktion, wurden wertvolle Daten erzeugt. Dies hilft dabei den Herausforderungen in der Prozessentwicklung zu begegnen und schlussendlich den Kapselfüller erfolgreich in die kontinuierliche Produktion zu integrieren.

Table of Contents

1 Introduction and Motivation

The world population is constantly growing [1] and thus more and more people must be supplied with medical care and drugs. At the same time the life expectancy of people is growing [2] and a variety of specialized drugs are needed to cure e.g. diseases of ageing. In consequence, the demands on the pharmaceutical industry are changing. Greater amounts of drugs must be produced quickly, while on the other hand, some very specialized drugs must be manufactured in small amounts. This requires a flexible production and development of pharmaceutical products. It is obvious that it is not sufficient to maintain on traditional technologies. It is important to search for new technologies which could improve research, development and manufacturing of pharmaceuticals.

One new technological approach can be found in the manufacturing structure of how drugs are produced. Traditionally a batch production [3] is commonly used in the pharmaceutical industry. Each process step is executed on its own and the quality is checked after each step. In contrast to this, other industries (e.g., chemical industry, biotechnological industry) are successfully using a different manufacturing structure: continuous manufacturing. The different process steps are connected and the product is produced in one step. This offers several advantages in terms of quality, efficiency and flexibility (Chapter 1.2.1). A change to this manufacturing has already started, but still, it is a new technology for the (pharmaceutical) industry and scientific work has to be done. Especially the process development differs from the classic batch process development and has to be investigated in particular.

1.1 Pharmaceutical Process Development

Pharmaceutical process development combines several different areas. Starting with the research and development of the active pharmaceutical ingredient (API), subsequent domains like manufacturing, quality assurance, regulatory affairs, are involved [4]. In the development of a new drug (after a new API is found), at some time, the final manufacturing process comes into view (e.g., in clinical phase 2 or 3 [5]). A dosage form that delivers the API to the patient in a secure and efficient way has to be chosen. The choice of a dosage form also means the choice of a certain production process because both are connected. One example: tablet and capsule. A tablet press requires a certain flowability and compactability and often pre-processes like, for example, a fluid bed granulation, are upstreamed [6]. For a capsule, a wider band of material attributes can be filled and less pre-processing is required [7]. Certainly, this is a simple example, but both dosage forms demand significantly different processes.

With regard to the process development, processes can influence the composition of the final drug. Most of the time it is not possible to use pure API to create the final dosage form; hence, a formulation is designed [8]. Beside the API, the formulation contains excipients which help to achieve the desired attributes. For example, one task of an excipient can be to dilute a high potent API to dose it accurately on a fast running machine. Another example concerns the dissolution of a tablet. Disintegrants help to break down tablets into small granules, which improve the dissolution profile. Lubricants like magnesium stearate can be used to enhance the processability on the production machines. Overall, when a different process is used, the composition of the drug is likely to change.

The development of the formulation and thus the design of the final process is however not a trivial task. The reason for that can be described with the aid of Figure 1. Here, the process is illustrated as a black box. It is called a black box, because before the process is finally developed (i.e., understood) it is unknown what is happening inside of it. The critical material attributes (CMA) and the critical process parameters (CPP) are given to the black box. Both, CMA and CPP, can be adjusted in the process development. They are called critical, because they have a significant influence on the critical quality attributes (CQA) which represent the quality attributes for the final produced drug. These are in a capsule filling process for example, the content uniformity, the mean capsule weight and the relative standard deviation (deviation of the capsule weight).

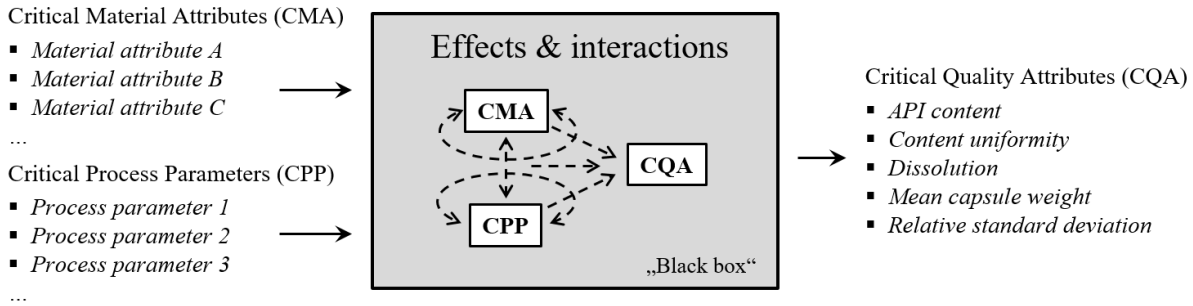

Figure 1: Black box of the process, with illustrated effects and interactions. The approach of Quality by Design: determine the effects and interactions.

The CMA can be adjusted in the development of the formulation. Some material attributes are, for example, particle size, moisture content, bulk density, dapped density or electrostatics. When the composition of the formulation is changed, the material attributes of the mixture change. Thus, it is possible to adjust the CMA of the mixture. In the view of the wide range of different excipients, there seem to be an endless number of possible combinations

of excipients to design a formulation. Like the CMA, the CPPs are adjustable within the process development. Examples for these parameters are the speed of the machine, powder level, or compression. The parameters must be matched to each specific formulation. Different formulations require different process parameters. With the adjustment, it is possible to optimize and to stabilize the production process.

Considering a process development, it is obviously difficult to understand and describe all the effects and interactions which occur between a wide range of possible material attributes and the process parameters. Inside the process (black box), the CMA and CPP effect the CQA. At the same time, there are interactions between the CMA and CPP. For example, if one material attribute is adjusted, the effect of a CPP on the CQA can change. If the flowability of a material changes, the effect of the machine speed might change. These possible interactions and effects are illustrated inside the black box (Figure 1) as dashed lines. To understand the process, it is vital to determine the effects and interactions inside the process. This has to be achieved for all different combinations of CPP and CMA.

In 2004, the food and drug administration (FDA) demanded an improvement of today's pharmaceutical production, Quality by Design (QbD) is stated as a key element [9]. In the ICH Q8 R2 [10], QbD is described as: "A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management". Obviously, the understanding of the process is an important part of QbD. A process is understood when all the effects on the process are determined, interactions are described and the outcome (product quality) is predictable. Consequently, the black box must be investigated. To investigate the black box can be a difficult task. First, most of the time, only the inputs and outputs are accessible. If this is the case, the content can be accessed only with external experiments. Experiments however require effort. Time is needed to execute the experiments and product is need to run the process. To achieve a good prediction quality it is important to use the same material as in the subsequent production process. Especially for new developed APIs this is a very costly option.

In summary, it is important to understand the process to implement QbD. This is getting more and more important for the process development. Authorities demand higher product quality. To achieve better quality, more systems and parameters, which could have an influence on the process, must be taken into account. New systems like continuous productions systems are used where the development process is yet not well established at all. In addition, drug development costs are getting more and more expensive [11]. Consequently, the process development must become more efficient. Efficient does not mean to minimize the executed

experiments, but rather to execute the “right” experiments with less effort. With an efficient process development, the final production process is improved. High product quality connected with less waste or losses due to out-of-spec batches is the result. The process development is an important part and an essential subject where scientific research needs to be carried out, especially for new production methods like continuous manufacturing.

1.2 Continuous Manufacturing

Today, continuous manufacturing is a well-known topic in the pharmaceutical industry. Several scientific publications, talks, and conferences illustrate the great opportunities of this topic. Irrespective of the common awareness, this chapter shortly introduces this topic, illustrates once more the benefits of the production method and states a challenge for the process development.

Continuous manufacturing represents the idea to produce drugs in a continuous operation. Typically, in the pharmaceutical industry, the production is batch-driven. That means every production step is executed on its own, tested for quality on its own and validated on its own. Looking at an exemplary tablet manufacturing process, the production consists of several small process steps: feeding (weighing of each component), blending, wet granulation, drying, milling, blending (external phase), compression and coating [12]. In a batch process, all process steps are executed one after the other. A continuous process combines all the steps to one single process. The handling of each separate batch (a certain amount of material, e.g., 50-500 kg) is no longer required. The final product is produced in one-step and after a certain time the desired amount is produced.

1.2.1 Advantages of Continuous Manufacturing

There are several advantages which can be achieved with continuous manufacturing ([13], [14] and [15]). To understand the reasons for the overall trend for continuous manufacturing, which are also the motivation of this work, some of the advantages are presented in the following. These advantages are stated in the view of a solid oral dosage form production, like a tablet or a capsule. The presented list of advantages does not claim completeness nor are the advantages generally applicable. The topic continuous manufacturing is still widely discussed.

Reduced footprint

In the view of the previously described tablet production process, it is obvious that a greater amount of space (i.e., pharmaceutical production environment) is needed for batch manufacturing than for continuous manufacturing. Each process step needs machinery, which

is set up in a certain location or space. The produced batches must be handled and stored between the process steps. After a process step is finished, the production of the batch is frozen until it is released. To release a batch it must be assured that the previously produced material is within the specification limits. With a switch to a continuous process all the floor space, handling equipment and stockpiling is not needed anymore. This can reduce the footprint up to 80 % [14].

Better product quality

A main driver for the continuous manufacturing approach is the quality improvement, which can be achieved for the final product. To run a continuous production line a prerequisite is that the process is well known and well designed. The process has to run at a stable set point. To ensure this, process analytical technology (PAT) is used. With sensors inside the process, like for example a particle size measurement, a moisture analysis or a content uniformity check, it is possible to measure the stability of the process at a certain point. Previously this has to be done offline or in dependency of time. This means that a mixing process should achieve a certain content uniformity after a defined time. In a continuous system, the production process is independent from the time; it is dependent on where the measurement point is set up in the process. Therefore, in a continuous system it is possible to measure inside the process more easily. This is a great opportunity, first in the development of the process, second in the controlling of the process. With the control option and a well-designed process, a greater product quality can be achieved. Waste of product should be minimized and the CQA stay accurately at a stable set point.

Real time release

In consequence, if a process is stable and the CPP and the CMA are known and controlled, it is possible to achieve a real time release. Of course, this is a very difficult and well-discussed point; however, the benefits would be impressive. The whole laboratory testing would decrease significantly. This is might reduce the laboratory cost for the product; a lot of laboratory work would be saved. If the whole product cost decreases, however, must be investigated. Often PAT are very expensive and must be operated and maintained by specialists. Nevertheless, the release of a batch would be tremendously faster than in a classic batch process. All the loss of time for testing and releasing each single batch would be saved and the product could be produced as fast as the market demands.

Benefits for the supply chain, decentralized manufacturing

With a fast release, it is possible to react on certain events, where fast and great amount of drugs are needed. If a pandemic disease occurs somewhere in the world, it is possible to produce great amounts of drugs in a short time. Continuous systems could release great amount of drugs quickly. With a small footprint, it is also possible to transfer whole production lines easily into certain countries or areas. This helps to provide drugs to people living in countries where an import of drugs is not feasible (due to laws and regulations) and the drugs could be produced locally.

Flexibility

The equipment for a batch production is normally designed for a certain batch size. Therefore, all the handling equipment and process steps have a certain size. In a continuous production, the size is not that important. An increase or decrease of the produced amount of drugs is possible, just by the change of the duration how long the continuous system is running.

No scale up

A great benefit: there is no real scale-up. Traditionally in a batch process, first small quantities of a formulation are produced. This is done on smaller equipment. For example on a 5 kg blender instead of a 500 kg blender. After a first formulation is developed, the process needs to be scaled up to the production scale. If now the same mixture composition and process parameters are used on the bigger equipment, a different output quality is likely the result. Then again, the formulation or the process parameters have to be adjusted, to achieve the same quality out of the process. This is a time and product consuming work, which needs a lot of technological experience. Moreover, even in some cases it is not possible to achieve the same result on the bigger scale equipment, just because the process behaves that differently. In comparison to this problem, developing a process on a continuous system is more or less independent from any scale-up problems. This is because for the development and for the final production the same size of equipment is used. Thus, the effects in the development and in the final production are the same. Thinking about the timeline of a drug development, this can also provide an advantage in the time-to-market. The process is faster developed, possible scale-up problems are bypassed and the final production process is faster established.

1.2.2 Challenges and Opportunities for the Process Development

Stating the benefit “no scale up” is only half the truth. Beside the benefit to develop the processes with nearly no scale-up issues, the continuous development is connected with higher effort, especially in the beginning. In general, when a new API is developed only view amount of API is available and it is highly expensive. Consequently, in a batch process first formulations are created in very small quantities.

A continuous system needs (at least in the beginning) a higher amount of API for developing the process than a minimized batch process. This can be very expensive. Nonetheless, at the end when it is developed, the continuous process can be better than a batch process. As already mentioned, for example, the control of the CQA is improved and waste of product is reduced to a minimum. Therefore, a continuous process can be cheaper and much more efficient than a batch production, yet the first development is more expensive.

Despite other topics like a PAT development, which includes the calibration of models and the control strategy, a continuous system is more complex than a simple batch process step. In a batch process step, there are only the CPP of this process step. A user can execute simple experiments to determine the influences of the CPP on the CQA. In a continuous system, all the process steps are connected together. The CPP can influence the final CQA while the process is running. With all steps combined, there is a great amount of parameters, which have to be adjusted at once. If the mixture composition is included, also the CMA of the mixture can be adjusted in the system. For an operator, it is complicated to understand and determine all the effects and interactions of this black box without any special tools. Obviously, this is a challenge.

Nevertheless, when the process is seen in the view of QbD, both production types have a similar amount of CPP and CMA. If the single process steps are the same, it is does not matter whether they are connected or not. In a theoretical example, where all process steps are the same (in reality they differ to a certain extent, e.g., a batch blender operates different from a continuous blender), they influence the final CQA on both systems in the same way. When something is changed, for example, in the granulation step, the result of the tablet press is likely to change when the compactability of the mixture changes. This is independent from the type of manufacturing system. For sure in a continuous process, the change will be noticed much faster as the whole process is running continuously. If there is a change in a batch process, it takes a long time until the influence of a changed granulation reaches the tablet press. Especially, if the granulation process is adjusted to its desired set point, no information is

available at all. It is unknown what influence the CPP change of the granulation has on the tableting process step.

Analyzing this theoretical example can find an opportunity. Without a doubt, the complexity in a continuous system increases for the operator. However, with a continuous system all the effects and interactions on the CQA can be determined in one system. The system can be investigated as a whole. Especially for QbD this can be a key answer. When the measured CQA at the end of a continuous system can be linked to the adjustment of CPP and the CMA, it is feasible to understand the process as a whole. If this is the case, a much faster and easier option is available compared to several batches process steps, which have to investigate the whole process to the same depth.

At this point, this thesis tries to substantiate the idea that a continuous process could enhance the process understanding, hence the final product quality. With one of the simplest continuous processes, the continuous direct capsule filling, it should be possible to illustrate the benefits, which can be gained for the process development. New ideas, methods and techniques help to face the challenge of a process development on a continuous system. At the same time, options are shown how to integrate a capsule filling process into continuous manufacturing.

1.3 References

[1] United Nations, Department of Economic and Social Affairs. World Population Prospects, The 2017 Revision. 2017 [cited 2019 May 30]. Available from: https://esa.un.org

[2] World Health Organization, World Health Statistics. Life expectancy and Healthy life expectancy Data by country. 2019 [cited 2019 May 30]. Available from: https://www.who.int/en

[3] Plumb K. Continuous Processing in the Pharmaceutical Industry. Chemical Engineering Research and Design. 2005;83:730–738.

[4] Fischer D, Breitenbach J. Die Pharmaindustrie. Heidelberg: Spektrum Akademischer Verlag; 2013.

[5] Griffin JP, Posner J, Barker GR. The textbook of pharmaceutical medicine. 7th edn. Chichester West Sussex: Wiley-Blackwell; 2013.

[6] Bauer-Brandl WA. Die Tablette: Handbuch der Entwicklung, Herstellung und Qualitätssicherung. 3rd edn. (Der pharmazeutische Betrieb; vol. 7). Aulendorf: ECV, Ed. Cantor-Verl.; 2012.

[7] Podczeck F, Jones BE. Pharmaceutical capsules. Great Britain: Pharmaceutical Press; 2004.

[8] Rowe RC, editor. Handbook of pharmaceutical excipients. 6th edn. London: APhA (PhP) Pharmaceutical Press; 2009.

[9] U.S. FDA. Pharmaceutical CGMPs for the 21th Century, Final Report. 2004 [cited 2017 August 29]. Available from: http://www.fda.gov

[10] ICH. Pharmaceutical Development Q8 (R2). 2009 [cited 2017 October 06]. Available from: http://www.ich.org

[11] DiMasi JA, Hansen RW, Grabowski HG. The price of innovation: new estimates of drug development costs. Journal of Health Economics. 2003;22:151–185.

[12] Fonteyne M, Vercruysse J, Leersnyder F de, et al. Process Analytical Technology for continuous manufacturing of solid-dosage forms. Trends in Analytical Chemistry. 2015;67:159–166.

[13] Plumb K. Continuous Processing in the Pharmaceutical Industry. Chemical Engineering Research and Design. 2005;83:730–738.

[14] Kleinebudde P, Khinast J, Rantanen J, editors. Continuous Manufacturing of Pharmaceuticals. Chichester, UK: John Wiley & Sons, Ltd; 2017.

[15] Lee SL, O'Connor TF, Yang X, et al. Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production. J Pharm Innov. 2015;10:191–199.

2 Automation of a Dosing-Disc Capsule Filler from the Perspective of Reliability and Safety

(This chapter is based on the publication Wagner B, Brinz T, Otterbach S, Khinast J, Automation of a dosing-disc capsule filler from the perspective of reliability and safety, Drug Development and Industrial Pharmacy, 2018 44:502–510.)

2.1 Introduction

Automation technologies are routinely used in many industries and in everyday life. Systems containing components, such as actuators, sensors and microcontrollers, can be found everywhere in our environment (e.g., in mobile phones [1], in cars [2], at home [3]). Connecting these devices is the next big challenge and communications between the different components is the basis of concepts, such as *Industry 4.0* and the *Internet of Things*. In the pharmaceutical industry, a paradigm shift towards automated manufacturing is currently underway, mainly in the context of continuous manufacturing [4, 5]. For example, automated continuous manufacturing systems for tablets are already commercially available (e.g., MODCOS m-line [6], ConsiGma [7], Xelum [8]). Different types of processing units, such as feeders, blenders, granulators and a tablet press, are connected and sensors are implemented (process analytical technology) to improve the process, and hence, the quality of the final product. However, automated continuous capsule filling processes do not exist as of yet. Consequently, automation of the capsule filling process is of significant interest.

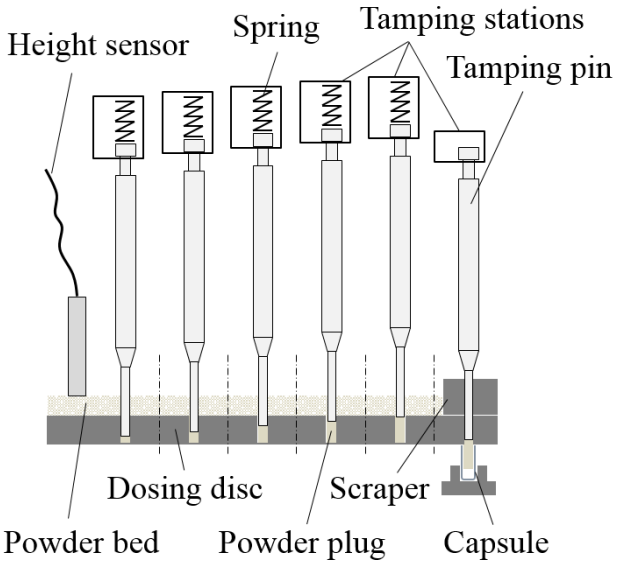

Figure 1: Schematic drawing of tamping-pin system

There are several ways to fill hard-gelatin capsules using manually-operated equipment or fully-automated fillers. The most important automated capsule filling techniques are based on the tamping-pin and dosator-nozzle principles [9]. In our study, a GKF 702 (Robert Bosch Packaging Technology GmbH, Germany), which is a tamping-pin system, was considered. In such a system (Figure 1), powder is filled into die-holes of a dosing disc via tamping pins. Typically, five tamping pins are used per tamping station and in the GKF 702 six tamping

stations are arranged in a circle. At every station more powder is added to each die-hole and the powder is simultaneously compacted to form a powder plug. In the final (6^{th}) tamping station, the powder is then transferred in the capsule bodies. For details please refer to the literature [9].

Figure 1 shows a schematic view of the tamping-pin principle. The main part of the system is the dosing disc containing the die-holes. On top of the disc there is a certain amount of powder (the powder bed). In the Figure, the formation of a powder plug is illustrated. Although each of the 6 tamping stations has 5 pins, in Figure 1 each station has only one pin to ease the illustration. The pins move up and down, pushing the powder into the die-holes in the disc. After each filling event by the pins, the disc turns 60 degrees and powder is pushed into the dies at the next station. Inside the die-holes, the powder is compacted to form a plug. At the 6^{th} (last) station, the plug is transferred into the capsule. A scraper at station 6 ensures that no powder other than the powder plug is filled into the capsule. Clearly, several parameters impact the filling process, including operating parameters (speed, force, immersion depth), powder-bed height and uniformity, as well as material parameters, including flowability, compactability, adhesiveness, and tendency to segregate. A precise control of the machine parameters is a prerequisite for achieving consistently high product quality. Disassembly and reassembly after cleaning, or a product change, often involves manual adjustments of the process parameters. Automation of these steps may save time and effort. Validating a new production process is a critical step in the process development for a new compound or product. In that context, the effect of process parameters must be understood. Although capsule-filler operators are typically very experienced, the influence of process parameters on the product quality (fill weight and variability) can change depending on the formulation [10]. Especially, for complicated powders, optimizing the operating and machine parameters is not a straightforward task. Automation can thus be used for process development and validation, making it easier to identify the effects on the final product and change the process parameters faster, possibly based on designed experiments (DOE).

In this paper we analyze what is needed in order to automatize a hard-gelatin-capsule filling machine based on the tamping principle and to control in an automatized way the important process parameters. Within this study, two sensor implementations are made in order to enable a fully automated process. The use and benefit of this implementation is demonstrated by two experiments challenging normal operation of a capsule filling machine.

2.2 Materials and Methods

2.2.1 Critical Process Parameters

Today, quality risk management is required in the development and production of pharmaceuticals [11]. Consideration of the risks associated with each process step is important and quality should be achieved by a robust design of the process, according to the quality by design (QbD) framework. The critical process parameters (CPPs) are the parameters which affect, together with the critical material attributes (CMAs), the critical quality attributes (CQAs) of the products [12]. The CMAs include properties, such as particle size distribution, flowability, shape, density, cohesiveness and electrostatic chargeability of the materials. Typical CQAs in capsule filling processes are the fill weight, the fill weight variability and the compaction level of the powder plug, since strong compaction of the powder (leading to the formation of hard plugs) can have a detrimental influence on the dissolution or dispersion behavior [13]. During capsule filling processes, there are several process parameters that can influence the CQAs. Parameters identified in this study are the dosing disc height, the dosing disc diameter, the powder bed height, the powder feed rate, the machine speed, 5 tamping pressures (one for each station), 5 immersion depths (for each station). These 15 parameters can be changed within a normal machine setup and must be adjusted for each material to be filled into capsules. Thus, developing and validating a capsule filling process requires significant effort [10]. Below, we discuss various CPPs and their influence on the process and provide a brief review of feasible stages of automation.

2.2.1.1 CPP Dosing Disc Height and Dosing Disc Diameter

The tamping-pin principle is a volumetric filling method, i.e., a predefined volume is filled with powder. Its main element is the dosing disc that determines the dosing volume. A change in this volume significantly affects the capsule fill weight. To set up a filling process, a correct volume for the product density has to be established. The dosing disc volume is linked to the capsule size, i.e., larger volumes require larger capsule shells. However, the diameter of the die-hole cannot be adjusted since the compressed powder has to fit into the capsules. Thus, each capsule size has a corresponding dosing disc die-hole diameter. Therefore, the volume is adjusted by the height of the dosing disc. Typically the dosing disc is a one-part piece with a fixed height and therefore a fixed volume. By varying the design, an adjustable volume can be achieved. In certain capsule fillers (e.g., GKF 2600, Robert Bosch Packaging GmbH, Germany), a two part-dosing disc may be used (Figure 2). By adjusting the location of the upper part, the height, and therefore, the volume can be changed. As a result, the geometry of the die-hole is not exactly

cylindrically anymore, which may affect the powder compression and dosing (e.g., the transfer into the capsule), since the gap between the die-hole and the pin varies during the transfer movement.

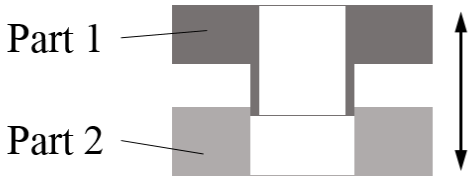

Figure 2: Adjustable dosing disc

The adjustment of the height is performed by an electric motor. With regard to automated adjustments of the capsule filling machine, the adjustable dosing disc is advantageous in certain situations, e.g., for control purposes if a high influence on the fill weight is required. However, for most situations a fixed-volume dosing disc is preferable, since it is less expensive and it has a simple die-hole geometry. For logging purposes and to ensure that the correct disc is used, an identification technique could be applied, such as scanning a laser-engraved code on the disc during the assembly to ensure that only correct parts are installed in the machine.

2.2.1.2 CPPs Powder Bed Height and Powder Feed Rate

In the beginning of the dosing process, the product is fed into the powder bowl on top of the dosing disc. The disc rotates in a stop-and-go motion and the powder is distributed and develops a certain powder level. As the capsule filling process continues, powder has to be fed to keep the powder level constant. Clearly, if the powder level drops below a certain critical value, the die-hole filling cannot be maintained. Therefore, a minimal height has to be set to produce capsules within the desired range. For some products (especially with poor flowability), the dosing process is affected by the powder level. For example, Podczeck and Newton (1999) [10] showed that a poorly-flowing corn starch results in an increased capsule fill weight when the powder bed height is increased. The fill weight variation was also affected. It was shown that an increase of the powder bed height level was necessary to satisfy the requirements on the fill weight variation for products with poor flowability. The investigation of Nair et al. (2004) [14] confirmed that for poorly-flowing products the powder bed height affects the capsule fill weight. Podczeck (2001) [15] reported a risk of a larger fill weight variability for powders which can be well compacted. This seemed to result from a poorer flowability and fluctuations

of the powder bed height which originates from an intermittent powder feed.

Consequently, the height of the powder bed is a CPP, since it has an influence on the CQAs, at least in some cases. On the GKF 702, a change of this process parameter typically involves a mechanical adjustment (see below). The powder bed height is connected to the powder feed rate, which is basically determined by the speed of the auger that feeds the product onto the dosing disc. When small capsules are filled on the machine little amount of powder is consumed, whereas large capsules need a greater amount of product. To obtain a quasi-continuous product feed rate, and thus, a stable powder bed height, the user has to adjust the powder feed rate. Obviously, the powder bed height and its stabilization are critical process parameters. A possible solution based on automation is reviewed below, where a machine modification is presented and associated experiments are reviewed.

2.2.1.3 CPP Machine Speed

Capsule fillers have one or more electrical drives to carry out the various movements of the capsule transport mechanism and of the dosing disc/tamping system. The movements are precisely tuned and depend on the main machine speed. Clearly, this speed influences the dosing process. At higher filling speeds, the dosing disc rotates faster, changing the forces on the powder, i.e., centrifugal forces increase at higher rotation speeds of the powder bowl. Moreover, acceleration and deceleration of the disc are a function of the speed. Finally, the compression of the powder in the die-holes is affected, as the same compaction process occurs in a shorter period of time and at higher speeds. On the GKF 702 the speed can be varied within a range of 50 to 140 cycles/minute. This setting is already automated as the PLC (programmable logic controller) controls the main machine drive of the system.

2.2.1.4 CPP Tamping Force and Pressure

The tamping pins are attached to the tamping stations. Inside the stations, compression springs (Figure 1) are mounted above the pins. The springs are pre-loaded and support the pins with a specific initial force. The stations move downwards (nearer to the dosing disc) to push the pins through the powder bed into the die-holes. As the pins move down into the dosing disc, the die-holes are filled with a certain amount of powder. The pins compress the powder and a force develops between the powder and the pins. If this force is higher than the pre-load force of the springs, the springs start to compress. With increasing station numbers the spring compression is increased as well, as more powder is already inside the die-hole. The force increases and so does the pressure on the powder. Clearly, the force of the pin onto the powder depends on the spring constant. A weaker spring will apply less force onto the powder in comparison to a

stronger spring which add more force onto the powder. Obviously, it is possible to vary the force acting on the powder in the die-hole, by changing the spring constants (i.e., by using different springs). Springs with different constants and maximum compression loads are available. For example, on the Bosch GKF 702 springs within a range of 10 – 200 N are available. However, an advanced process understanding is required for choosing a suitable spring setting, as the force acting on the powder plug is an important parameter: It influences the densification (compaction) of the powder fill, which affects the capsule weight, RSD and dissolution/dispersion of the produced capsule content [15]. The latter effect was reported by Heda et al. [13].

In order to automatically adjust the spring constant, mechanic springs can be replaced with pistons in air chambers. The spring constant can then be simply adjusted by controlling the air pressure. For example, Podczeck (2000) [16] used a pneumatic tamping pin station like this for assessing a fill weight control. Equipping all 5 stations with air chambers is a possible way to fully automate the spring constant adjustment at all stations. Such a system was installed on the GKF 702 and was successfully used in the experiments. Furthermore, this option enables the machine to measure the compaction force applied at each station, as described by Podczeck [16].

2.2.1.5 CPP Immersion Depth

The tamping pin principle uses two mechanisms to transport the powder into the die-holes. First, powder flows into the die-holes due to various forces (gravimetric, centrifugal, inertia due to the stop-and-go motion of the dosing disc). The better the flowability of the powder, the more consistent this effect will be. The second contribution is the movement of pins, which travel through the powder bed and help to convey the product above, and subsequently, into the die-hole. Furthermore, once the pins move down, powder is pushed into the die-holes. How deep the pins travel (i.e., the immersion depth) can be adjusted. The pins are fixed to the tamping station (see Figure 3). The tamping stations themselves are connected with a screw to a mount. This mount is moved by the main drive. It provides an up and down movement above the dosing disc. The distance between the main mount and the tamping stations can be adjusted by turning the screw with the hexagon head. The screw thread changes the height of the tamping station, making it possible to set various immersion depths for the pins at each station.

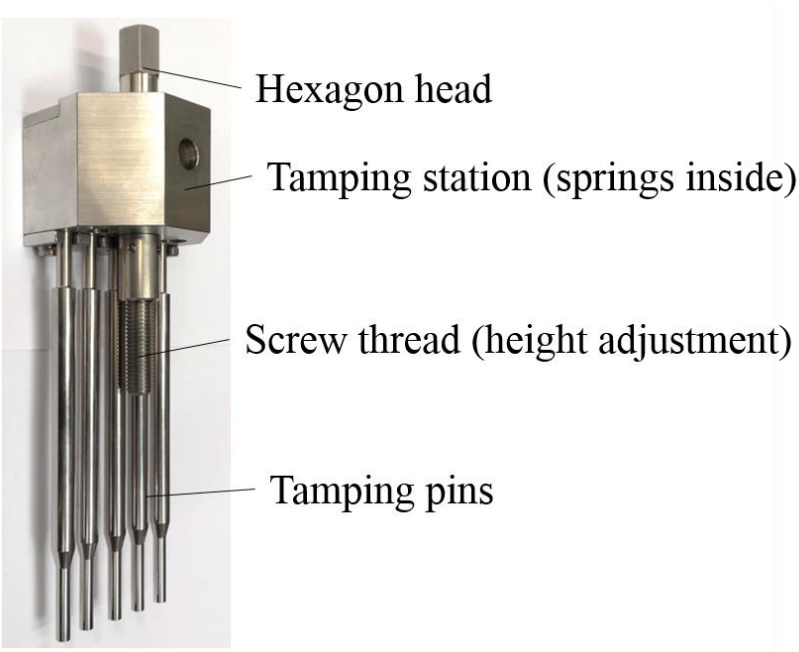

Figure 3: Image of a single tamping station with 5 pins

The influence of the tamping pin distance is described in the literature. The immersion depths are added up to the so-called cumulative tamping distance (CTD) [10]. For example an immersion into the dosing disc (from station 1-5) of 5, 4, 2, 1, 0 mm can be summed up to a CTD of 12 mm. Podczeck [10] reported an increase in capsule weight with an increase in the CTD for granules of micro-fine cellulose. This is expected as the material in the die-holes is more compressed for higher CTDs and thus, more material can enter the die.

For each one of the five tamping stations involved in die filling, the height must be adjusted. Various combinations of settings are possible. Typically, the immersion depth is reduced station by station, from the first one to the last one. However, there are cases where other profiles are more suitable. Even an opposite profile is possible for some materials, i.e., the immersion depth increases along the tamping stations: For a fine and loose product, an initially lower immersion depth can be beneficial. In the first stations the powder bridges above and inside the die-holes are destroyed and air can escape slowly at the first two or three stations. This reduces the variation of the capsule fill weight and increases the same. Clearly, the immersion depth of the pins is a CPP and is often adjusted by the user. A possible automation of this parameter can be realized by attaching a motor to the hexagon head. The experiments in this study were performed with such a setup and it was possible to adjust all immersion settings by software command.

2.2.2 Materials

For this study, two pharmaceutical excipients, lactose monohydrate (SpheroLac® 100, Meggle, Germany) and starch (Maize Starch Extra White, Roquette Pharma, Lestrem, France) were selected due to their different physical properties (Table 1, see particle size and flow function coefficient (ffc)). The powders were filled into Coni-Snap hard gelatin capsules size 1 (Capsugel, Belgium). The empty capsules were pre-weighted (KKE 1700, Robert Bosch Packaging Technology GmbH, Germany). The mean empty capsule weight was 75.1 mg. Capsules deviating with more than ±1.4 mg from the mean were sorted out.

Table 1: Material properties

Material	x_{10} (µm)	x_{50} (µm)	x_{90} (µm)	Span $(x_{90}-x_{10})/x_{50}$	BD (g/ml)	TD (g/ml)	CI (%)	ff_C (-)
SpheroLac® 100	42.26 ± 0,29	119.02 ± 0.16	203.18 ± 0.20	1.35 ± 0.00	0.711 ± 0.002	0.878 ± 0.000	18.95 ± 0.22	11.60 ± 1.29
Maize Starch Extra White	7.86 ± 0.09	14.26 ± 0.07	21.05 ± 0.02	0.92 ± 0.01	0.554 ± 0.003	0.704 ± 0.000	21.40 ± 0.44	2.80 ± 0.09

Particle properties are reported in Table 1. The particle size distribution was determined via laser diffraction (HELOS BR, Sympatec, Clausthal-Zellerfeld, Germany) after dispersing the dry powders with compressed air (RODOS M, Sympatec, Clausthal-Zellerfeld, Germany). Bulk and tapped densities were analyzed using a jolting volumeter (JEL STAV II, J. Engelsmann, Germany). For the determination of bulk density (BD), a certain quantity of powder was filled into a 250 ml graduated cylinder and the volume was recorded. After mechanically tapping the powder sample 2500 times and reading the new volume, the tapped density (TD) was calculated. The bulk and tapped densities were used to estimate the Carr's compressibility index (CI) according the following equation:

$$CI = \left(\frac{TD - BD}{TD}\right) \times 100\% \quad (1)$$

Carr suggested a relation between the difference of bulk and tapped density and the powder flowability [17]. In general, low values of CI indicate good flowability. A FT4 powder rheometer (Freeman Technology, Gloucestershire, UK) equipped with the 50 mm measuring geometry was used to evaluate the powder shear properties in terms of flow function coefficient (ff_C). To this end, the FT4 standard protocol for shear testing is applied at a normal stress of 3 kPa. All powder properties were measured in triplicate. As can be seen, the powders differed significantly in terms of particle size (median particle size of SpheroLac® 100 is 119 µm and Maize Starch Extra White is 14 µm) and flow function coefficient. In general, the larger the ff_C value, the better the flowability of the material [18, 19]. The ff_C value of SpheroLac® 100 is

higher than 10 representing a free-flowing powder whereas Maize Starch Extra White is classified as cohesive (ff_C value between 2 and 4).

2.2.3 Modification of the Powder Bed Height Sensor

To control the powder bet height the current solution in a GKF 702 is to detect whether the actual height is above or below a chosen set point. A capacitive sensor (Figure 4, left) was set to a defined height above the dosing disc. A signal was sent to the control unit when powder touched the sensor surface. To change the powder bed height, the sensor has to be adjusted manually in its position above the dosing disc.

In order to automatically adjust the powder bed height the capacitive sensor in our work was exchanged for an ultrasonic sensor (Figure 4, right). The ultrasonic sensor is mounted at the same position as the capacitive sensor. Now it is possible to measure the height of the powder bed and to adjust the powder bed height automatically by choosing a different target parameter in the control software.

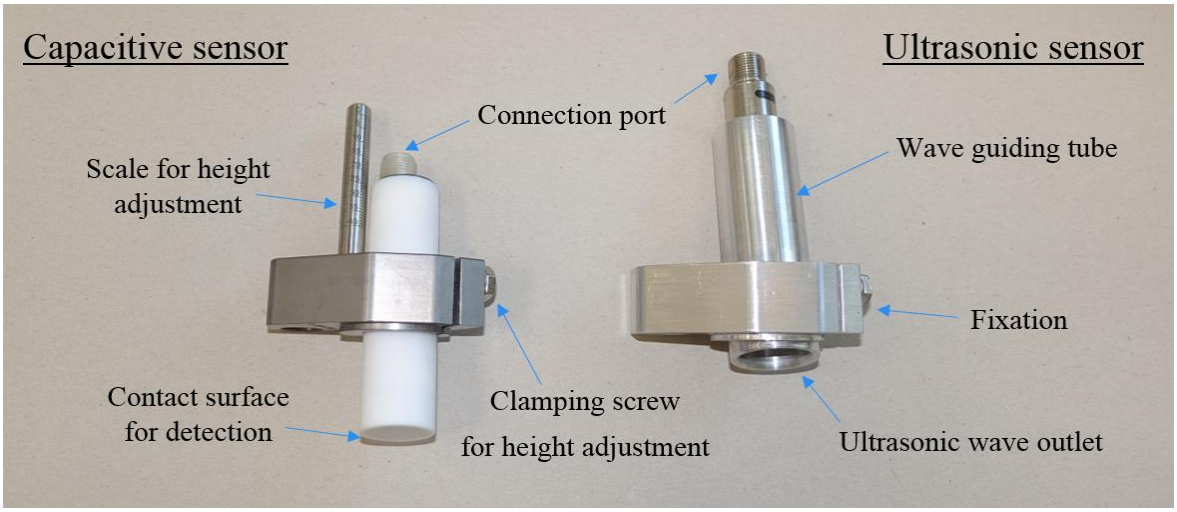

Figure 4: Modification of powder bed height sensor: (left) traditional capacitive sensor, (right) novel ultrasonic sensor

The classic capacitive sensor outputs a two-state signal. When the powder bed level drops below the sensor location, the powder feed was activated and an auger feeds powder from a buffer onto the dosing disc. For this classic control algorithm two parameters can be adjusted. The first one is the speed of the auger. The second one is a delay time which is used to keep the feed running for a longer time. With this control setup the powder bed height oscillates around the desired set point of the powder bed height. Depending on the experience of the user the oscillation can be small or big. In contrast, an ideal behavior would be a continuous feed

matching the capsule fill rate in kg/h of the machine, ensuring a constant powder bed height. By using the ultrasonic sensor the level can be controlled in much better manner. The PID algorithm automatically chooses the right auger speed to reduce the deviation from the target to zero. Below, an experiment with a combination of a PID control algorithm and the ultrasonic sensor is presented and compared to the classic powder feeding based on the capacitive sensor.

2.2.4 Introduction of a Transfer Force Sensor

A capsule filling machine has to operate in a reliable and safe manner. Thus, sensors are critical components of an automated capsule filler to ensure that no processing problems occur during operation. Examples for typical sensors are the detection system for missing empty capsules (optical), the pressure monitoring for the vacuum which opens the pre-closed empty capsules (strain gauge pressure transducer) and detection systems to ensure the correct fill weight (e.g., gravimetric [20], capacitive [21], x-ray exposure [22]).

Measuring the force needed to transfer the powder plug(s) into the capsule(s) at the last (6^{th}) tamping station is another interesting sensor application. However, technical solutions to measure transfer forces in an automated way are not standard implementation on current capsule fillers. The last station of a capsule filler is the most critical one as the powder is transferred into the capsule. A certain amount of force has to be applied to push the powder out of the die-hole. The impact of system parameters on the transfer force has been discussed in the literature. For example, Heda et al. (2002) [13] reported different transfer forces for different products and compression forces. Clearly, the magnitude of force is a function of several factors, such as the wall friction coefficient of the material pairing (e.g., powder and dosing disc steel), the geometry of the die-hole and the densification of the powder, which determines the radial stresses (via the lateral stress ratio) in the plug, and thus, the friction forces during plug ejection.

Basically, high transfer forces indicate inadmissible stress in the machine. If the transfer forces exceed a certain level the powder plug cannot be pushed through the die-holes. Another problem can occur if deposits between the pins and the die-holes lead to strong friction. This friction can increase to levels at which the machine is not able to pull the pin back out of the dosing disc. In both cases severe machine damage is the result. Therefore, experienced operators carefully set up a new capsule filling process and detect transfer-force related problems already by the sound of the machine. However, when the machine is operated automatically or by inexperienced users, severe problems can arise and critical combinations of process parameters are likely to occur, which cannot be recognized.

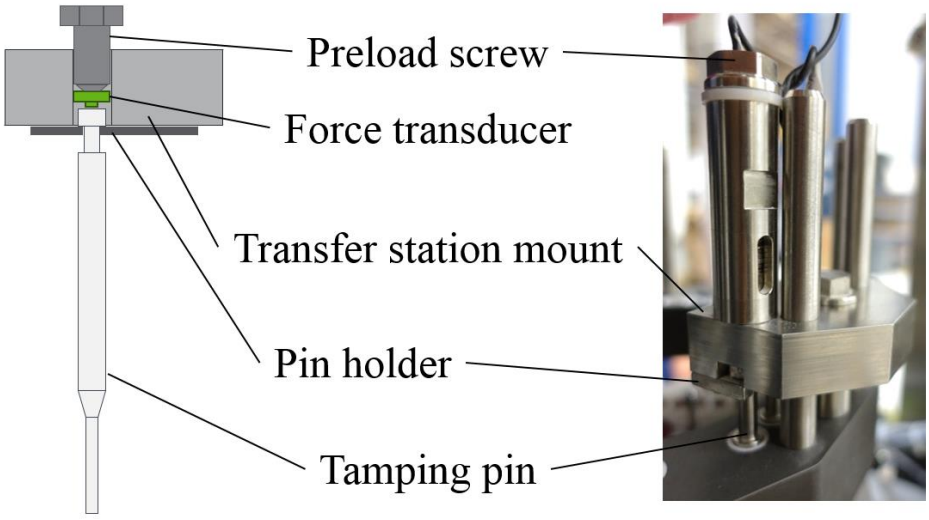

Figure 5: Transfer force sensor

In order to detect the transfer forces on the GKF 702 a sensor system was implemented. Figure 5 (right) shows the actual sensor. A schematic view is presented on the left side of Fig. 5. The force transducer (green element) used in this application is able to measure forces between 0 – 500 N. The accuracy is 1 %. Relative variance for the linearity is below 0.1 % for the maximum load of 500 N. The proper function is checked by the manufacturer. A measurement amplifier is connected to the sensor with a cut-off frequency of 2.5 kHz. As the transfer action happens in a short amount of time (i.e., 50 – 150 ms, depending on the dosing disc thickness and the machine speed) a fast amplifier is need. The preload screw secures the force transducer and eliminates any gap between the sensor and the pin. The preload force was set to about 50 N in this study and was corrected by the data acquisition system (Software LabVIEW, Hardware National Instruments cDAQ-9174 with NI 9203). By using this system transfer forces can be automatically measured and logged. The system shows whether the capsule filling process is operating within the design specifications or, in contrast, if operational problems occur. A force limitation was defined. If the force exceeds a pre-defined value a signal was sent to the capsule filler to immediately initiate an emergency stop.

2.3 Results and Discussion

2.3.1 Control of Powder Bed Height and Its Impact on Fill Weight Variability

The two excipients were chosen to represent the two different cases, i.e., a freely flowing powder (lactose) and a highly cohesive one (starch). For each powder two runs were executed. In the first run a strong variation in the powder bed height was induced by setting up the powder feeder to the classic behavior, i.e., an on-off control of the feed rate based on a certain level set

point. In the second run PID control was enabled. In this case the feed rate automatically matched the powder consumption of the machine. In both experiments the ultrasonic sensor was used. In order to simulate the classic on-off control (described previously) a two-state signal controlled the powder feeder, similar to the implementation with the capacitive sensor.

The following settings were kept constant for the whole investigation: dosing disc height (17 mm); machine speed (120 cycles/min); immersion depth from the first to the last station (6, 8, 11.5, 13, 14 mm); pressure in all pneumatic stations (0.2 MPa). Two machine settings are varied between the two products: the target powder bed height and the feed rate of the classical powder feed. The sample time of the control system was 6 ms. To determine the powder bed height a moving average of 200 measurements (approximately 1.2 s) was applied. This powder bed height value was used to detect whether the powder drops below the desired set point to activate the powder feeder for the classic method and also used to calculate the control error for the PID algorithm. The produced capsules were online weighted using a KKE 1700. The KKE is a gravimetric check-weighing system for hard gelatin capsules. As the capsules are faster weighed than produced, an online measurement was realized. Only a small delay occurred as the capsules were transported form the GKF to the KKE (~5 s). The mean capsule weight shown in the following figures was calculated from a time window of 2.1 s. With a production speed of 120 cycles per minute and 5 capsules per cycle, a time of 2.1 s correspond to 20 capsules on average.

In the first experiment, the powder bed height was set to 10 mm and the powder bowl was prefilled with starch. Then, the capsule filler was run for 2 minutes. After this time a stable operation was obtained and data were recorded. The results can be seen in Figure 6, which shows the powder bed height and the capsule fill weight over time. As soon as the powder bed height (light blue) dropped below the target powder bed height (dashed line) the powder feed was activated. The auger in the feeder rotated with 80 rpm for 4 s. As a result, the powder bed level increased by about 4 mm. In the beginning of the experiment a large peak is visible. This peak does not originate from the feeder. Starch is a very poor flowing product and some of the product was piled up in the center of the dosing disc. This pile of powder broke down periodically and increased the powder bed height. This effect can be corrected by an insert mounted on the dosing disc. This, however, was not used in this study.

The dark blue line represents the mean capsule weight (calculated from a period of 2.1 s, see above). Apparently, there is a strong correlation between the capsule fill weight and the powder bed, i.e., the capsule weight follows the variation of the powder bed. As the bed height increased, an increase of the fill weight was immediately observed. Excluding the first peak,

the following values were measured (1-4 min): average weight of 361 mg, RSD of 3.5 %, weight variations in a range of 34 mg (377-343 mg).

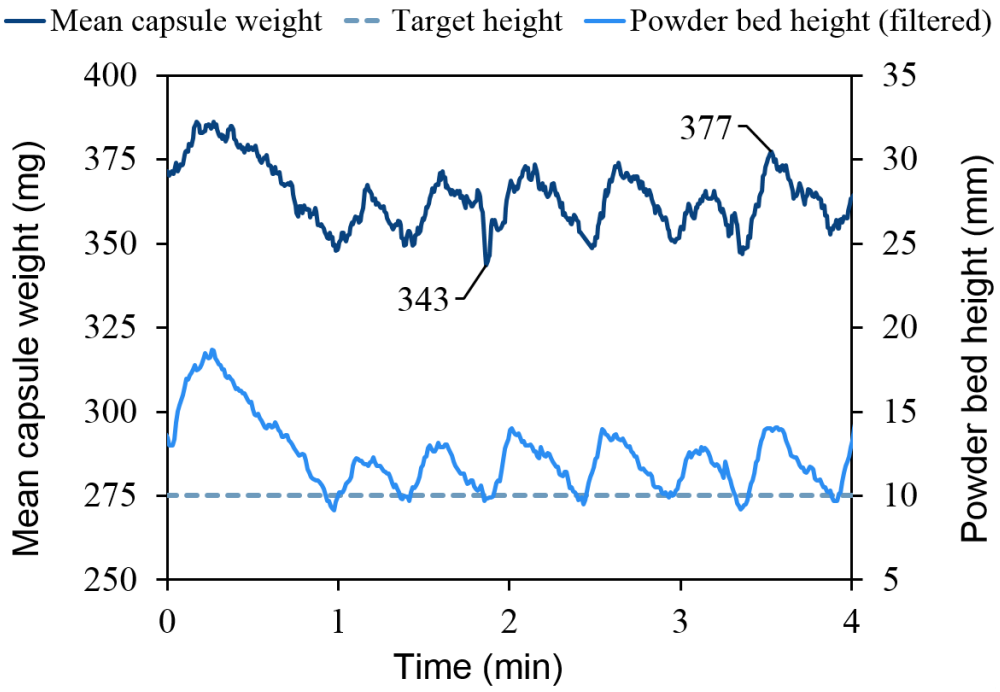

Figure 6: Powder bed height of starch without PID control (classic control)

In the next experiment, the control of the powder bed was switched to the PID algorithm. The machine was run for 1 minute to stabilize the powder feed. Subsequently, the data presented in Figure 7 was recorded. Clearly, the powder bed height is controlled in a much better way, and fluctuations are significantly reduced. The powder bed height is close to the set point of 10 mm (i.e., deviations are less than ±1.5 mm). The control automatically adjusts the speed of the auger, reducing a powder feed rate matching the consumption. The peak visible at the end originates from a powder pile up as described before. The average weight of the capsules from minute 0 to minute 3 is 359 mg and the RSD is 2.9 %. Thus, fluctuations are significantly reduced compared to the case above (i.e., without PID control). The variation of the mean weight is in a range of about 19 mg which is significantly smaller. The PID control of the powder bed led therefore to a better filling performance, since the RSD of the filled capsules was optimized (decreased about 0.6 %).

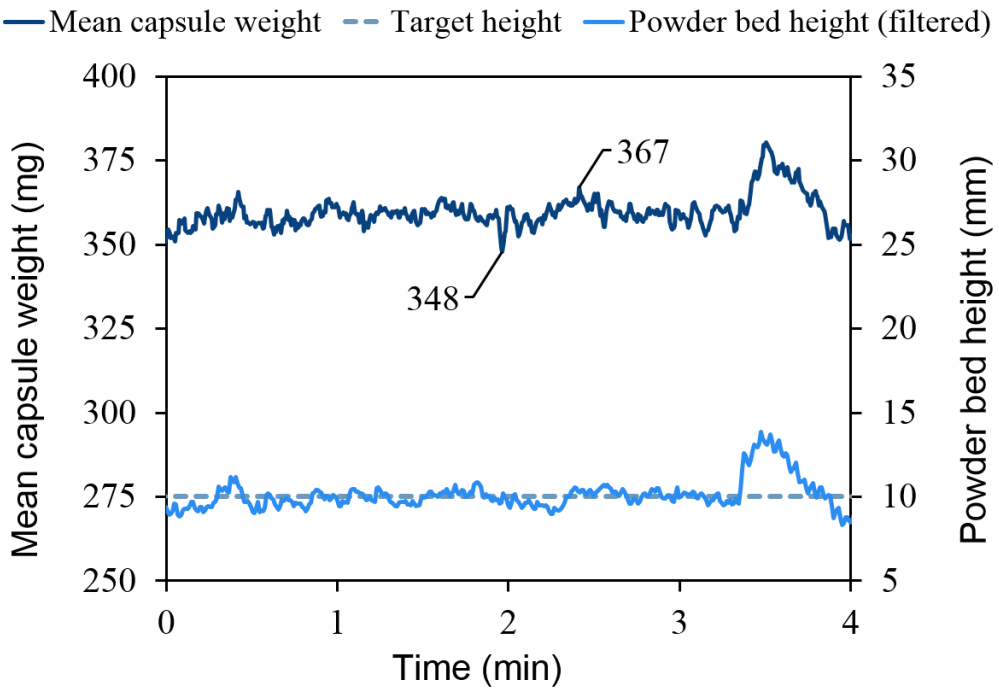

Figure 7: Powder bed height of starch with PID control

A different behavior of the capsule filler was observed when a well-flowing material was used. In order to set up a challenging process the powder bed height was reduced to 5 mm. The feeding properties of the classic control was adjusted to 80 rpm and a delay time of 6 s was set. A rubber disc was positioned beneath the feed auger to prevent the lactose from freely flowing onto the dosing disc without agitation. Figure 8 shows the results for this case. The powder bed levels (light blue) fluctuated in a periodic manner, with a maximum increase of about 3.5 mm, even using the longer powder feeder delay time. Clearly, the powder bed height signal is much smoother compared to the case of the cohesive material. The lactose distributes more effectively on the dosing disc and the signal does not suggest any unevenness of the bed surface. Moreover, in this case the mean capsule weight dark blue line was not affected at all by the variations in the powder bed height. Despite an increase of about 70 % in powder bed height, the weight variations were below 15 mg (408-393 mg). The average capsule weight was 402 mg with an RSD of about 2.8 %. Interestingly, the variations in the weight signal were not correlated with the powder bed height.

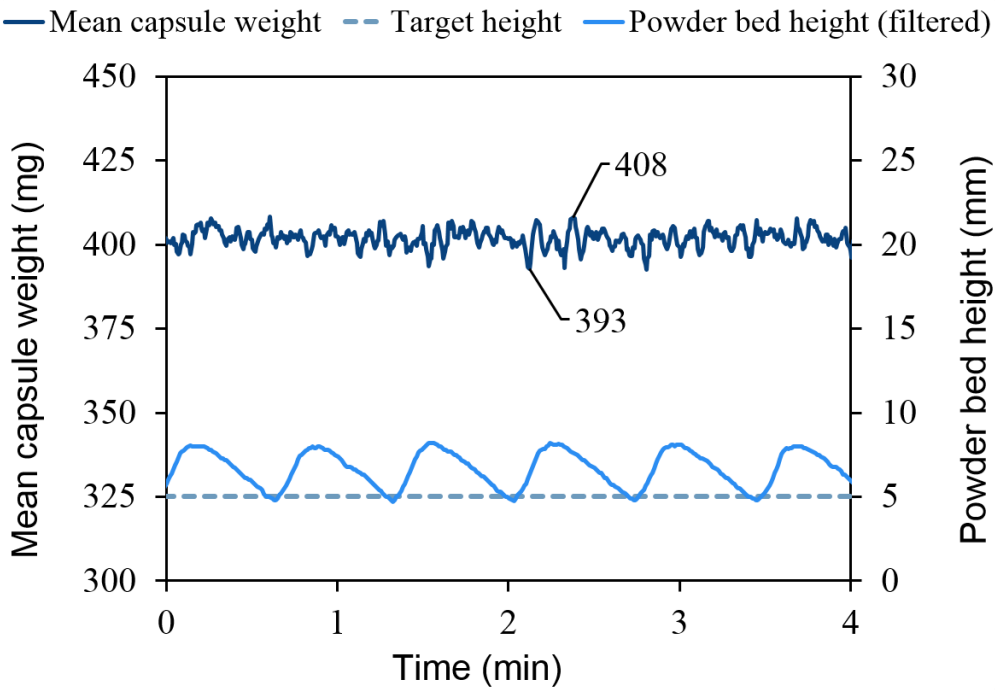

Figure 8: Powder bed height of lactose without PID (classic control)

In the last experiment the PID control was activated and the powder feed rate was automatically adjusted (Figure 9). With a well-flowing product, such as the lactose, the deviation from the target level are negligible (about ±0.3 mm), highlighting the better control action. The mean capsule weight was 404 mg and the RSD was 2.7 %. The maximal deviation of the mean capsule weight was 12 mg (410-398 mg) which is slightly less than the deviation from the experiment without PID (15 mg). However, this effect cannot be attributed to the change of the control algorithm. Analyzing the results from the experiments involving different powders with and without effective level control, it becomes clear that there is a strong dependence on the properties of the material. For cohesive starch, a strong influence of the bed height on the fill weight and RSD is seen. In contrast, for free-flowing lactose this effect is now observed, which has also been reported in the literature (see above).

In our experiments, a very low powder bed height was used. In a typical filling process the powder bed height should be higher. When the powder bed height of the starch is increased to normal values (e.g., 120 % of the dosing disc height) the influence of changes in the powder bed height becomes very small (data not shown). Therefore, the classic filling principle is a robust and reliable method to feed the powder onto the disc for many (yet not all) cases. However, the benefits of the PID control become evident when special requirements, such as a small powder bed height, have to be accommodated. For example, during the shut-down as much material as possible should be filled into capsules. Once the powder bed level is below

the set value, the material needs to be discarded, as the fill weight would decrease. Thus, operating at a low powder bed height can help to minimize the discarded material and PID-controlled feeding becomes valuable.

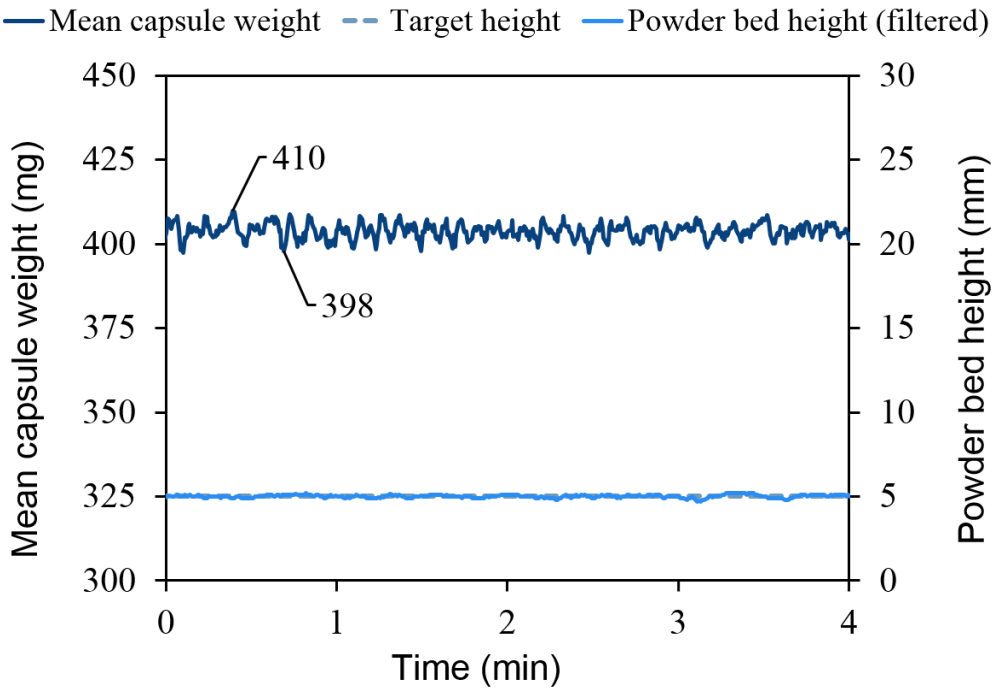

Figure 9: Powder bed height of lactose with PID control

Another scenario, where control of the bed height at a low level may be relevant, is the transition of manufacturing from batch to continuous manufacturing. Here, another parameter, i.e., the so called residence time distribution (RTD), becomes important, with a narrow RTD being better than a broad one. The RTD is the basis for addressing issues such as the traceability of materials and the effect of out-of-spec events in manufacturing processes [23]. The residence time of the filling process is influenced by the amount of powder located on the dosing disc. The more powder, the higher the residence time is, as the powder is constantly mixed by the scraper in the bowl. As the amount of powder on the dosing disc is dependent on the powder bed height, the height influences the RTD. A reduction of powder bed height might be an option to reduce the residence time of the process and a PID control can help to facilitate this objective.

In any case, the PID control of the powder bed is an advantage for automated operation, since the operator does not have to check whether the powder bed height has an impact on fill weight and RSD. Moreover, the feed rate of the powder matches the consumption of the machine. In summary, by implementing this option, the CPP powder bed height becomes an automated process parameter.

2.3.2 Analysis of Transfer Forces

For analyzing the transfer forces during capsule filling, experiments were executed with five runs for each of the two products. The pressures in the tamping stations were varied in order to simulate a high load on the machine. With these experiments we wanted to demonstrate that it is necessary to control tightly the process parameters as they can have a significant influence on the CQAs and on the safety of the machine operation. Using the sensor setup too high transfer forces are recognized and the machine is stopped automatically. In order to operate within a safe operating window the force limit was set to 100 N, i.e., the capsule filler initiates an emergency stop when transfer forces above 100 N are measured. Although the machine is able to generate tamping forces greater than 200 N (GKF 702), 100 N should also be a safe limit for the transfer station, since wear and tear are starting to become significant at higher transfer forces.

A dosing disc with a thickness of 17 mm and capsule size 1 was mounted on the GKF 702. The transfer station was equipped with the sensor setup. Modified tamping pins which have a slight reduction in diameter 3 mm behind the tip were applied. This was used to reduce the friction between the die-holes and the pins. The settings of the process parameters were: powder bed height 25 mm; speed 110 cycles/minute; pin immersion 16, 12, 8, 8, 8 mm (stations 1-5, respectively). The pressure of the pneumatic springs at stations 1 and 2 was set to 0.1 MPa and was maintained in all of the following runs. The pressures at stations 3, 4 and 5 were increased between each run from 0.1 MPa to 0.5 MPa. A cleaning step was executed between the two products. After the product was fed to the machine, it was run for 10 minutes with 0.1 MPa in all stations. Then, the first run was started and the forces were collected (measurement time 1.5 minutes). After the run the machine stopped, the pressures of station 3, 4, 5 were increased, and the next run started. Each time, before the machine was stopped, 100 capsules were collected and their weight was measured (KKE 1700).

Figure 10 shows an example of a force time profile collected from the transfer sensor. In this example the setting of the pressure in station 3, 4, 5 was set to 0.5 MPa. It can be observed that a large difference exists between the two products, i.e., starch and lactose. The starch can be transferred with a relative low peak force (14 N), even at this high compression level (0.5 MPa). In contrast, the lactose showed a complete different behavior. The force profile showed a much higher values (peak value 67.5 N). Significant fluctuations can be observed at 20 ms to 40 ms in the signal for lactose. This originates from the strong friction between the powder plug and the dosing disc die-hole, causing a stick-slip effect.

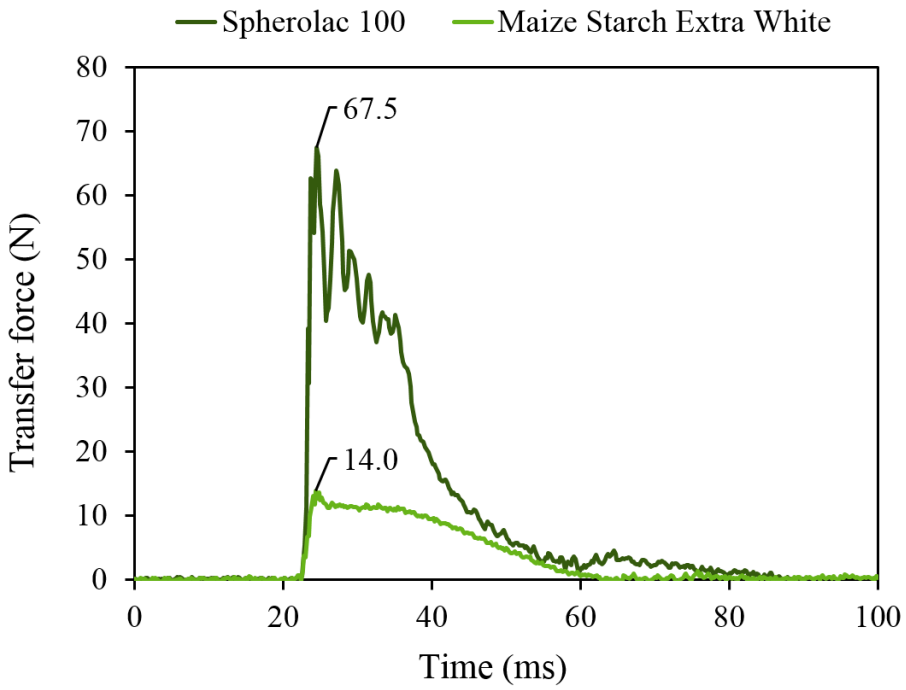

Figure 10: Transfer force diagram for starch and lactose. The maximum transfer force is noted in the diagram.

The complete results of the experiment are presented in Figure 11. Dashed lines show the mean capsule weight for each run. The mean capsule weights were calculated from the 100 capsules collected during each run. The solid lines show the peak forces for each experiment. The peak forces were calculated as the average of the 4 highest peaks measured in each run. This was necessary, to eliminate singular effects.

From Fig. 11 it can be seen that if the pressure in the stations was increased, the weight of the capsule increased significantly. The lactose and the starch capsule weight increased both by about 10 mg when the pressure was changed from 0.1 MPa to 0.5 MPa (starch 388 mg to 398 mg; lactose from 385 mg to 396 mg). This gain of 2.5 % is rather small compared to experiments with different excipients (e.g., see Podczeck and Newton (1999) [10]). The peak transfer forces, however, showed an intricate behavior: While the maximum force for the starch increased moderately (from 6.2 N to 15.6 N), the maximum force for the lactose drastically increased (from 17.4 N to 106.1 N). In the last run using lactose the machine stopped twice as the transfer force peaks reached forces above 100 N.

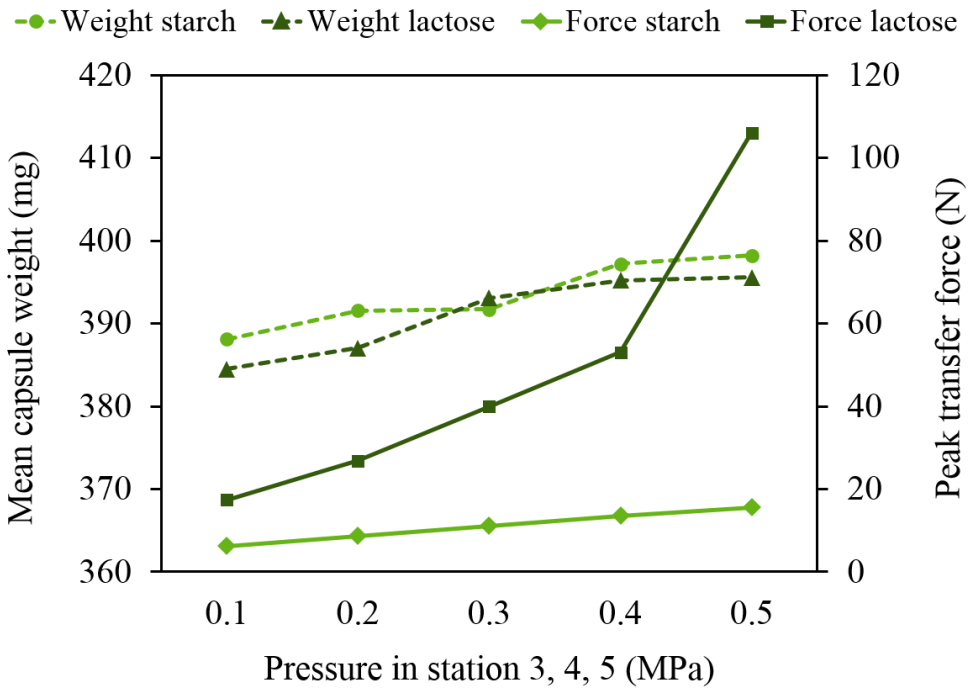

Figure 11: Mean capsule weight and maximum transfer forces for different tamping pressures

Figure 12 illustrates the measured peak forces of the 5th run. The first emergency stop occurred after about one minute of run time (E1). After the second emergency stop (E2) the station pressure was reduced to 0.1 MPa. Interestingly, the mean transfer forces increased in time when the machine was operated at 0.5 MPa. The fluctuation of the individual peak forces increased as well over the time until an emergency shutdown was initiated. After the pressure was reduced the transfer forces instantaneously decreased. In comparison to the 1st run with 0.1 MPa the measured forces were slightly higher at the same pressure level of 0.1 MPa (peak force values above 25 N instead of 17 N). This effect can be assigned due to deposits left in the die-holes from the high pressure setting which increased the friction during the low pressure setting, and therefore, the forces. This highlights how complex capsule filling is and that it is necessary to monitor a wide variety of parameters, including pin forces.

Figure 13 shows the deposits developing on the pins when filling lactose, after the 5th run. Deposits were on the pins of the transfer station and in the die-holes of the dosing disc. These deposits, which are very stable, are the explanation for the strong fluctuation of the peak forces. These deposits developed due to the strong compression of the material and due to the friction applied during the transfer into the capsule. When the pins move in the die-holes with deposits, high friction forces occur, leasing to high transfer forces. Nevertheless, the pins were able to remove some of the deposits as they move up and down through the die-holes and the force drops from time to time to a lower level. Overall the deposits increased and the force

needed to push through the die-holes increased. Interestingly, the capsule weights did not show significant fluctuations, and the RSD for all the runs was below 5 %. The RSD of the 5th run (before the last emergency stop) was calculated to be 3.3 % (mean fill weight 395 mg). The RSD of 1st run was 4.6 % (mean fill weight 385 mg).

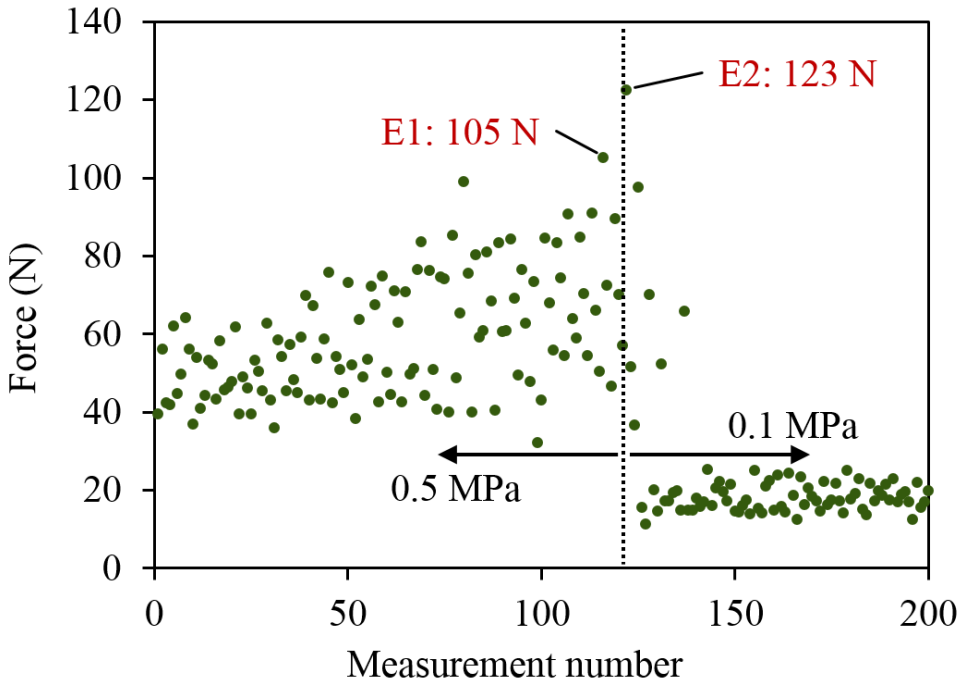

Figure 12: Peak forces during the 5th run for the lactose

As shown in Figure 11, we observed a substantial relation between the station pressure and the transfer force. The effect was much stronger for the lactose, but was also visible for the starch. Moreover, deposits built up in the die-hole and increased the transfer forces for the lactose. This may be due to some partial melting of the lactose and the formation of a hard surface layer (which can be easily removed with water). Thus, operating the capsule filler at a high pressure setting is not a problem for the starch. However, processing the lactose with a pressure of 0.5 MPa can lead to significant problems.

In summary, the station pressure can have significant influence on the transfer force. In general, other process parameters can have an influence too. For example, if the immersion depth is increased a similar effect may occur. The depth directly influences the pressure on the powder in the die-hole, and thus, the tamping and transfer force. Monitoring the transfer force can prevent the machine from damage and the user can explore different variations of the process parameters and define the feasible process space without the risk of a machine damage.

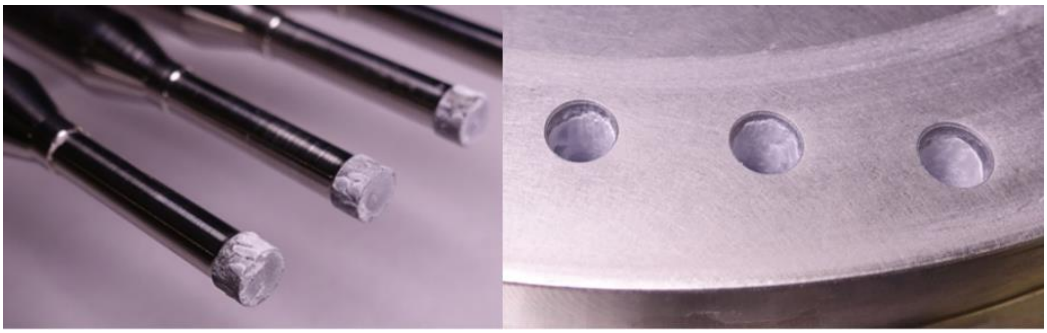

Figure 13: Deposits of lactose past the 5th run

2.4 Conclusion

In our work, the automation of a capsule filling machine based on the tamping principle was investigated. First, the process parameters that can affect the tamping process were reviewed. The potential for automation was discussed and a powder height sensor and a transfer force sensor were successfully implemented in a GKF 702, and used in two series of experiments. It was shown, that the process depends strongly on the materials used. The mean capsule weight was strongly affected by the powder bed height when starch was filled. In contrast, the powder bed height did not show a significant influence for the lactose, as expected from literature. However, experiments with a station pressure of 0.5 MPa with lactose led to high transfer forces, whereas starch could easily be filled without any problem. Thus, measurements of the transfer force is highly relevant in order to keep a capsule filling process within the limits of safe operating conditions.

In summary, automatic adjustable process parameters, additional sensors and advanced process control options (e.g., PID control) are the basis for the implementation of innovative pharmaceutical production processes, such as continuous manufacturing within a QbD framework.

2.5 References

[1] Lane N, Miluzzo E, Lu H, et al. A survey of mobile phone sensing. IEEE Commun. Mag. 2010;48:140–150.

[2] Gerla M, Lee E-K, Pau G, et al. Internet of vehicles: From intelligent grid to autonomous cars and vehicular clouds. In: 2014 IEEE World Forum on Internet of Things (WF-IoT). Proceedings; 6/3/2014 - 8/3/2014; Seoul, Korea (South); 2014; p. 241–246.

[3] Cook DJ, Das SK. How smart are our environments? An updated look at the state of the art. Pervasive and Mobile Computing. 2007;3:53–73.

[4] Rehbaum H, Groß-Weege C. Automatisierung kontinuierlicher Herstellungsprozesse [Automation of Continuous Production Processes]. TechnoPharm. 2016;6:336–345.

[5] The Key to Continuous Manufacturing. PharmaAsia. 2013 March-April;1:9–11.

[6] Glatt.com [Internet]. Germany, Binzen: Glatt GmbH; [cited 2017 October 06]. Available from: http://glatt.com/

[7] Gea.com [Internet]. Germany, Düsseldorf: GEA Group AG; [cited 2017 October 06]. Available from: http://www.gea.com/

[8] Boschpharma-blog.com [Internet]. Germany, Waiblingen: Robert Bosch Packaging Technology GmbH; [cited 2017 October 06]. Available from: http://boschpharma-blog.com/

[9] Podczeck F, Jones BE. Pharmaceutical capsules. Great Britain: Pharmaceutical Press; 2004. Chapter 6, Dry filling of hard capsules; p. 119-138.

[10] Podczeck F, Newton J. Powder filling into hard gelatine capsules on a tamp filling machine. Int J Pharm. 1999;185:237–254.

[11] ICH. Quality Risk Management Q9. 2005 [cited 2017 October 06]. Available from: http://www.ich.org

[12] ICH. Pharmaceutical Development Q8 (R2). 2009 [cited 2017 October 06]. Available from: http://www.ich.org

[13] Heda PK, Muteba K, Augsburger LL. Comparison of the formulation requirements of dosator and dosing disc automatic capsule filling machines. AAPS Pharm Sci. 2002;4(3):E17.

[14] Nair R, Vemuri M, Agrawala P, et al. Investigation of various factors affecting encapsulation on the in-cap automatic capsule-filling machine. AAPS Pharm Sci Tech. 2004;5:E57.

[15] Podczeck F. The development of an instrumented tamp-filling capsule machine II, Investigations of plug development and tamping pressure at different filling stations. Eur J Pharm Sci. 2001;12:515–521.

[16] Podczeck F. The development of an instrumented tamp-filling capsule machine I, Instrumentation of a Bosch GKF 400S machine and feasibility study. Eur J Pharm Sci. 2000;10:267–274.

[17] Carr RL. Evaluating flow properties of solids. Chem Eng. 1965;72:163–168.

[18] Freeman R. Measuring the flow properties of consolidated, conditioned and aerated powders - A comparative study using a powder rheometer and a rotational shear cell. Powder Technol. 2007;174:25–33.

[19] Schulze D. Powders and bulk solids: Behavior, Characterization, Storage and Flow. Berlin: Springer-Verlag; 2008. Chapter 3, Flow properties of bulk solids; p. 41–47.

[20] Podczeck F, Jones BE. Pharmaceutical capsules. Great Britain: Pharmaceutical Press; 2004. Chapter 8, Capsule processing and packing; p. 161-163.

[21] Bürmen M, Pernuš F, Likar B. High-speed precision weighing of pharmaceutical capsules. Meas. Sci. Technol. 2009;20:115–203.

[22] Runft W, Maga J, Schlipf J, Vogt M; Robert Bosch GmbH, Stuttgart (DE). Device for checking pharmaceutical products in particular hard gelatin capsules. United States patent US 9,042,515. 2015 May 26.

[23] Engisch W, Muzzio F. Using Residence Time Distributions (RTDs) to Address the Traceability of Raw Materials in Continuous Pharmaceutical Manufacturing. J Pharm Innov. 2016;11:64–81.

3 Rapid Automated Process Development of a Continuous Capsule-Filling Process

(This chapter is based on the publication Wagner B, Brinz T, Otterbach S, Khinast J, Rapid automated process development of a continuous capsule-filling process, International Journal of Pharmaceutics, 2018 546:154–165.)

3.1 Abbreviations

API – active pharmaceutical ingredient

BD – bulk density

CGMPs – current good manufacturing practices

CI – Carr index

CQAs – critical quality attributes

DoE – design of experiments

EMA – European medicines agency

FDA – food and drug administration

GKF – gelatin capsule filler

KKE – capsule control unit

LOD – loss on drying

MW – mean fill weight

RSD – relative standard deviation

TD – tapped density

3.2 Introduction

According to the FDA guidance on pharmaceutical CGMPs for the 21th Century [1], new technological advances should be deployed to enhance product quality in the pharmaceutical industry. As a result, continuous manufacturing [2] has become a driver for process and quality improvements and much effort has been devoted to implement continuous manufacturing across the industries. Several continuously made products have been filed and approved by the FDA and EMA (e.g. Orkambi, Prezista, Symdeko). To the best knowledge of the authors, current continuous technology focuses mainly on the manufacturing of tablets (e.g., [3]).

However, hard gelatin capsules for oral delivery offer several advantages. First of all, capsule-based formulations are less complex (i.e., they contain fewer excipients). Second, a wide range of products with a broad range of material attributes can be filled into capsules. Although the flowability has a major influence on the capsule filling process, even powders with poor flowability can be filled into capsules [4]. For example, Podczeck and Newton (1999 [5]) successfully filled capsules with a CI (Carr, 1965 [6]) ranging from 13.1 % to 35.6 %. Third, in tablet production the powder has to be compacted to form tablets with sufficient strength ([7], [8]). Disintegration/dissolution characteristics have to meet pharmacopoeial standards. Thus, additional excipients (compression aids, disintegrants) may be required depending on the application and the active pharmaceutical ingredients (APIs). In a capsule, a loose powder plug is sufficient for capsule filling. Thus, even demanding APIs (i.e., poor flowability and compactability) can be directly filled into capsules. Numerous combinations of excipients can be blended and directly filled into a capsule, reducing the required quantity and number of excipients. In addition, no granulation (e.g., roller compaction, wet granulation) and coating steps are required, reducing development and scale-up efforts. Consequently, a continuous capsule-filling process is another relevant technique for efficiently manufacturing oral dosage forms continuously.

Despite the significant flexibility, process development for pharmaceutical capsule filling is not straightforward and requires a high level of sophistication, depending on the complexity of the formulation. The optimal set-point in terms of machine settings (e.g., powder bed height, tamping forces, immersion depth) is subject to extensive development work, often done in a trial-and-error mode. Moreover, the optimal settings, yielding a product with optimal CQAs (e.g., fill weight and variability), depend strongly on the material attributes ([4], [9], [10]). Nevertheless, even if a (close to) optimal set-point was established, validating such a process is not trivial [11]. In order to successfully validate a process, the process have to

be well-understood and the impact of the process parameters on the product's CQAs should be established.

A schematic of a continuous capsule-filling process with three feeders, a blender and a continuous mixer is shown in Figure 1. Several parameters have to be controlled, such as the mass flow rates of the various gravimetric feeders. The individual mass flow rates influence the total mass flow rate, as well as the composition of the final product. A change in the mixture also impacts the material attributes (e.g., flowability, compactability, adhesion, etc.). In the blender, the blender speed has impact on the blend homogeneity, yet also may change the particle size distribution. A buffer located in the capsule filler uncouples the direct connection of the mass flow between the blender and capsule filler. Otherwise, a deviation of the mass flow rates of the two units (blender and capsule filler) could lead to a change of the powder bed height (critical process parameter of the capsule filler). The control parameter of the buffer (feeding rate) adds another parameter to the process. However, with an automatic control of the feed rate this parameter can be neglected [12]. Finally, capsule filling is determined by several more parameters (e.g., machine speed, powder bed height, tamping pressure, immersion depth) [12]. At the end of the line, a weighing system (KKE) enables 100 % control of the produced capsule in real-time. It does not increase the number of controlled parameters but is rather a monitoring tool used in the capsule-filling process.

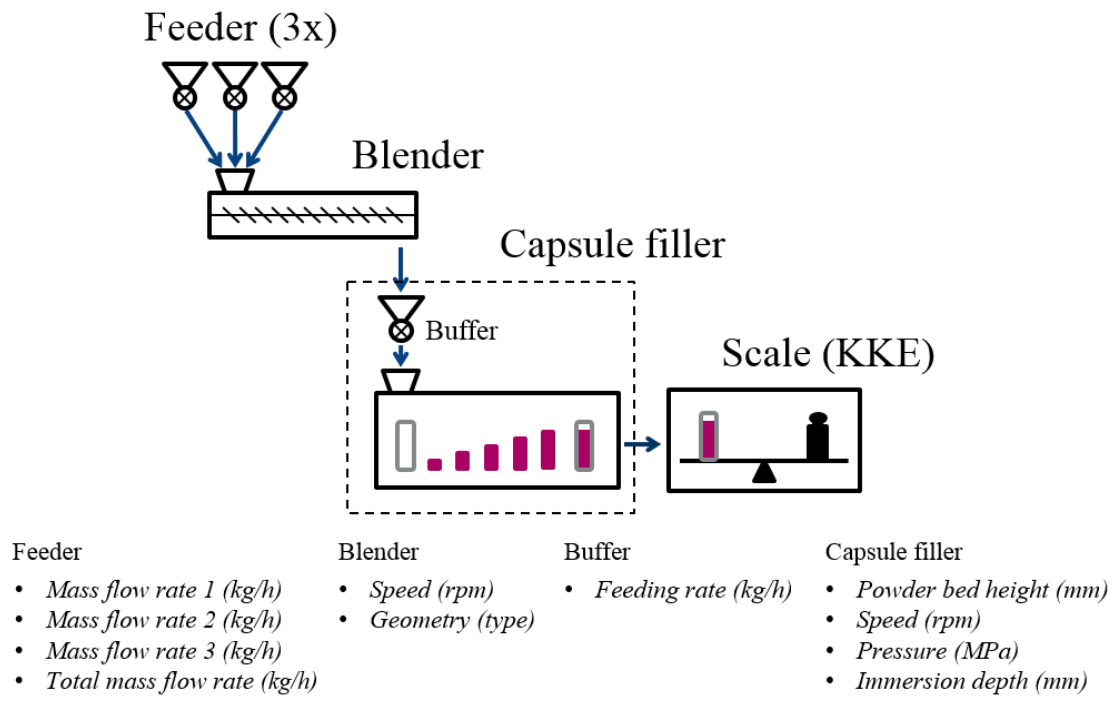

Figure 1: Continuous capsule-filling process, schematic. For each process step, the critical process parameters are added.

These considerations demonstrate that even in a simple continuous process several parameters have to be monitored and controlled. Since these parameters can influence the process significantly, it is important to (1) predict their effect and (2) to control them. Development of process understanding and the associated (statistical) control concept is not a trivial task. Therefore, an automated process development approach may be beneficial. Automated process development can be defined as a method which combines statistical process modelling (optimal designed experiments for the process) and a method to optimize the execution of experiments by a high level of automation (both automation of the change in process parameters and the measurement of the target quality attributes). For the development of statistical process models, automated experiments can significantly reduce the effort, especially when conducted via the design-of-experiments (DoE), since automation technology may allow execution of the experiments in a fast, safe and efficient way.

Specifically, the objectives of our paper are (i) the demonstration of automated experimentation for the development of a design space, (ii) the development of a statistical process model to predict critical quality attributes of capsules, (iii) validation of the process model and (iv) demonstration of the use of the model for controlling the continuous capsule-filling process.

3.3 Material and Methods

3.3.1 Materials

In the experiments three-component mixtures of varying amounts of the specific components were used. Ascorbic acid (Elco P-100 K, Mühlenchemie MC1923, Germany) represents a well-known and easy-to-handle (i.e., operator-safe) API. Lactose was used as a filler (Spherolac 100, Meggle-Pharma, Germany). The third component, magnesium stearate (Nutri Mag ST-v, Calmags GmbH Lüneburg, Germany), was used as lubricant.

Table 1 summarizes the raw material properties. All measurements were performed in triplicate. The particle size distribution was measured via laser diffraction (HELOS BR, Sympatec, Germany) after dispersing the dry powders with compressed air. The residual moisture content of the powders was determined with a moisture analyzer (Moisture Analyzer HR73, Mettler Toledo GmbH, Germany). For this, a sample of approximately 5 g was dried at 80 °C until the weight change was constant for 30 s and the percentage loss on drying (LOD) was recorded.

The Carr Index (CI) [6], widely used as flowability indicator, was evaluated using a jolting volumeter (JEL STAV II, J. Engelsmann, Germany). After filling a certain quantity of

powder into a 250 ml graduated cylinder and determination of bulk density (BD), the powder sample was mechanically tapped 2500 times and the tapped density (TD) was determined. The CI is expressed in percent and quantifies the relative difference between bulk and tapped densities.

Hard gelatin capsules (CAPSUGEL, size 1) from two capsule batches were used. The capsule batch used in the first experiment (process modeling) had a mean fill weight of 74.2 mg and a relative standard deviation (RSD) of 1.6 %. The batch used in the second experiment (validation) had a mean fill weight of 77.1 mg with and an RSD of 1.5 %.

Table 1: Raw material properties (n = 3, mean ± sd)

Material	x_{10} (µm)	x_{50} (µm)	x_{90} (µm)	Span $(x_{90}-x_{10})/x_{50}$	LOD (%)	BD (g/ml)	TD (g/ml)	CI (%)
Ascorbic acid	9.48 ± 0.15	31.95 ± 0.62	77.91 ± 0.97	2.14 ± 0.02	0.06 ± 0.00	0.56 ± 0.00	0.88 ± 0.00	36.2 ± 0.4
Lactose	42.26 ± 0,29	119.02 ± 0.16	203.18 ± 0.20	1.35 ± 0.00	0.15 ± 0.01	0.71 ± 0.00	0.90 ± 0.00	19.0 ± 0.2
Magnesium stearate	0.69 ±0.02	2.46 ± 0.05	12.20 ± 0.29	4.68 ± 0.01	4.63 ± 0.04	0.27 ± 0.00	0.37 ± 0.00	26.1 ± 0.4

From Table 1 it can be seen that the ascorbic acid has a smaller particle size which is an explanation for the poorer flowability (CI of 36.2 % is an indicator for poor flowability) [6]. For lactose the CI is 19.0 %, indicating better flowability than the ascorbic acid. Both excipients contained only a low amount of water (important for reproducibility). The LOD for magnesium stearate is in a typical range [13].

As the capsule-filling process is a volumetric dosing process, the density of the powder (and its variability) is important. The tapped density of the lactose and ascorbic acid are nearly the same (0.90 g/ml and 0.88 g/ml). However, mixtures of both components result in different tapped densities, as can be seen in Figure 2. For a mixture of 20 % of ascorbic acid and 80 % of the lactose the tapped density slightly decreases. However, above ascorbic acid mass fractions of 20 % the tapped density strongly increases up to 0.94 g/ml. Assuming that the powder in the capsule-filling process is densified to tapped density, the weight dosed by a constant volume would, for example, increase the filled powder weight from 500 mg to 535 mg. This effect cannot be predicted using only the tapped density of the two single components. The interaction of the materials leads to a change in tapped density, and thus, to a change in capsule weight.

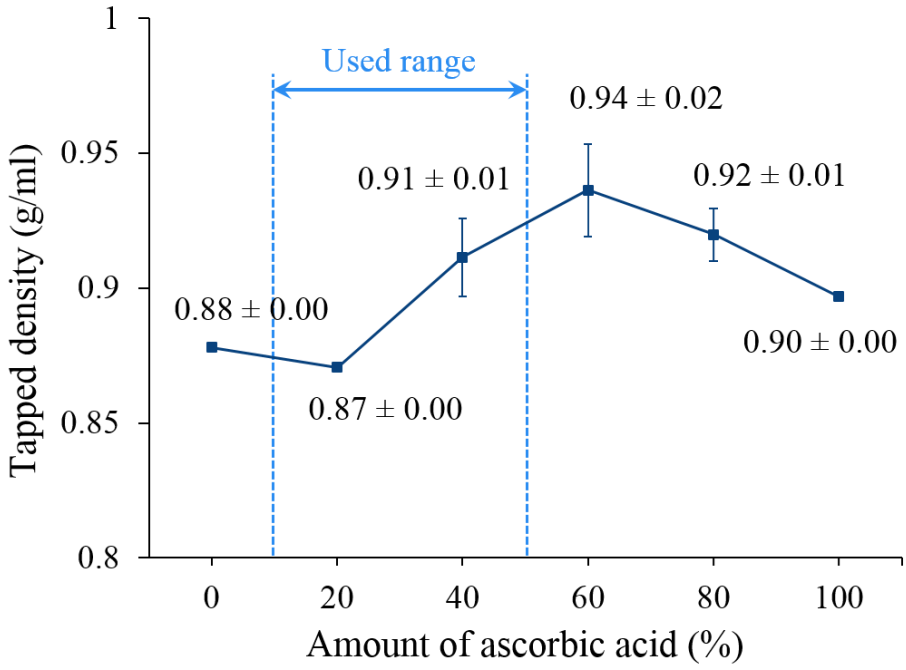

Figure 2: Tapped density of mixtures containing ascorbic acid and lactose. The range used in the experiments (15 – 50 % of ascorbic acid) is marked with light blue, dashed lines.

3.3.2 Continuous Capsule-Filling Process

A continuous capsule-filling process with a feeder-blender unit and an automated capsule filler was developed (Figure 3). The capsule filler was a GKF 702 (Robert Bosch Packaging Technology GmbH, Germany). The critical process parameters of this system were automated as reported earlier [12], except for the dosing disc height. In order to develop a statistical process model, changes in the critical process parameters of the automated capsule filler have to be made rapidly. The automated system enabled us to change process parameters within seconds.

Three twin-screw loss-in-weight feeders were integrated, i.e., two Brabender (DDSR 20) and one Coperion K-TRON (MT-12) feeder. The mass flow rate of each feeder can be controlled individually. Thus, the composition of the whole mixture can be varied in each experiment. The powders were fed directly into the horizontal continuous blender located under the feeder.

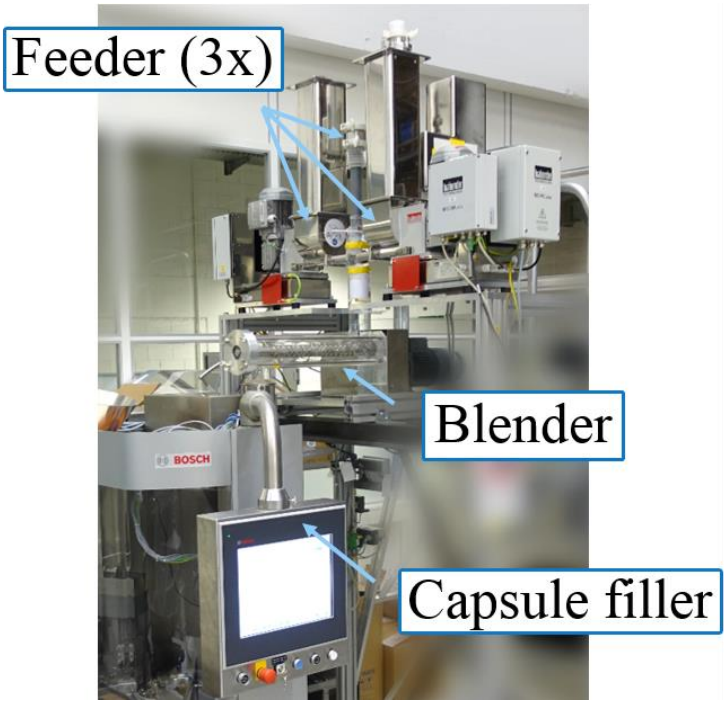

Figure 3: Continuous capsule-filling process.

3.3.3 Design of Experiments (DoE)

DoE is an important element in the development of a statistical process model. A multitude of different DoE approaches has been reported with the goal of creating an efficient experimental design (i.e., minimizing the amount of experiments but maximizing the significance at the same time). Nowadays, several software tools and algorithms are available to create an efficient design that matches the objective of the experiments. However, it is still important to fit the design to the actual process, e.g., to determine the range of the process parameters (so-called factors). The following section describes the design and the process parameters used in this study.

3.3.3.1 Critical Material Attributes

The feeders create the in-process mass flow rate and determine the composition of the material filled into the capsule. The material attributes (i.e., flowability, compactability, adhesion, etc.) of the mixtures depend on the compounds. For example, if one of the three components has a high compactability and its amount is increased, the mixture is likely to have an increased compactability. However, the interaction of the components is not always straightforward: for example, a mixture of two very cohesive powders can under certain circumstances result in good flowability.

The material attributes have a strong influence on the process. To vary the material attributes, and thus, to model the influence on the process, different mixture compositions were

used. For the mixture experiments, a special experimental design was selected, since all components add up to 100 % and one component cannot be changed without effecting the others. Furthermore, each component plays a different role, and consequently, will not occur at arbitrary mass fractions (i.e., lubricant will never be at 80 %). Figure 4 is a ternary plot of the mixture. Lines parallel to the base line opposite of a corner correspond to states with constant concentration of ingredient corresponding to this corner. The corners of the ternary plot represent 100 % of each component, while the opposite base line corresponds to 0 % of each component. The range of API was defined to be 15 – 50 %. For the filler material 45 – 84 % were chosen, and for the lubricant 1 – 5 %, respectively. These borders are shown as lines in Figure 4. Note that the scales of each component in the ternary plot were modified to better illustrate the design space.

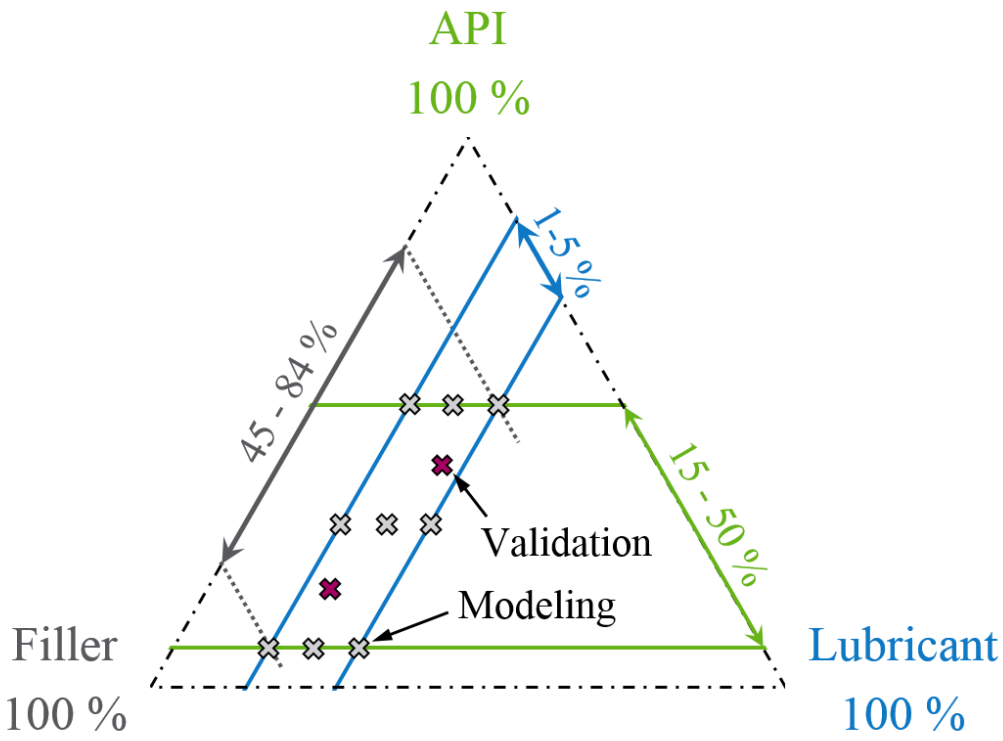

Figure 4: Ternary plot of mixture components. The specific mixtures are shown (grey crosses for modeling experiments, purple crosses for validation runs). The boarder of each component is represented by colored lines, labeled with the percentage amount.

After defining the borders, the design of the mixture experiments was chosen. Similarly to a D-optimal design ([14]), the main points were primarily chosen on the edges of the quadrangle. Additional points were added in the center and in between the corners. Points used

to build the model are represented by grey crosses in Figure 4. Moreover, two validation mixtures were chosen, represented by the two purple crosses.

Generally, a change in the mixture composition (i.e., change of the feed rates) requires much effort, as it takes significant time for the mixture to pass through the blender and the capsule filler. To decide whether a new mixture has completely passed through the continuous capsule-filling process (i.e., the "washout time"), it is important to have a detailed knowledge of the residence time distribution. An investigation of the residence time distribution can form the basis for such a decision. Alternatively, the system can be cleaned after each mixture, which was done here. In order to minimize experimental effort (i.e., cleaning), our experiments were grouped (and not in random order as required by DOE principles). For details of the design, refer to the Appendix A1.

3.3.3.2 Critical Process Parameters

In addition to the critical material attributes, critical process parameters are relevant. In contrast to the material attributes, changing the process parameters is relatively easy. An adjustment can be made immediately, especially in an automated capsule filler [12]. For example, a higher tamping pin pressure is achieved within seconds and the result can be directly related to the changes. The ease of variation is considered in the design of the experiments. Similar to the material attributes, the critical process parameters have an upper and lower limit. To enable an automated process development, the design of experiments is crucial, especially for the process parameters of the capsule-filling process. The experimental design has to be robust to enable the use of all possible materials fed to the capsule filler.

In a tamping-pin system up to 15 different parameters can be defined: the dosing disc height, the die-hole diameter, the powder bed height, the powder feed rate, the machine speed, five tamping pressures (one for each station) and five immersion depths (for each station) [12]. An investigation of all process parameters is not reasonable as they have only small effects or are predefined (e.g., dosing disc diameter by the capsule size). Consequently, we only studied the following four critical process parameters: speed, powder bed height, immersion profile and pressure (all stations were set to the same pressure level).

Changing the pressure of one single tamping stations has only a minor effect. However, changing the pressure of all stations at the same time can result in a dramatic effect (data not mentioned). Therefore, the pressure of the stations was set to the same level and was adjusted in the DoE as one factor, i.e., pressure. The speed of the capsule filler can be changed within a wide range (50 – 140 cycles/min), which affects the capsule filling process. A higher speed causes the powder to be densified in a shorter time. Moreover, the powder on the dosing disc is

influenced due to changing inertial forces. Consequently, the speed of the capsule filler was varied to determine the influence. The process parameter powder bed height determines how much powder is located on the dosing disc, and therefore, how much powder is on top of the die-holes. A low powder bed height is desired for a continuous process (discussed below), but can have a strong influence on the filling process (Wagner et al., 2017). To determine the influence of the powder bed height this parameter is investigated within this study.

In terms of immersion depth (immersion of the tamping pins into the dosing disc [12], several combinations are available, since each station height can be adjusted independently within the range of 0 – 20 mm. However, some of these combinations are infeasible, e.g., a great immersion depth in the last station (5th) where the die-hole is already significantly filled. As such, four settings were defined (so-called immersion profiles). Figure 5 illustrates these four profiles. The surface of the dosing disc is represented by the black line at an immersion depth of 0 mm (in the diagram). The four colored curves show the immersion profiles. Profile II represents a decreasing pattern. For profile II, the first station penetrates 11 mm into the dosing disc and the second station is set to 9 mm immersion depth (marked in Figure 5). On the right, a schematic view of profile II is provided. Each station is illustrated with one pin. The pins are shown at their maximum immersion in the dosing disc. A decreasing immersion is observed in stations 1 to 5. In the design of experiments, two decreasing (II, IV), one increasing (III) and a constant immersion (I) settings were used.

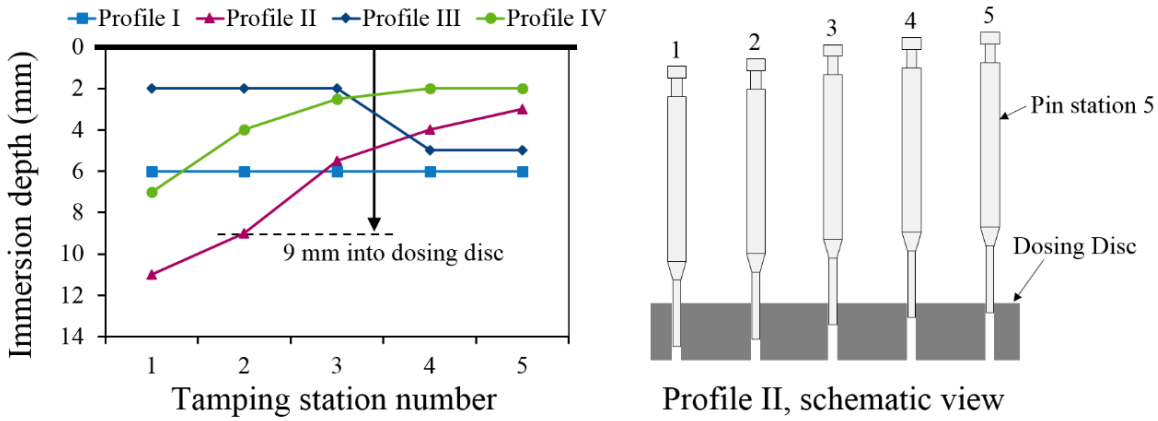

Figure 5: Immersion profiles, two decreasing profiles (II, IV), one increasing (III) and a constant profile (I).

For the experimental design of the critical process parameters a Monte-Carlo design [15] was chosen. Compared to a D-optimal design the experiments are distributed over the design space. To generate this design an option would be to randomly spread the

experiments over the design space. However, the used method, the so-called Sobol sequence [16], allowed the experiments to be distributed even more regular over the design space. Figure 6 shows the design space for 3 of the 4 process parameters (pressure, powder bed height and machine speed).

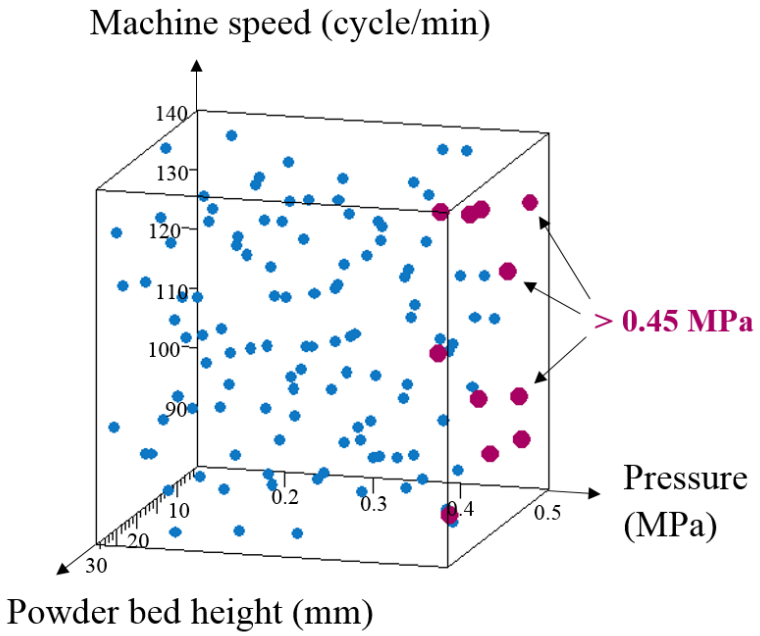

Figure 6: Design space for 3 of 4 critical process parameters varied on the capsule filler. Runs with pressure settings above 0.45 MPa are died purple.

One advantage with this design is the fact that if some experiments cannot be executed there is still a certain amount of experiments left to model the process in a smaller design space. For example, a too high compaction of the powder in the capsule-filling process can lead to a machine stop as the transfer force (i.e. the force to push the powder out of the dosing disc) increases above a maximum threshold [12]. If pressure settings greater than 0.45 MPa lead to a stop of the machine (fictional experiment), no data would be collected at these points (marked purple in Figure 6). However, as the points are equally distributed over the design space only a small amount of runs would be infeasible and a model can still be obtained. In a D-optimal design, more data points would likely be lost. Limiting the pressure to only lower values would help to get a more robust model. Nevertheless, higher pressures are useful and feasible for some materials and should not be removed from the design.

3.3.3.3 Designed Experiment for Modeling

In order to investigate and optimize the process the following terms were included in the model: linear (x), quadratic (x^2), two-way interactions (x*y) and three-way interactions (x*y*z). To fit the model, at least 79 experiments are required. Nevertheless, 123 experiments were executed to compile a larger data basis. The final ranges for the parameters are shown in Table 2. A total mass flow rate of 7 kg/h was set for the feeder blender unit.

Table 2: Process parameter range of experiment 1.

Speed (cycles/min)	Powder bed height (mm)	Pressure (MPa)	Profile (type)	API (%)	Lubricant (%)
80 - 140	5 – 30	0.1 – 0.5	I, II, III, IV	15 – 50	1 – 5

3.3.3.4 Designed Experiments for Validation

The second experiment is based on the model created in the first experiment. This model was not yet validated within the first experiment. Having an excellent adjusted R^2 (representing the model fit based on data used to train the model) does not guarantee a good prediction ability. Thus, validation is required. Different techniques exist for validation. Examples are: cross validation [17], evaluating the model with data not used for the modeling, or to make predictions with the model which are then executed and compared. The latter approach was chosen in this study to validate the model, and simultaneously, to demonstrate a feasible process control for defined targets (mean API content) at different machine speeds.

Two mixtures were selected, visible in Figure 4 as validation points (purple crosses). These mixtures were used because they have a significant distance to the previous ones, in order to challenge the model. Two API amounts were targeted: 183.6 mg of API (for mixture A) and 101.7 mg of API (for mixture B). To achieve the target amount of API, the corresponding mean fill weight for each product mixture can be calculated: 445 mg (for mixture A) and 428 mg (for mixture B).

For an efficient production process the production speed is relevant. In order to achieve a desired low RSD an algorithm minimizing the RSD would always select a low machine speed. To achieve different speeds, six minimum speed settings were defined which “have” to be used within the experiments. In Table 3 an overview of the parameter setting is given. The amount of API and lubricant were defined. Eight runs were executed for each mixture (16 altogether for validation). Out of these, six different speed limitations are set and two were repeated. The three parameters: powder bed height, pressure and immersion profile were chosen by the model (controlled) to achieve the defined target responses (i.e., the mean fill weight of the capsules and the RSD).

Table 3: Process parameter setting of experiment 2.

Variable type	Speed (cycles/min)	Powder bed height (mm)	Pressure (MPa)	Profile (type)	API (%)	Lubricant (%)	Target mean fill weight (mg)	Target RSD weight (%)
	Minimum set	Controlled	Controlled	Controlled	Fixed	Fixed	Response	Response
Mixture A	90, 100, 110, 120, 130, 140	X	X	X	41.25	4	445	Minimize
Mixture B	90, 100, 110, 120, 130, 140	X	X	X	23.75	2	428	Minimize

The optimization function of Cornerstone (Camline) was used to calculate the process parameters based on the model developed in section 3.1. The algorithm searches the predicted response surface and selects the corresponding optimal responses. If there is more than one response (i.e., mean fill weight and RSD) a weighing factor for each response needs to be chosen. The factor for the target mean fill weight was set to 0.8 and the factor for the RSD was set to 0.2. The parameters chosen by the algorithm and the corresponding results for the 16 runs are shown in the Appendix A2.

3.3.4 Experimental Procedure

The following procedure was used to start the feeder-blender unit for the experiments. The feeders were set to the desired mass flow rates. During the startup time of 1 minute the product fed from the feeders was extracted with a vacuum cleaner. When a stable operation point was achieved (confirmed by the feeders), the product was directed into the blender. The capsule filler was started after a sufficient amount of product was fed into the capsule filler hopper to execute one run. The critical process parameters of the capsule filler were set automatically to the desired set point, as defined in the design of experiments. As soon as the capsule filler achieved a steady operation (i.e., the powder bed height on target ± 1 mm), at least 100 capsules were collected. Then the filler was stopped and the next parameters were set. The feeder blender unit produced the required material for one mixture in a continuous run.

After running the experiments for one given mixture, the capsule filler and the blender were cleaned. The material remaining in the blender was about 250 – 350 g. The material in the capsule filler was not analyzed and, as Figure 7 illustrates, there was only little material left in the bowl. This was achieved by letting the filler run for additional 60 seconds after the last experiment. The figure also shows an insert that was implemented to reduce the amount of powder on the dosing disc. Finally, the collected capsules were weighted, and the mean fill weight (capsule weight minus mean empty capsule weight) and the RSD were determined using a KKE 2500 (Robert Bosch Packaging Technology GmbH, Germany).

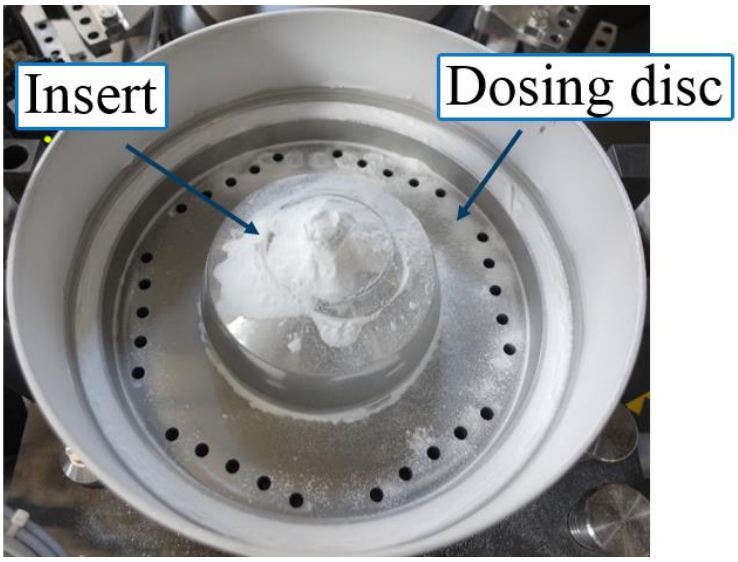

Figure 7: Empty powder bowl.

3.4 Results and Discussion

3.4.1 Process Modeling

In order to develop the process model, regression was applied to the data of the first experiment (123 runs) using the software Cornerstone 7.0 (Camline). By using the Box-Cox plot (see Appendix A3) we determined if a transformation of the results was necessary: the mean fill weight remained untransformed, while the RSD was transformed (reciprocal square root). After that, the residuals were normal distributed. Next, the model was optimized using only significant terms in the model equation. The significance for each term in the model was calculated and the automatic software algorithm determined the less significant terms. The significance levels for removing a term and bringing a term back were 0.0075 and 0.015, respectively. A hierarchical model was constructed (lower factors remained within the model). No outliners were detected.

For the model development the 123 runs were executed within only 2 days. The mean fill weight ranged from 390.1 mg to 466.6 mg. The RSD was between 0.25 % and 0.68 %. The amount of product needed per run was about 0.36 kg. This relatively high amount was needed to adjust the powder bed height and to ensure a stable filling process. In an optimized automated process development, these values could be reduced using an optimized control systems (e.g., better powder bed height control).

3.4.1.1 Modeled Mean Fill Weight

The model of the mean fill weight showed an adjusted $R^2 = 0.997$, indicating a very good fit to the data points. For the coefficients of the model refer to the Appendix A4. Figure 8 shows the adjusted response graph for the mean fill weight. The six sections of the diagram represent one factor (process parameter), respectively. Within each section the effect of a factor is given and all data points of the experiment are visible. For a data point, the effects of the other factors included in the model were averaged, and thus, the data points are adjusted such that only the effect of the designated factor on the response is visible (adjusted response graph). Although an actual value of a data point cannot be obtained from this diagram, since the data points were recalculated, the values indicate how the effect was modeled. Moreover, scattering is observable that cannot be described by the model.

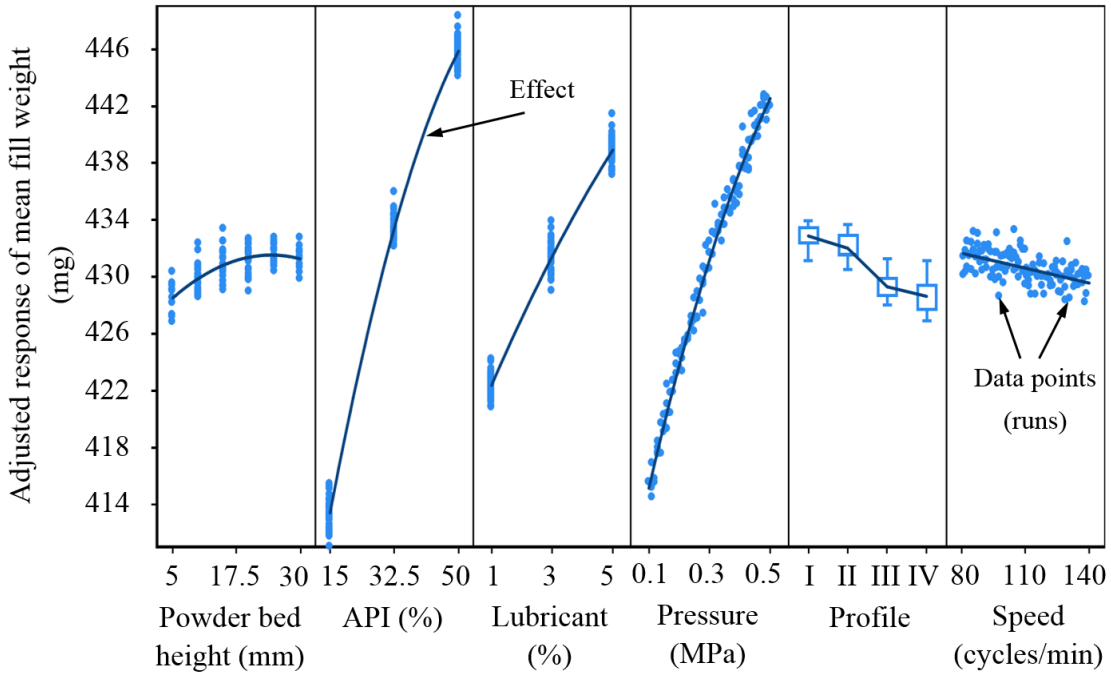

Figure 8: Adjusted response of the mean fill weight as a function of the model factors. Response data points were adjusted (recalculated: effects of other factors were averaged out) and the effect modeled for each factor is visible.

From Figure 8, the following trends can be observed: The effect of the powder bed height is small compared to others. Since the powder bed height only reaches a certain level (above 17 mm), the weight does not increase further with powder bed height, since there is enough powder below the pins to fill the die-hole. Additional powder would be pushed aside.

With regard to the API content, a strong connection between the mean fill weight and the API can be observed. As mentioned in the materials section the tapped density changes as the amount of API increases. The API by itself has a smaller tapped density than lactose (0.88 g/ml vs 0.90 g/ml). However, for a mixture of both components the mixture's tapped density increases. This behavior fits well with the observed effect in the model. The powder plug weight increased about 30 mg (414 – 444 mg) as the amount of API was changed from 15 % to 50 % within the experiments.

A similar effect can be seen for the amount of the lubricant. The weight of the capsule increases with the amount of lubricant. Despite its lower tapped density (3 times smaller), the capsule weight increased with lubricant addition. The lubricant is assumed to reduce the friction in the dosing disc die-hole, resulting in a more regular density distribution along the height of the powder plug. As a result the force applied by the pins can be transmitted through the entire powder plug leading to a denser plug. Moreover, it increases flowability, and thus, the density of the mixture, leading to higher capsule weights.

The next effect is the tamping pressure, which has significant and strong impact on the capsule weight. At higher pressure a denser powder plug is created, i.e., an increased mean fill weight is achieved. The profiles of the immersion depth were identified to have a significant effect. However, compared to other effects (e.g., the pressure), it is a small contribution in the model. Note, that the immersion depth profile is plotted in a box plot. The box ranges from the 25th to the 75th percentile of the data points. The 1st and the 2nd profile led to a higher fill weight than the other two, suggesting that for a high fill weight it is beneficial to increase the immersion of the pins into the dosing disc. The speed of the machine had a small impact on mean fill weight: At higher speeds, the mean fill weight slightly decreased. This is possibly due to a lower densification for fast runs, since the time during which the pin can apply force to the plug is reduced (dwell time). In general, the scattering of values was small compared to the effects (e.g., effect of API concentration and pressure).

Next, an analysis of the model terms was performed. Figure 9 shows the orthogonally-scaled effects of factors used in the model for the mean fill weight. Note that orthogonal scaling requires the factors to be in a range of -1 to 1. Then, the scaled effects can be compared with each other. With normal scaling of the coefficients in the model it would be difficult to compare them since they would be fitted to the unit and are within the range of the related process variable.

The three biggest effects are represented by the linear terms: the API amount, the pressure setting and the amount of lubricant. Clearly, pressure was identified as a critical control

parameter, which can be used to adjust and control the fill weight of the capsule. Other terms, such as interactions (e.g., powder bed height multiplied with profile) and quadratic terms, are considerably smaller. For example, the powder bed height had only a small influence on the weight. Based on the above, it is clear that this model can be used to predict, optimize and control the process.

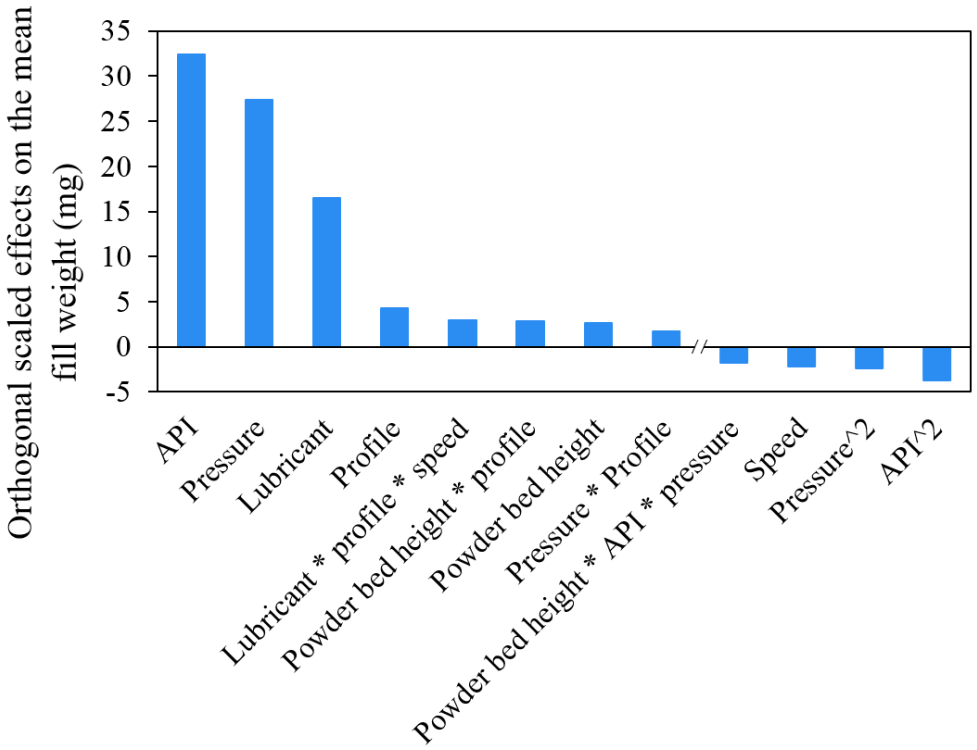

Figure 9: Orthogonally-scaled effects of the model terms on the mean fill weight. Factors are forced to range -1 to 1, thus the (scaled) effects can be compared. Effects smaller than 1.6 mg were removed to improve clarity. The detailed model is provided in the Appendix A4.

3.4.1.2 Modeled Relative Standard Deviation

The detailed model of the RSD of the fill weight can be found in Appendix A4. The effects are illustrated in the adjusted response graph in Figure 10. The first factor, the powder bed height, has no significant impact (within the tested range of 5 – 30 mm). Based on this result, the process can be optimized by reducing the powder bed height to an absolute minimum of 5 mm. This reduces powder holdup in the bowl, which is beneficial for continuous manufacturing (e.g., lower average residence time). The capsule fill weight slightly decreases but this can be compensated for, e.g., by a higher tamping pressure.

With the regard to the other process parameters, only small effects were identified compared to scattering, which cannot be determined by the model. This is reflected by the

inferior fit of the model for the RSD (adj. R^2=0.633, calculated for the back-transformed model). In general, the RSD measured in the experiments was excellent, with the values ranging from 0.25 % to 0.68 %. Considering that a maximum deviation of ±7.5 % [18] is allowed, the overall filling process is very steady, regardless of the choice of the process parameters. The reason could be the use of a high amount of lubricant (> 1 %). Profile I and profile III reduced the RSD, possibly due to a greater immersion of the tamping pins at station 4 and 5. The increased RSD at increased speeds could be due to a reduced densification time. Although the other effects are calculated as significant, they are minor in terms of the general RSD variation (e.g., see the lubricant's effect).

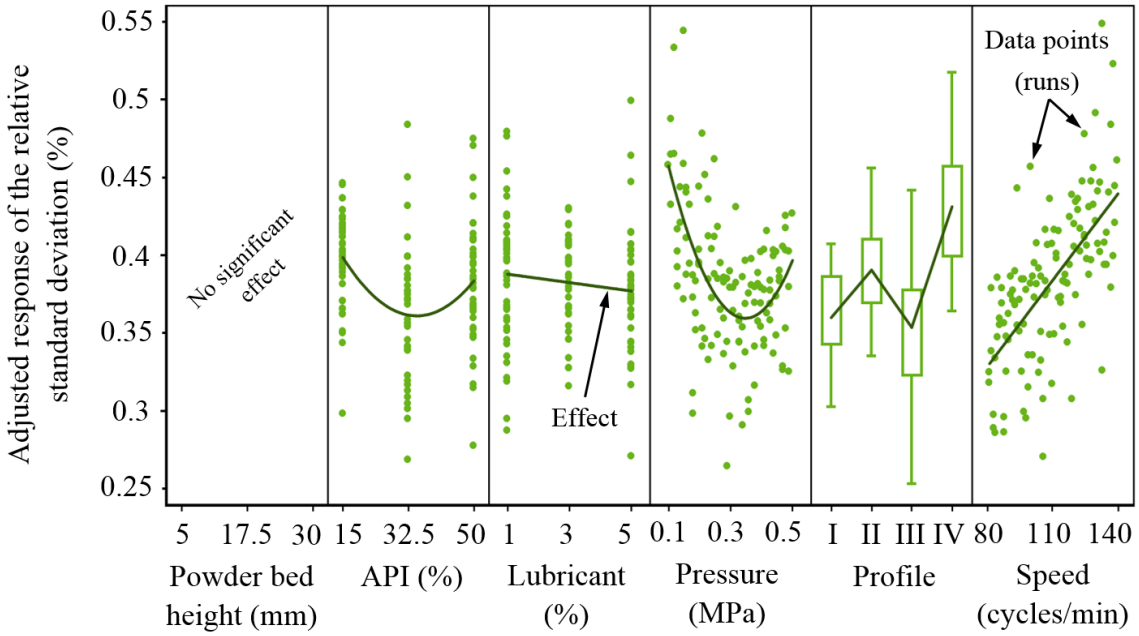

Figure 10: Adjusted response of the relative standard deviation as a function of the model factors. Response data points were adjusted (recalculated: effects of other factors were averaged out) and the effect modeled for each factor is visible.

The orthogonally-scaled effects are shown in Figure 11. The most important terms are machine speed and the immersion profile. Several interactions are relevant, such as the amount of API multiplied by the amount of lubricant or the machine speed multiplied by the tamping pin pressure.

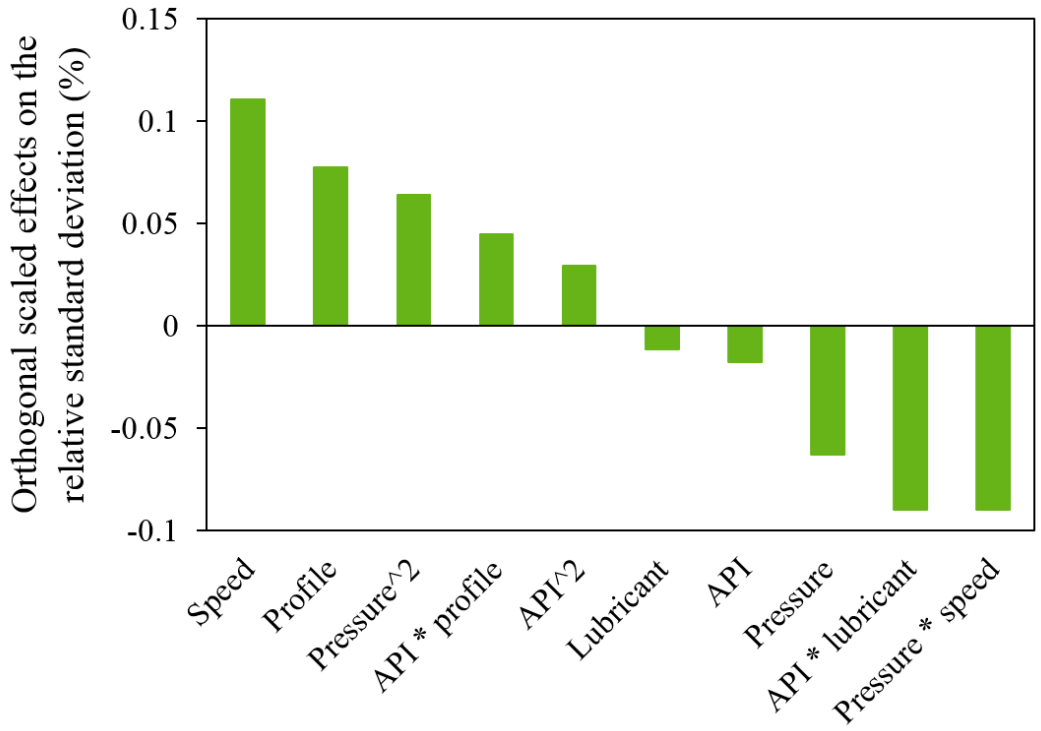

Figure 11: Orthogonally-scaled effects of the model terms on the RSD. Factors are forced to range -1 to 1, thus the (scaled) effects can be compared.

3.4.2 Process Validation

The algorithm (see 2.3.4) was used to determine the specific process parameters required to achieve the targets of the validation runs (results see in the Appendix A2). For mixture A the pressure was adjusted from 2.9 MPa to 4.0 MPa, the powder bed height from 5.7 mm to 15.3 mm and immersion profile 3 was chosen. For mixture B the pressure changed from 3.5 – 4.3 MPa and the powder bed height was adjusted in a range between 7.7 – 28.7 mm. The setting of the immersion profile was set to profile 1, except for the runs above 130 cycles/min. Here, profile 3 was chosen. Figure 12 gives an example of a calculated set point. The solution algorithm selected the process parameters to achieve an optimal setting for reaching the target of 445 mg with a low RSD. This example refers to a minimal speed of 130 cycles/min.

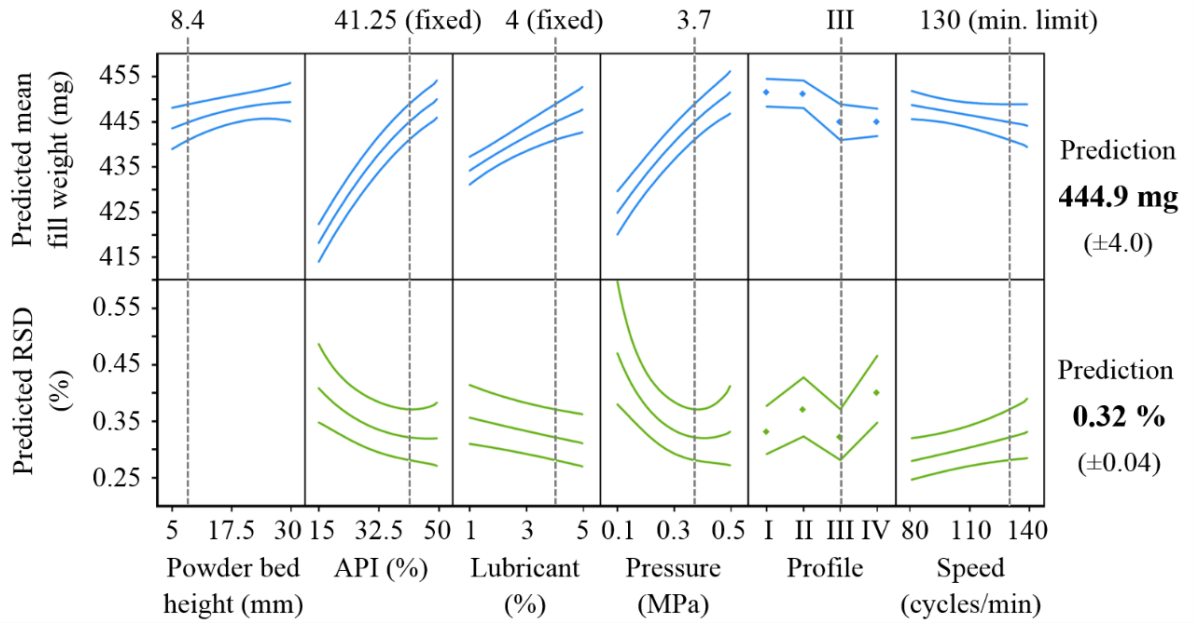

Figure 12: Predicted response graph of the mean fill weight and the relative standard deviation. The line in the middle (of each process parameter) represents the prediction how a target will change if a process parameter is varied. The two lines above and below each prediction illustrate the confidence interval (confidence level of 95 %). The dashed vertical lines represent the calculated process parameter settings.

3.4.2.1 Control of Mean Fill Weight

The mean fill weight determines the mean amount of API in the capsule. Thus, it should be accurately controlled. Figure 13 shows the result for mixture A. The x-axis is the machine speed (90 – 140 cycles/min). Note that the data points are not always at the minimum speed, since for achieving the desired target a higher speed may be required and was selected by the algorithm. The y-axis represents the mean capsule weight. The algorithm was able to produce mean capsule weights in a range of 5.2 mg (440.8 mg – 446 mg). The mean fill weight of the 8 runs was calculated to 444.4 mg which is close to chosen target fill weight of 445 mg. The two repeated experiments (near minimal speed of 100 cycles/min and 130 cycles/min) showed good repeatability (difference was smaller than 1.2 mg, not shown in the figure).

In the Pharmacopoeia European 8.0 chapter 2.9.40 the uniformity of dosage units is described [19]. Depending on the mean API content and RSD of the API content two methods are mentioned to demonstrate the uniformity of dosage units (i.e., test for content uniformity, test for weight variation). In both methods maximum acceptance values (L1, L2) are defined which must not be exceeded. A combination of the relative standard deviation and the deviation of the mean value determines the acceptance value.

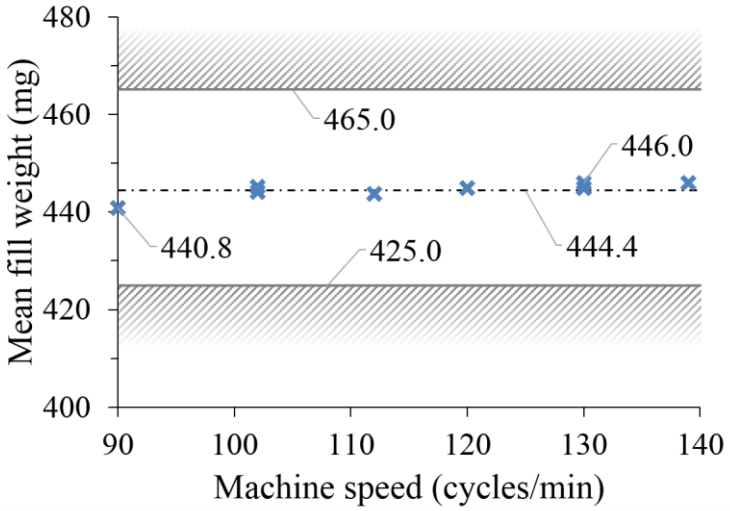

Figure 13: Mean fill weight of 8 runs executed for mixture A, boarders of the maximum tolerated deviation indicated with grey shading (calculated after Pharmacopoeia European [19], estimated RSD: 5 %): The mean based on 8 runs is 444.4 mg (dash-dot line).

To demonstrate the quality of the mean fill weight the boarders of the acceptable mean fill weight were shown in the figure. With a target mean capsule weight of 445 mg, the mean capsule weight should be between 425 – 465 mg. With respect to the achieved mean fill weight, all runs were well within the limits, independently of the machine speed.

Mixture B showed a similar result (Figure 14). The mean fill weight was 429.2 mg (target 428 mg) and ranged from 427.8 – 432.3 mg. Capsules were produced close to the target of 428 mg well within the required range (408.7 mg, 447.3 mg). Specific results can be seen in the Appendix A2. In general, the results for the mean fill weight were excellent. Only small deviations occurred which can easily be adjusted via a closed-loop control algorithm (e.g., using the tamping pin pressure). The goodness of prediction Q^2 [20] was calculated and showed an excellent quality of prediction for the mean fill weight: Q^2 was 0.939, which is slightly lower than the adjusted R^2=0.997. Assuming a uniform mixture (i.e., no segregation), the maximum and minimum amount of API filled into the capsules can be calculated. For the required 183.6 mg in mixture A, a mean API weight range of 181.8 – 184.0 mg was achieved. Mixture B with a desired amount of API of 101.7 mg ranged between 101.6 – 102.7 mg. Thus, regulatory targets (±4.5 %, see above) were easily satisfied, attesting to the feasibility of the rapid automated process development approach.

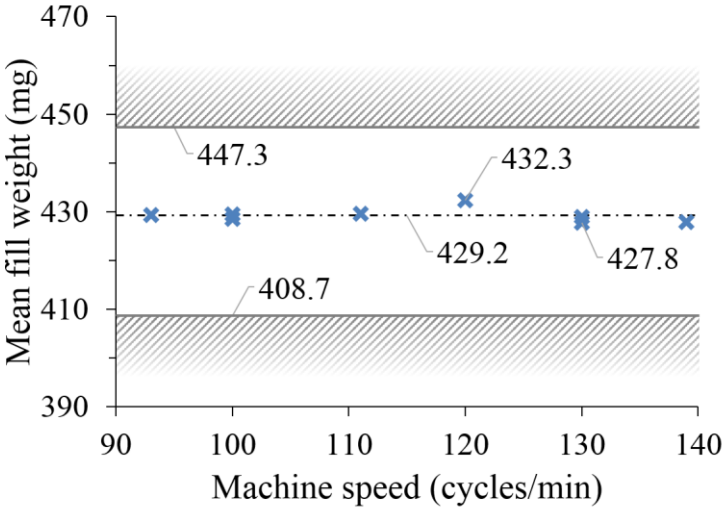

Figure 14: Mean fill weight of 8 runs executed for mixture B, boarders of the maximum tolerated deviation indicated with grey shading (calculated after Pharmacopoeia European [19], estimated RSD: 5 %). The mean value based on 8 runs is 429.2 mg (dash-dot line).

3.4.2.2 Control of the Relative Standard Deviation (RSD)

In addition to the mean fill weight the relative standard deviation is another critical quality attribute. Figure 15 shows the results for the RSD of the fill weight, achieved for mixture A. In all runs the RSD was below 0.41 %. A linear regression line was added. Notably, the RSD scatters around the line, as expected based on the previous experiments. Despite scattering, the regression lines seem to agree with the trend established by the model. As the setting for the machine speed is changed the RSD increases with speed.

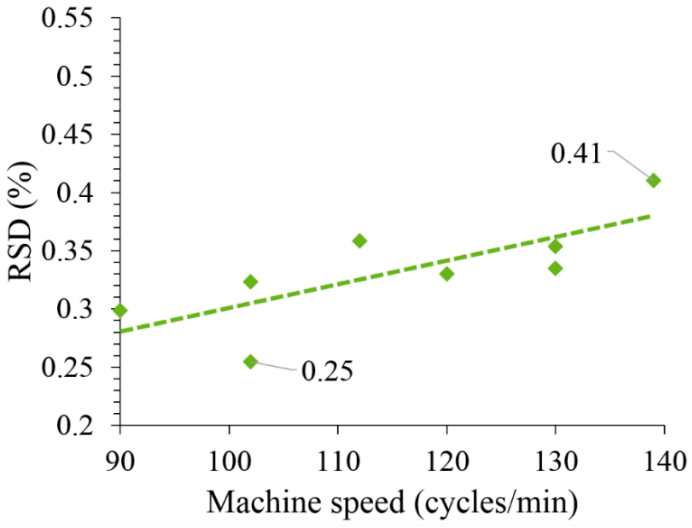

Figure 15: Relative standard deviation of the fill weight, mixture A.

Figure 16 shows the RSD for mixture B. The same increase of the RSD with speed can be observed. The RSD was higher than in mixture A, yet still below 0.5 %. The range was in between 0.32 % and 0.49 %. An overall deviation of about 0.1 % from the predicted RSD of mixture B was observed (compare data Appendix A2). However, the well-known fact that RSD is lower at the minimum speed was shown to be correct. In general, the RSD was excellent, and capsules could be filled practically at any speed in terms of the RSD of mean fill weight.

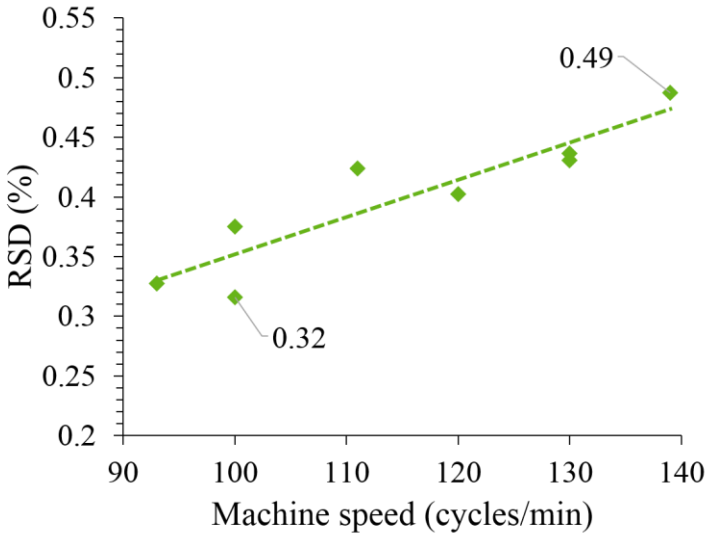

Figure 16: Relative standard deviation of the fill weight, mixture B.

In contrast to the prediction of the mean fill weight, the prediction of the relative standard deviation was less accurate. Mixture A had a Q^2 of 0.408, which does not correlate well to the adjusted R^2 (0.633) of the RSD model. However, although predicting the exact RSD was difficult, the trend (i.e., effect of speed) was identified in the validation experiments. The Q^2 of mixture B was negative, indicating a low prediction quality.

As stated above, the RSD effects explained by the model were small compared to the overall scattering. Such a result can be expected, especially if the overall RSD of the filling process was very small. Specifically, the RSD of mixture B had a higher RSD (0.07 %), which could not be explained by the model and resulted in an inaccurate prediction. The cause was not investigated further in light of the small effect on the overall low RSD.

3.5 Summary and Conclusion

A detailed process model was created based on 123 experiments, which were executed within only two days. This was possible by using process automation on a Bosch dosing disc capsule filler. Several effects were established and documented. The main factors (significant effects)

influencing the fill weight were the API concentration, the pressure and the amount of lubricant. With regard to the relative standard deviation, several interactions and influences were observed, although they were minor compared to the scattering in a very low overall RSD range. Apparently, the amount of magnesium stearate contributed to a low standard deviation (< 1 %) in all experiments. Within the design space, the powder bed height had no significant impact on the RSD. Therefore, the powder bed height can be reduced to a minimum of 5 mm without jeopardizing the filling process. This leads to a shorter residence time in the capsule filler.

Furthermore, the model was used for predicting the optimal processing conditions for a new capsule-filling task. Two mixtures were chosen inside the design space and the target was the amount of API (183.6 mg and 101.7 mg). The target fill weight was achieved with minimal deviations at various filling speeds. Specifically, with the help of the model, the mean API amounts were maintained within a range of 1.1 mg (mixture A) and 2.2 mg (mixture B), which is clearly within specifications. Although the model had an excellent prediction quality (Q^2 0.997) for the weight, the RSD was difficult to model since the effects were very small.

In this study, a new principle for developing and conducting production processes in the pharmaceutical industry was proposed. A continuous capsule-filling process was augmented with a rapid automated process development approach. Such a combination allowed us to screen, analyze, optimize and validate the process as a whole, while significantly reducing the time and effort involved.

With the help of automation technology (software and hardware), the efforts required for process development can be reduced significantly. This is especially important when developing continuous processes, where a design space and a control concept (including strategies for out-of-spec handling) are needed. Process development can be automated, running optimized experiments (design of experiments) without operator presences required. When using continuous systems, a scale-up of the process is not necessary since the same system can be used both for developing and production.

In general, our approach can make the entire process development phase transparent and comprehensive. A rapid automated process development connected to a continuous capsule-filling process can improve the development and production of pharmaceutical products using the capsule as a target dosage form.

3.6 References

[1] U.S. FDA. Pharmaceutical CGMPs for the 21th Century, Final Report. 2004 [cited 2017 August 29]. Available from: http://www.fda.gov

[2] Plumb K. Continuous Processing in the Pharmaceutical Industry. Chemical Engineering Research and Design. 2005;83:730–738.

[3] Van Snick B, Holman J, Vanhoorne V, et al. Development of a continuous direct compression platform for low-dose drug products. International Journal of Pharmaceutics. 2017;529:329–346.

[4] Podczeck F, Jones BE. Pharmaceutical capsules. Great Britain: Pharmaceutical Press; 2004. p. 101–116.

[5] Podczeck F, Newton J. Powder filling into hard gelatine capsules on a tamp filling machine. International Journal of Pharmaceutics. 1999;185:237–254.

[6] Carr RL. Evaluating flow properties of solids. Chem Eng. 1965;72:163–168.

[7] Patel S, Kaushal AM, Bansal AK. Compression Physics in the Formulation Development of Tablets. Crit Rev Ther Drug Carrier Syst. 2006;23:1–66.

[8] Bauer-Brandl A, Ritschel W A. Die Tablette: Handbuch der Entwicklung, Herstellung und Qualitätssicherung. 3rd edn. Aulendorf: ECV, Ed Cantor-Verlag; 2012. p. 586-588.

[9] Heda PK, Muteba K, Augsburger LL. Comparison of the formulation requirements of dosator and dosing disc automatic capsule filling machines. AAPS PharmSci. 2002;4:E17.

[10] Hardy IJ, Fitzpatrick S, Booth SW. Rational design of powder formulations for tamp filling processes. J Pharm Pharmacol. 2003;55:1593–1599.

[11] Hauer B, Remmle T, Sucker H. Gezieltes Entwickeln und Optimieren von Kapselformulierungen mit einer instrumentierten Dosierroehrchen – Kapselabfuellmaschine [Aimed Development and Optimization of capsule formulation on an instrumented dosator capsule filling machine]. Pharm Ind. 1993;55:780-786.

[12] Wagner B, Brinz T, Otterbach S, et al. Automation of a dosing-disc capsule filler from the perspective of reliability and safety. Drug Dev Ind Pharm. 2017:1–9.

[13] Rowe RC, Sheskey PJ, Quinn ME. Handbook of pharmaceutical excipients. 6th edn. London: The Pharmaceutical Press; 2010. 405.

[14] Eriksson L, Johansson E, Kettaneh-Wold N, Wikström C, Wold S. Design of Experiments Principles and Applications. Sweden, Umea: Umetrics AB; 2000. p. 213–220.

[15] Siebertz K, van Bebber D, Hochkirchen T. Statistische Versuchsplanung: Design of Experiments (DoE). Dordrecht: Springer; 2010. p. 42–43.

[16] Sobol I M, On the distribution of points in a cube and the approximate evaluation of integrals. USSR Computational Mathematics and Mathematical Physics. 1967;7:86–112.

[17] Siebertz K, van Bebber D, Hochkirchen T. Statistische Versuchsplanung: Design of Experiments (DoE). Dordrecht: Springer; 2010. p. 219.

[18] Council of Europe. European Pharmacopoeia 8th ed: Vol 1. Strasbourg: Council of Europe; 2013. p. 297–298.

[19] Council of Europe. European Pharmacopoeia 8th ed: Vol 1. Strasbourg: Council of Europe; 2013. p. 357–359.

[20] Eriksson L, Johansson E, Kettaneh-Wold N, Wikström C, Wold S. Design of Experiments Principles and Applications. Sweden, Umea: Umetrics AB; 2000. p. 87,92.

3.7 Appendices

A1: Experimental set 1

Table 4: Executed experiments to build a process model for the mean fill weight and the relative standard deviation.

No.	v	pbh	P	profile	API	lubri	MW	RSD	No.	v	pbh	p	profile	API	lubri	MW	RSD
1	100	30	1.2	2	50	1	425.0	0.68	63	110	15	1.2	3	32.5	3	418.3	0.41
2	95	25	4.0	2	50	1	446.8	0.45	64	118	10	4.5	4	32.5	3	439.1	0.44
3	127	25	3.6	1	50	1	444.2	0.42	65	126	10	3.3	3	32.5	3	433.1	0.33
4	90	25	4.3	3	50	1	446.6	0.36	66	112	5	2.6	2	32.5	3	430.5	0.37
5	121	25	2.8	4	50	1	436.4	0.47	67	115	25	2.2	3	32.5	5	436.2	0.31
6	134	20	4.8	4	50	1	447.6	0.47	68	133	25	1.5	3	32.5	5	428.0	0.64
7	106	20	3.4	3	50	1	440.6	0.30	69	81	25	2.4	1	32.5	5	441.3	0.28
8	112	20	4.6	1	50	1	449.9	0.41	70	97	25	3.6	4	32.5	5	445.4	0.31
9	109	20	2.3	3	50	1	433.1	0.44	71	95	25	4.2	4	32.5	5	448.6	0.37
10	86	15	2.9	4	50	1	438.8	0.44	72	121	25	4.4	2	32.5	5	453.4	0.39
11	114	15	1.3	3	50	1	423.9	0.44	73	103	20	4.9	1	32.5	5	457.2	0.35
12	107	15	2.7	1	50	1	438.2	0.38	74	130	15	3.2	4	32.5	5	442.3	0.51
13	93	10	1.5	1	50	1	429.6	0.42	75	116	15	2.8	1	32.5	5	443.0	0.33
14	98	10	4.9	4	50	1	445.4	0.42	76	87	10	3.7	3	32.5	5	444.9	0.32
15	111	10	4.4	3	50	1	443.8	0.34	77	99	10	2.3	2	32.5	5	437.3	0.30
16	129	10	2.5	3	50	1	431.6	0.47	78	139	10	4.3	1	32.5	5	450.4	0.35
17	125	10	2.2	2	50	1	432.7	0.66	79	122	10	1.7	4	32.5	5	428.0	0.51
18	120	5	3.1	2	50	1	438.2	0.49	80	140	30	3.2	1	15	1	407.6	0.39
19	118	30	3.9	4	50	3	450.1	0.42	81	111	25	2.3	4	15	1	398.6	0.44
20	124	30	1.3	2	50	3	435.3	0.47	82	86	25	4.8	3	15	1	416.3	0.36
21	87	25	1.6	4	50	3	437.8	0.42	83	126	20	1.4	4	15	1	390.3	0.53
22	89	25	3.8	1	50	3	455.9	0.30	84	92	20	3.7	2	15	1	412.9	0.33
23	117	20	1.7	1	50	3	440.3	0.38	85	88	20	2.5	2	15	1	405.2	0.31
24	103	15	3.5	1	50	3	454.4	0.36	86	119	20	1.1	1	15	1	390.1	0.50
25	139	15	1.1	2	50	3	433.3	0.65	87	132	15	4.7	2	15	1	417.4	0.37
26	131	10	1.9	1	50	3	440.2	0.41	88	100	15	3.0	1	15	1	408.5	0.33
27	96	5	3.4	2	50	3	448.5	0.39	89	94	15	3.3	4	15	1	406.6	0.36
28	101	5	1.8	4	50	3	434.6	0.39	90	127	15	1.6	2	15	1	393.9	0.40
29	105	10	4.1	3	50	3	453.5	0.33	91	133	10	2.9	3	15	1	402.3	0.29
30	92	30	3.0	1	50	5	456.4	0.29	92	136	5	3.8	3	15	1	406.1	0.36
31	102	25	2.7	4	50	5	452.6	0.38	93	108	5	4.4	4	15	1	410.1	0.42
32	130	25	1.0	3	50	5	437.7	0.44	94	83	30	1.9	3	15	3	408.2	0.30
33	82	20	4.6	4	50	5	463.8	0.37	95	104	30	2.1	4	15	3	407.1	0.39
34	138	20	2.4	2	50	5	452.5	0.39	96	137	25	4.7	3	15	3	424.2	0.34
35	135	20	3.3	2	50	5	459.1	0.36	97	135	25	2.1	1	15	3	408.5	0.42
36	106	20	1.8	1	50	5	448.7	0.25	98	99	20	4.5	1	15	3	427.7	0.35
37	138	15	2.5	4	50	5	444.9	0.57	99	129	20	4.3	4	15	3	418.5	0.47
38	84	15	1.5	2	50	5	443.0	0.29	100	98	20	2.8	3	15	3	411.1	0.36
39	81	15	4.3	2	50	5	462.1	0.32	101	120	15	2.3	1	15	3	411.8	0.41
40	113	15	3.9	1	50	5	460.8	0.32	102	122	15	5.0	3	15	3	423.2	0.43
41	105	10	4.1	3	50	5	459.2	0.27	103	91	15	2.4	4	15	3	409.9	0.42
42	89	10	3.1	3	50	5	453.7	0.27	104	85	10	4.2	1	15	3	424.1	0.40
43	128	5	4.8	1	50	5	466.6	0.34	105	82	10	2.6	3	15	3	409.4	0.36
44	94	5	2.1	3	32.5	1	413.0	0.39	106	115	5	4.0	4	15	3	413.8	0.42
45	132	30	2.6	1	32.5	1	424.2	0.36	107	107	10	4.0	2	15	3	422.6	0.37
46	101	25	3.9	3	32.5	1	430.9	0.33	108	97	10	1.6	3	15	3	404.7	0.40
47	114	25	3.5	4	32.5	1	428.4	0.37	109	125	10	2.0	4	15	3	404.5	0.53
48	137	25	2.0	4	32.5	1	417.7	0.62	110	116	30	4.9	2	15	5	436.8	0.42
49	124	20	4.1	1	32.5	1	435.5	0.38	111	84	30	3.3	1	15	5	427.6	0.36
50	85	20	2.0	2	32.5	1	421.9	0.33	112	123	25	3.5	3	15	5	424.2	0.43
51	134	15	4.1	2	32.5	1	433.2	0.36	113	113	25	1.8	2	15	5	414.0	0.44
52	117	10	3.6	2	32.5	1	431.5	0.32	114	109	25	3.1	4	15	5	423.4	0.43
53	119	10	1.8	3	32.5	1	414.8	0.31	115	96	20	1.3	1	15	5	412.8	0.39
54	83	10	3.8	4	32.5	1	427.7	0.32	116	131	20	3.8	2	15	5	429.3	0.45
55	105	10	1.3	4	32.5	1	410.4	0.41	117	123	15	3.4	1	15	5	428.2	0.41
56	88	5	4.7	1	32.5	1	437.2	0.30	118	102	15	4.6	3	15	5	431.2	0.42
57	108	30	4.5	2	32.5	3	447.6	0.36	119	88	15	1.9	2	15	5	417.1	0.33
58	93	25	1.4	3	32.5	3	424.4	0.34	120	107	10	4.0	2	15	5	430.4	0.44
59	110	20	3.0	3	32.5	3	435.7	0.28	121	97	10	1.6	3	15	5	412.2	0.41
60	128	20	2.9	2	32.5	3	435.7	0.37	122	125	10	2.0	4	15	5	412.9	0.60
61	90	20	1.1	4	32.5	3	419.3	0.42	123	104	5	2.8	2	15	5	422.4	0.41
62	91	15	4.8	2	32.5	3	448.7	0.41									

Abbreviations: No. - run number, v - speed (cycles/min), pbh - powder bed height (mm), p - pressure (MPa), profile - immersion profile, API - amount active pharmaceutical ingredient (%), lubri - amount of lubricant (%), MW - mean fill weight (mg), RSD - relative standard deviation (%)

A2: Experimental set 2

Table 5: Executed runs for the validation of the process model.

Speed (cycles/min)	Powder bed height (mm)	Pressure (MPa)	Profile (type)	API (%)	Lubricant (%)	Weight (mg)	Predicted weight (mg)	RSD (%)	Predicted RSD (%)
90	15.3	2.9	3	41.25	4	440.8	445.2	0.30	0.28
102	8.8	3.3	3	41.25	4	445.2	444.8	0.32	0.29
102	8.8	3.3	3	41.25	4	444.1	444.8	0.25	0.29
112	11.9	3.3	3	41.25	4	443.7	445.1	0.36	0.30
120	8.9	3.5	3	41.25	4	444.9	444.7	0.33	0.31
130	8.4	3.7	3	41.25	4	444.9	444.9	0.33	0.32
139	5.7	4	3	41.25	4	446.0	444.9	0.41	0.33
130	8.4	3.7	3	41.25	4	446.0	444.9	0.35	0.32
93	13.4	3.5	1	23.75	2	429.3	427.5	0.33	0.31
111	28.7	3.7	1	23.75	2	429.6	427.8	0.42	0.33
120	7.7	3.8	1	23.75	2	432.3	427.8	0.40	0.34
100	16.5	3.5	1	23.75	2	429.4	427.5	0.38	0.32
100	16.5	3.5	1	23.75	2	428.5	427.5	0.32	0.32
130	18.6	4.2	3	23.75	2	427.8	427.6	0.44	0.34
130	18.6	4.2	3	23.75	2	429.0	427.6	0.43	0.34
139	16.2	4.3	3	23.75	2	427.9	427.4	0.49	0.35

A3: Box-Cox plot and model transformation

A transformation was applied to the measured values of the relative standard deviation. The transformation was chosen based on the Box-Cox plot. The Box-Cox plot (Figure 17) compares the residual sums of squares (the error term) of different transformations (from λ = -1 to λ = 2). Transformations with a lower error term indicate a better fit. The significance line illustrates the border between transformations having a worse fit than the best fit (based on a likelihood-ratio test). For the mean fill weight no transformation was chosen as the untransformed response has not a significantly worse fit than a square root transformation (both below significance line). The data of the RSD were transformed using a reciprocal square root transformation.

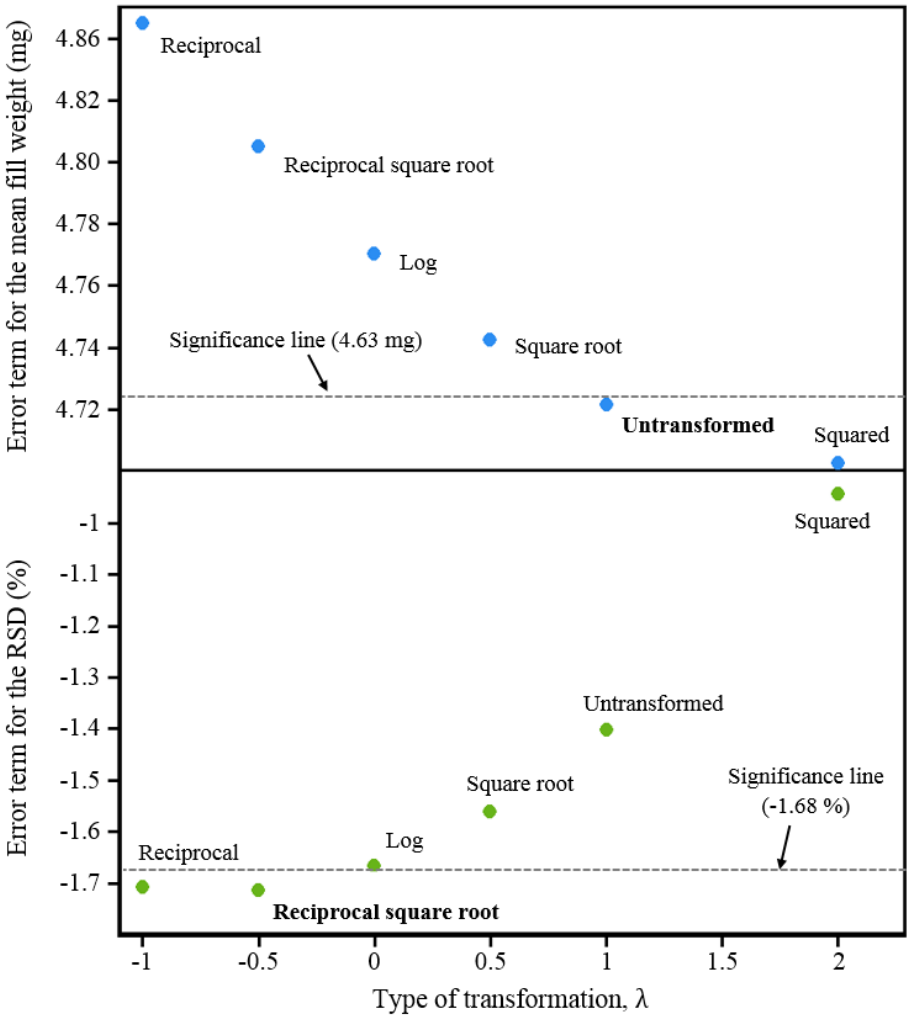

Figure 17: Box-Cox plot for the mean fill weight (MW) and the relative standard deviation (RSD). Lower values indicate a better fit, points above the significance line result in a significantly worse fit than the best fit in the comparison.

A4: Detailed information about the process model

The equation of the mean fill weight (MW) and the relative standard deviation (RSD) are given below. The abbreviations are: *v - speed (cycles/min), pbh - powder bed height (mm), p - pressure (MPa), profile - immersion profile, API - amount active pharmaceutical ingredient (%), lubri - amount of lubricant (%).*

Equation of the mean fill weight

$$\mathbf{MW} = a * \mathbf{v} + b * \mathbf{pbh} + c * \mathbf{p} + d(\mathbf{profile}) + e * \mathbf{API} + f * \mathbf{lubri} + g(\mathbf{profile}) * \mathbf{v} + h * \mathbf{v} * \mathbf{lubri} + i * \mathbf{p} * \mathbf{pbh} + j(\mathbf{profile}) * \mathbf{pbh} + k * \mathbf{pbh} * \mathbf{API} + l(\mathbf{profile}) * \mathbf{p} + m * \mathbf{API} * \mathbf{p} + n(\mathbf{profile}) * \mathbf{lubri} + o * \mathbf{API} * \mathbf{lubri} + p * \mathbf{pbh}^2 + q * \mathbf{p^2} + r * \mathbf{API^2} + s * \mathbf{lubri^2} + t * \mathbf{pbh} * \mathbf{API} * \mathbf{p} + u(\mathbf{profile}) * \mathbf{lubri} * \mathbf{v} + const.$$

Equation of the relative standard deviation

$$\mathbf{RSD} = 1/\left(a * \mathbf{v} + b * \mathbf{p} + c(\mathbf{profile}) + d * \mathbf{API} + e * \mathbf{lubri} + f * \mathbf{p} * \mathbf{v} + g(\mathbf{profile}) * \mathbf{API} + h * \mathbf{API} * \mathbf{lubri} + i * \mathbf{p^2} + j * \mathbf{API^2} + const.\right)^2$$

Table 6: Factors of the model.

MW				**RSD**	
Variable	Factor	Variable	Factor	Variable	Factor
const.	353.698690139	*k*	0.008865713	*const.*	2.358607641
a	-0.012819607	*l(1)*	0.137186510	*a*	-0.009581265
b	0.037655098	*l(2)*	0.424784696	*b*	0.023771499
c	8.744599478	*l(3)*	-0.168727731	*c(1)*	0.021828114
d(1)	3.696754066	*l(4)*	-0.393243476	*c(2)*	0.072086027
d(2)	6.485413317	*m*	0.039428902	*c(3)*	-0.004238742
d(3)	-10.364024192	*n(1)*	-0.198621456	*c(4)*	-0.089675399
d(4)	0.181856809	*n(2)*	-2.736429670	*d*	0.006105110
e	1.625396829	*n(3)*	2.752946943	*e*	-0.080826739
f	6.670726882	*n(4)*	0.182104183	*f*	0.001888510
g(1)	-0.004688455	*o*	-0.014725939	*g(1)*	0.000864614
g(2)	-0.050630308	*p*	-0.008067276	*g(2)*	-0.002661256
g(3)	0.066850793	*q*	-0.588741100	*g(3)*	0.002077767
g(4)	-0.011532031	*r*	-0.012327437	*g(4)*	-0.000281125
h	-0.008145079	*s*	-0.196058185	*h*	0.002672827
i	0.100062502	*t*	-0.002439625	*i*	-0.033261512
j(1)	-0.097577490	*u(1)*	0.002631044	*j*	-0.000200904
j(2)	-0.047647514	*u(2)*	0.024775569		
j(3)	0.114030471	*u(3)*	-0.024686567		
j(4)	0.031194533	*u(4)*	-0.002720046		

4 Using Online Content Uniformity Measurements for Rapid Automated Process Development Exemplified via an X-ray System

(This chapter is based on the publication Wagner B, Brinz T, Khinast J, Using online content uniformity measurements for rapid automated process development exemplified via an X-ray system, Pharmaceutical Development and Technology, 2019 24:775–787.)

4.1 Introduction

4.1.1 Rapid Automated Process Development

Rapid automated process development (RAPD) is an approach, which was presented by Wagner et al. [1]. The RPDA allows a fast and efficient development of a continuous capsule-filling process, based on a high level of automation in combination with efficiently designed experiments. To develop a process, it is vital to understand the process as a whole. The impacts of the critical process parameters (CPPs) and the critical material attributes (CMAs) on the critical quality attributes (CQAs) must be known [2]. Interactions between the CPPs and the CMAs should be determined. The black box of the process must be elucidated to ensure an optimized and robust production process. With the help of a detailed process model, this is achievable. Subsequently, the process can be analyzed and optimized. A solution to investigate the process, by creating a process model, is to execute experiments. Without doubt, this is connected with effort; yet, an automated process development approach can significantly accelerate this process.

First, it is important to choose the right experiments. Design of experiments (DoE) and previously gathered process knowledge helps to use only a minimum amount of experiments, which in addition ensures a sufficient screening of the process parameters. To run experiments in an efficient way a high level of automation is applied. An example is the capsule filler. Normally process parameters on a capsule filler are manually adjusted or at least manually added to the software of the machine. This is sufficient to produce a certain batch or campaign of a product. For the process development this, however, is an issue. Several adjustments have to be made. A manual adjustment of the parameters can lead to mistakes and takes several minutes. Thus, process parameters of the capsule filler should be automated in that way that a main controller could adjust them, reducing time of experiments significantly. Beside the adjustment of the CPPs and the CMAs (i.e., changing the composition of the mixture), another important part is the automated measurement of the CQAs. The CQAs considered by Wagner et al. [1] were the mean capsule weight and the associated relative standard deviation (RSD). They were measured at the end of the continuous capsule-filling process using a gravimetric inline scale. Although weight and weight uniformity are essential for the development of a continuous capsule-filling process, the active pharmaceutical ingredient (API) content (assay) and the API content uniformity (CU) are equally important, especially for low-dose drugs (API < 25 %). However, to integrate a CU check reasonable into the RAPD it should be automated similarly to the weight detection and must be executed in a similarly efficient way.

4.1.2 Automated Content Uniformity (CU) Check

Machines for the online gravimetric weighing are commercially available from several manufactures and can detect the capsule weight within the RAPD concept. Compared to this, a CU check requires much more effort and equipment. On the one hand, there are the analytical techniques like for example HPLC (high performance liquid chromatography), TLC (thin layer chromatography) or GC (gas chromatography). These techniques require an elaborated sample preparation before the content can be determined. The measurements take a certain time and the content cannot be measured in-line within the capsule production. Thus, an integration into the RAPD would be challenging, as a requirement is a fast measurement of the samples in an automated way. Possibly, the measurements can be automated (e.g. Saitoh and Yoshimori 2008, [3]) or executed offline. However, significant time and effort is required.

On the other hand, there are spectroscopic technologies available such as NIR (Near Infrared), UV-Vis (Ultraviolet-visible) or Raman spectroscopy. Nowadays, they are frequently used as sensors (i.e., process analyzers) within the Process Analytical Technology framework (PAT, [4]). With the help of these techniques, it is possible to control the CPPs, and thus, to maintain the CQAs within an acceptable range, ensuring the final product quality. Different process steps and different CMAs require different technologies. Therefore, during continuous manufacturing a range of different spectroscopic sensors are currently used [5]. Fonteyne et al. ([6]), for example, identified various PAT options for particular steps in continuous manufacturing. An application example is the real-time measurement of a drug concentration in a continuous mixing process using NIR spectroscopy (Vanarase et al. [7]).

Aiming for the integration into the RAPD, a measurement of the API content (CQA) at the end of the process is desirable. First, it is beneficial that all of the influences of CPPs and CMAs on the CQA are determined for the final product (i.e., the closed capsule) and consequently no other influences are involved like, for example, a closing or a transporting step. Second, it is of interest to measure the capsule volume. Therefore, the actual API content of the capsule is known and not detected from a possibly misleading surface composition (compare figure 3 of chapter 3.1). Actually, there are studies that investigated this option. Ellison et al. [8] described, for example, the use of Raman spectroscopy in transmission to asses quantitative the content of API inside capsules. Commercially available products (e.g., TRS100, Agilent Technologies, Inc., Santa Clara, United States; SAM-Spec, Chauvin Arnoux Indatech, Clapiers, France) allow such measurements for the industry. In conclusion, the technology is available but at the same time connected with additional effort (e.g., high investment cost of machinery). However, within the RAPD, an automated content check is a worthwhile feature.

To highlight the benefits, and thus, to accelerate development and application, we provide a demonstration example, which allows an automated content check inside hard gelatin capsules. Summarized, an automated content check can be realized either by automating traditional measurement technologies (e.g., HPLC) or by implementing spectroscopy technology in an automated content check.

In this study, X-ray absorption is used as an example technology to check CU. Other techniques (Raman, UV-Vis, etc.), however, can be used as well.

4.1.3 Continuous Capsule Filling

A continuous capsule filling process consists of several different process steps that are combined into one process. A schematic is presented in figure1 [1]. The process has three gravimetric feeders, a horizontal blender and a hard gelatin capsule filler. The feeders can be set to various feed rates, changing the composition of the material fed into the blender. The blender mixes the materials such that a uniform mixture is delivered to the capsule filler. The mixture is filled into capsules and finally transported to a system, which checks the CQA. The system applied in this study is an automated content check, which uses an X-ray sensor to inspect content and content uniformity.

Obviously, there are several process parameters (i.e., CPPs), which may affect the CQAs. Likely, there are strong interactions between the CPPs of the different process steps. The CPPs influence each other. As such, rather than testing each single unit on its own, the combination of units should be examined as a whole via the RAPD. One example is given by the feeders that feed continuously into the blender. A fluctuation in the feed rate can induce variations in the final mixture. For some materials, feeding can be a challenging task and significant fluctuations may occur. However, whether these fluctuations are critical for the process cannot be determined without considering the subsequent process steps. For example, the blender may be able to dampen the fluctuations ([9], [10]) or fluctuations in the feed may be acceptable, if their influence on the content uniformity is negligible (or below the pharmacopoeia limits). This is why in terms of process development it is important to consider the process as a whole. Consequently, the combination of a content check and the RAPD can be a valuable solution for the development of a continuous-capsule filling process.

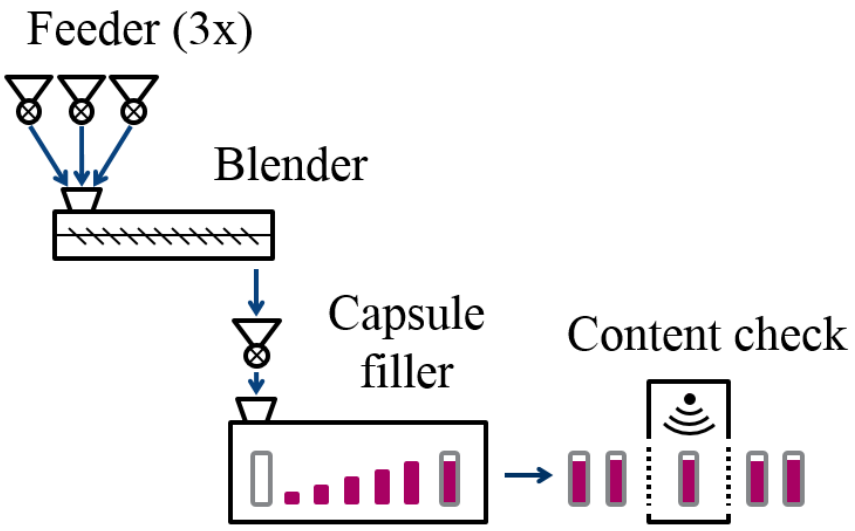

Figure 1: Schematic of a continuous capsule-filling process. A content check is implemented at the end of the process. The API content inside the capsules is determined.

In our work, we applied an X-ray system to detect barium sulfate (model API compound) inside hard gelatin capsules. Thus, we implemented a system that is able to determine quickly the content and content uniformity of one single ingredient (barium sulfate) inside capsules. In a final application, the component of interest is an active pharmaceutical ingredient (API). For such systems, NIR or Raman spectroscopy can be used. However, in this study X-ray absorption is applied as a model PAT method, as X-ray systems are by now used in capsule fillers. If a specific API can be monitored via X-ray absorption depends on the specific absorption characteristics. As mentioned above, alternatives to X-ray absorption exist. For the remainder of the study barium sulfate is termed “API”, without claiming that barium sulfate is a real pharmaceutical active ingredient.

In summary, our study demonstrates how valuable an automated CU checking system is within the RAPD. The integration helps to solve challenges like selecting the optimal mixture compositions (e.g., considering the influence on segregation and the content uniformity), the blender parameters (e.g., speed, design) or the capsule filler settings (e.g., speed, tamping pressure). With the RAPD the process is understood as a whole, and likewise analyzed in a fast and efficient way.

4.2 Materials

Four materials were used in this study. Barium sulfate (Schwerspat CH1, Sachtleben Bergbau GmbH & Co. KG, Germany) acted as the product of mature interest (i.e., API) since it strongly

absorbs X-ray radiation and can be detected via an X-ray system (discussed below). With its high bulk density (BD of 2.49 g/ml), it is up to 4-5 times denser than the typical excipients. However, the mixture filled into capsules contained only a relatively small amount of barium sulfate (10 wt % of barium sulfate) which can be challenging in a real process in terms of content uniformity. Lactose, i.e., Spherolac 100 (Meggle-Pharma, Germany), was used in this study as excipient for the development of the X-ray detection model. It was chosen since it can be dosed accurately via a small auger feeder due to the relatively good flowability [1] and a mean particle size of 119 µm.

Two common excipients, i.e., starch (Maize Starch Extra White, Roquette Pharma, France) and mannitol (Pearlitol 400 DC, Roquette Pharma, France), were mixed barium sulfate in the continuous capsule-filling process. The Pearlitol 400 DC was previously mixed with a small amount of magnesium stearate (0.5 %, Nutri Mag ST-v, Calmags GmbH, Germany), improving the flowability and compressibility of the excipient. The mixture of mannitol and magnesium stearate is referred to as the mannitol mixture in this study. The two excipients were chosen because of their significantly different particle size: the mean particle sizes of starch and mannitol are 14 µm and about 366 µm, respectively.

Table 1: Raw material properties (n = 3, mean ± sd).

Material	x_{10} (µm)	x_{50} (µm)	x_{90} (µm)	Span $(x_{90}-x_{10})/x_{50}$	LOD (%)	Bulk Density (g/ml)	Tapped Density (g/ml)	Zeff	X-ray coefficient
Barium sulfate	3.36 ± 0.04	25.90 ± 0.55	112.39 ± 1.72	4.21 ± 0.03	0.03 ± 0.01	2.49 ± 0.04	2.96 ± 0.01	45.5	94196.4
Maize Starch	7.86 ± 0.09	14.26 ± 0.07	21.05 ± 0.02	0.92 ± 0.01	10.55 ± 0.23	0.55 ± 0.00	0.70 ± 0.00	6.89	327.1
Mannitol mixture	19.29 ± 2.74	365.55 ± 8.98	589.11 ± 12.94	1.56 ± 0.01	0.11 ± 0.01	0.72 ± 0.01	0.79 ± 0.01	6.90*	328.5*
Lactose	42.26 ± 0,29	119.02 ± 0.16	203.18 ± 0.20	1.35 ± 0.00	0.15 ± 0.01	0.71 ± 0.00	0.90 ± 0.00	6.95	335.7

* values taken for pure mannitol only, the small amount of magnesium stearate is neglected

Table 1 summarizes the raw material properties. All measurements were performed in triplicate. The particle size distribution was measured via a laser diffraction (HELOS BR, Sympatec, Germany) after dispersing the dry powders by applying compressed air. The residual moisture content of the powders was determined using a moisture analyzer (Moisture Analyzer HR73, Mettler Toledo GmbH, Germany). For this purpose, a sample of approximately 5 g was dried at 80 °C until the weight change was constant for 30 s, upon which the percentage loss on drying (LOD) was recorded. This information was required for the replication of experiments since some excipients change their behavior when moisture levels are varied. After filling a certain quantity of powder into a 250 ml graduated cylinder and determining the bulk

density (BD), the powder sample was mechanically tapped 2500 times to establish the tapped density (TD). These two densities are relevant for a rough estimation of the dosing disc height.

To get an impression of the X-ray attenuation of the different materials, the X-ray coefficient is provided, which is part of the attenuation coefficient ([11]) described below. The X-ray coefficient represents the effective atomic number (Z_{eff}) to the power of 3. The effective atomic number is calculated after Murty [12] using the chemical compositions described in literature ([13], [14]). Barium sulfate has a much higher X-ray coefficient compared to the excipients (about 285 times higher). Mannitol, lactose and starch have very similar coefficients (ranging from 327.1 – 335.7). In conclusion, barium sulfate absorbs the X-ray much stronger than the other excipients. Thus it should be detectable by an X-ray system. In the experiments, hard gelatin capsules (CAPSUGEL) size 1 were used, which had a mean weight of 75.8 mg and a RSD of 1.5 %.

4.3 Methods and Experimental Design

4.3.1 X-ray Sensor System

In this study, we used an X-ray system (KKX 3900, Robert Bosch Packaging Technology GmbH, Waiblingen, Germany) to establish the mass of barium sulfate inside the capsules. This inline measurement system is typically used to detect the length of closed capsules, the fill weight, dented capsules, the number of tablets filled inside a capsule and the presence of foreign objects (Vogt et al. [15]).

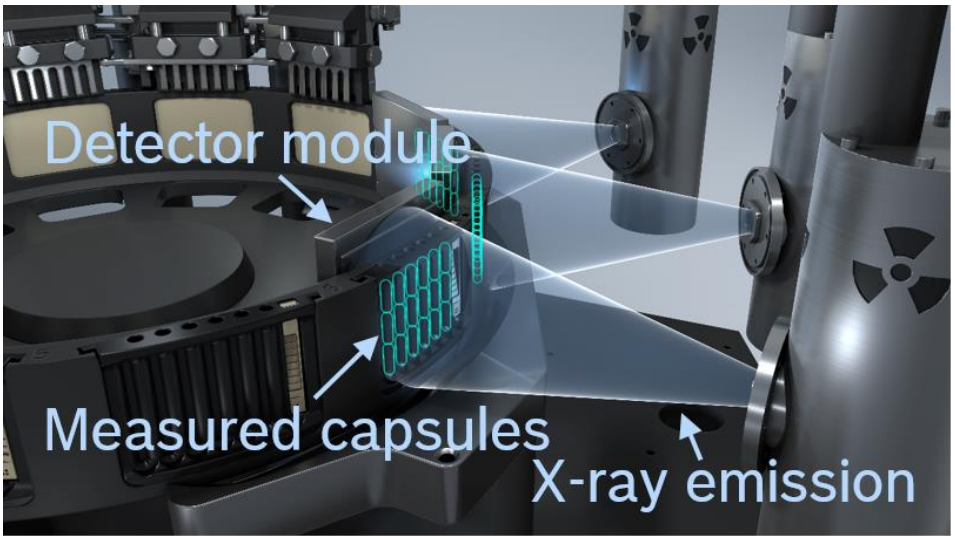

Figure 2: Operating principle of the X-ray system. Capsules are placed in front of a detector module and are irradiated via X-ray emission.

Figure 2 illustrates the system's operating principle. X-rays are passing through the capsules positioned inside the machine. Behind the capsules there is a detector module that translates the X-ray emission into an image. The system analyzes this image and displays the X-ray emission absorbed by the capsules. Depending on the capsule weight and the type of powder inside the capsule, the absorption varies. Note, that the user is adequately protected from the radiation by a protective housing (not illustrated in the figure). Additionally, a study by Vogt et al. [16] concluded that there is no significant negative influence on the medical product. The X-ray radiation was increased 120 times (2 hours), a light-sensitive API was exposed, and no significant degradation was detected. During an artificial light exposure of 30 minutes the same API degraded by 10 %.

Figure 3 shows a typical result of the X-ray measurement. A capsule filled with lactose and barium sulfate was examined. Dark areas in the image represent barium sulfate, which strongly absorbs the X-ray radiation, resulting in a lower X-ray intensity recorded by the detector and darker areas. Bright areas represent a low absorption of the X-ray radiation. For example, the upper quarter of the capsule is filled with air and only an insignificant absorption by the capsule shell is visible. Various barium sulfate concentrations can be observed inside the capsule: low barium sulfate concentration on the top surface of the capsule and a high barium sulfate concentration in the middle of the capsule. A surface measurement of the barium sulfate concentration alone would probably predict an incorrect content in the capsule.

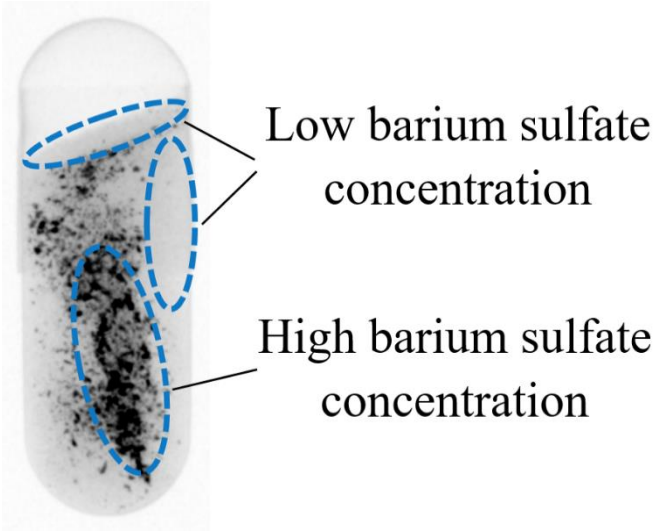

Figure 3: X-ray image of a manually-filled capsule, containing two products: barium sulfate and lactose. Darker areas illustrate significant X-ray absorption by barium sulfate. Lighter areas indicate weak absorbance by lactose and the gelatin shell.

4.3.1.1 X-ray Theory

The X-ray emitter produces X-rays that penetrate the capsules, are then transformed into visible light and are recorded by a camera. As a result, for each capsule a grey-scale image was captured. The mean grey value of the image represents the absorbed X-ray radiation. The basic principle of how an X-ray signal can be used to identify the amount of material inside a capsule is described below.

In general, the absorption of the radiation can be described by Eq. 1. The absorption (Abs) can be calculated via the ratio of X-ray intensity recorded with (I) and without (I_0) the capsule placed inside the measurement area. According to the Beer–Lambert law [11], absorption can be defined based on the combination of material attenuation coefficient (μ, containing among others the atomic number) and distance that the radiation travels through the material (x).

$$Abs = \frac{I}{I_0} = e^{-\mu x} \tag{1}$$

The signal we use for the detection of barium sulfate is calculated from the natural logarithm of the absorption and is therefore designed as in Equation 2.

$$Signal = \ln(Abs) = -\mu * x \tag{2}$$

If the X-rays pass more than one material consecutively, the total signal can be computed by summarizing the multiplication of the attenuation coefficient (μ) and thickness (x) of each material. For illustration following theoretical example is calculated. A parallel arrangement of two cubic materials in front of two X-ray detector elements is given. Each cube covers one of the two detector elements. The thickness of the cubes is represented by x_1 and x_2. Each cube is radiated with the intensity I_0 and the attenuated intensity is detected by the detector elements. The absorption can be calculated using the attenuation coefficient μ_1 and μ_2, thus the sum of the signal gathered from both detector elements can be calculated by Eq. 3 (materials in parallel arrangement). A different arrangement is given when a serial arrangement of the cubes is used. One detector element is now freely radiated, the other one shielded by the two cubes. The sum of the signal detected by both detectors is calculated as described in Equation 4. Notable is the same signal for both, the serial and the parallel arrangement of the materials.

$$\sum Signal_p = \ln\left(\frac{I_0 * e^{-\mu_1 * x_1}}{I_0}\right) + \ln\left(\frac{I_0 * e^{-\mu_2 * x_2}}{I_0}\right) = -\mu_1 * x_1 - \mu_2 * x_2 \tag{3}$$

$$\sum Signal_s = \ln\left(\frac{I_0 * e^{-\mu_1 * x_1} * e^{-\mu_2 * x_2}}{I_0}\right) + ln\left(\frac{I_0}{I_0}\right) = -\mu_1 * x_1 - \mu_2 * x_2 \tag{4}$$

With this consideration, the signal in a defined area does not depend on the order in which the materials are permeated or on the distribution of the materials inside of it. Thus, the signal can be described as the sum of logarithmic absorptions (Eq. 5) with n different materials.

$$Signal = \ln(\frac{I_1}{I_{0_1}}) + \cdots + ln\left(\frac{I_n}{I_{0_n}}\right) = -(\mu_1 * x_1 + \cdots \pm \mu_n * x_n) \quad (5)$$

With a signal independent from the orientation and location of the material in a constant detection area, following consideration can be made. If the material is equally distributed over the detector area A an equivalent distance $x_{equiv.}$ can be calculated for each material (considering volume constancy). Subsequently the equivalent distance $x_{equiv.}$ can then be described via a constant c and the mass of the material m (Eq. 6). The constant c is defined as the reciprocal of the material's density ρ multiplied by the constant detector area (A). If two materials are used, Equation 7 can be applied.

$$x_{equiv.} = \frac{1}{\rho * A} * m = c * m \quad (6)$$

$$Signal = -\left(\mu_1 * x_{equiv._1} + \mu_2 * x_{equiv._2}\right) = -(\mu_1 * c_1 * m_1 + \mu_2 * c_2 * m_2) \quad (7)$$

The equation has only three variables and several constants. To determine the amount of material m_1 the following substitutions are made:

$$p_i = \mu_i * c_i \quad (8)$$

$$m_2 = m_{tot} - m_1 \quad (9)$$

$$m_1 = -\frac{p_2}{(p_1 + p_2)} * m_{tot} - \frac{1}{(p_1 + p_2)} * Signal \quad (10)$$

To establish mass m_1 (e.g., barium sulfate mass), the parameters p, mass m_{tot} and the X-ray signal are required. The parameters (p_1, p_2) can be determined in calibration experiments and are material-dependent (constant detector area A presumed). As described above, we used two kind of materials: barium sulfate and excipients. Barium sulfate was chosen since it strongly absorbs X-rays. In general, the attenuation coefficient is influenced by different factors. One important factor is the effective atomic number [12], which depends on the type of atoms of the molecules. Lactose, starch, mannitol or gelatin using equal or similar atoms (C, H, O, N). The result is a similar attenuation number of the excipients compared to the barium sulfate ($\mu_{lactose} \approx \mu_{manitol} \approx \mu_{starch} \ll \mu_{barium\ sulfate}$). Thus, the excipients can be lumped into μ_2 and the mass of barium sulfate m_1 can be calculated according to Eq. 10 above.

4.3.1.2 Experiments 1: Creation of a Detection Model

To detect the amount of barium sulfate located in the capsule via the X-ray system, two parameters had to be determined (Eq. 11): the effect of total capsule mass $\boldsymbol{a}$ and the effect of measured X-ray signal $\boldsymbol{b}$:

$$m_{API} = -\boldsymbol{a} * m_{tot} - \boldsymbol{b} * Signal \quad (11)$$

To that end, the following experiment was performed. A small auger filler (diameter 5 mm) was used to dose powder into 49 capsules with various amounts of powder. First, barium sulfate was filled. Next, lactose was added. Random fill durations were applied to achieve random amounts of powder in the capsules. Since the capsules were weighed before and after barium sulfate was filled, the exact amount of barium sulfate was known (it ranged from 16.2 mg to 69.9 mg). After adding lactose, the total weight of the capsule was measured (it ranged from 337.7 mg to 463.6 mg). Additionally, capsules containing only the excipient were added. For details refer to Appendix A1.

Figure 4 illustrates 12 of 49 capsules used for developing a model of the capsule weight. The filled amount of barium sulfate (mg) and the total capsule weight (mg) are shown above and beneath the capsules, respectively. The capsules are arranged according to the amount of barium sulfate: the first two capsules on the left contain no barium sulfate, only various amounts of lactose. The capsules with the lactose are bright. The X-ray emission is only slightly absorbed. When the amount of barium sulfate is increased, a higher absorption is visible (i.e., the capsules are getting darker).

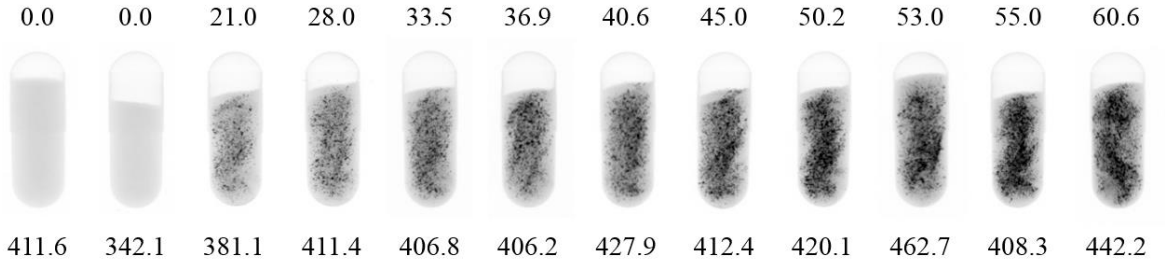

Figure 4: Examples of capsules used for model development of the detection model. The amount of barium sulfate (mg) and the total capsule weight (mg) are shown above and beneath each capsule, respectively. The first two capsules only contain lactose (no barium sulfate).

4.3.2 Continuous Capsule-Filling Process

4.3.2.1 Critical Process Parameters

A continuous capsule filling process has several process parameters. Each unit (i.e., feeder, blender and capsule filler) has its own CPPs, which have to be determined and controlled. For example, in the capsule filler there are the machine speed, pressure, immersion depth of the stations and the powder bed height [1]. The continuous capsule-filling process itself starts with three feeders located at the top of the process. For each feeder, a different feed rate (kg/h) can be set, and thus, different mixture compositions can be achieved. Changing the mixture composition can have a crucial influence on the final product [1]. The blender is designed as a horizontal blender (Figure 5, left).

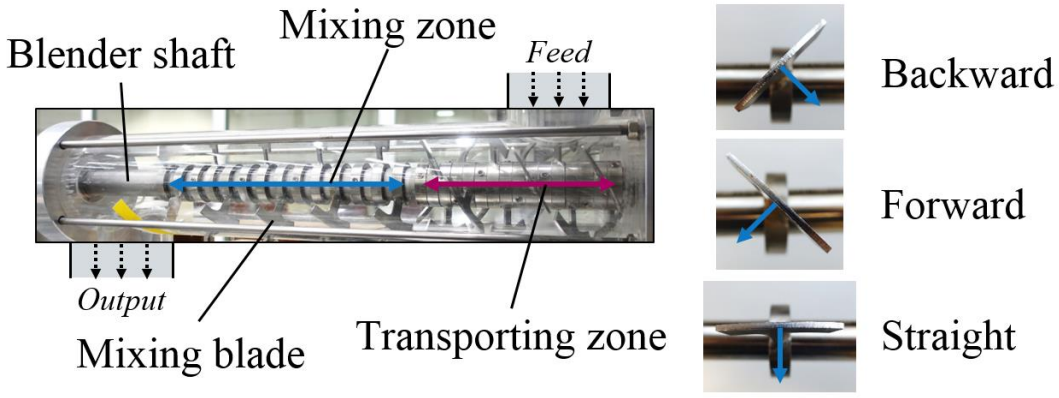

Figure 5: Details of the horizontal continuous blender, i.e., a prototype for experimental studies designed at the Robert Bosch Packaging Technology GmbH, Waiblingen, Germany. First, the product is fed into the blender, transferred to the output and moved into the capsule filler. Three types of mixing blades were used in the experiment. Their orientation is shown on the right.

In a blender, at least two parameters can be adjusted. First of all, this is the blender speed. Propelled by an electric motor, the blender's shaft can run at different speeds, which can influence the blending process (e.g., change the energy delivered to the powder). The second parameter is the geometry of mixing blades attached to the blender's shaft. The product is fed from the feeders into the blender. Below the feed (transporting zone, length about 17 cm), several blades form an auger forwarding the product into the mixing zone (24 cm) where the mixing blades scoop up the powder. 12 mixing blades were positioned at an relative angle of 120 degrees in all of our experiments. In order to adjust the geometry of the mixer, various mixing blades were used. On the right side of Figure 5, three available types of blades are

illustrated: one with a backward angle of -45°, one with a forwarding angle of 45° and one with an angle of 90°. The blender's shaft turns anticlockwise (in the direction of the powder flow). The blue arrows starting at the blades (right part of Figure 5) illustrate the direction of the impulse transmitted to the powder. The forward blade and the straight blade create a forwarding impulse and a radial movement of the powder, respectively.

In general, the task of the mixing blades is not to transport the powder rapidly through the mixer (backward plates can even shovel the powder backwards) but rather to mix the powder via cross-currents, while transferring energy to it. As powder is continuously fed, its amount in the blender increases and after a while a powder slope between the feed section and the output is formed. The height difference allows the powder to flow through the blender, even when backward-oriented mixing blades are used. Moreover, the kinetic energy introduced by the blades loosens up the powder, enhancing flowability. The orientation of the blades affects the height difference in the powder bed (Δh of feed to output), the amount of powder inside the blender, and therefore, the residence time in the unit. Different residence times lead to a variation of mixture efficiency. To vary mixing efficiency, three types of blades were used in the design of experiments with a forward, straight and backward orientation.

4.3.2.2 Experiments 2: Modelling of the Capsule-Filling Process

In the Design of Experiments (DoE), 24 runs were planned. The Cornerstone 7.0 (camLine, Germany) software and D-optimal [17] design were applied. For details, refer to the Appendix A2 (No. 1 – 24). In the capsule filler, two parameters were changed: the tamping pressure and the speed. The other parameters were constant. The powder bed height was 25 mm. The tamping stations (1-5) were set to heights of 15, 15, 12, 13 and 13 mm. A dosing disc of 17 mm was used. The starch and the mannitol mixture were the two excipients in the experiment. The amount of API (i.e., barium sulfate) fed by the feeder was set to 10 %, and the entire mass flow of the three feeders was maintained at 10 kg/h. The ratios of starch and mannitol mixture were 20 – 60 % and 30 – 70 %, respectively. The blender's geometry was varied as a categorical factor (i.e., forward, straight and backward). Table 2 provides an overview of the process parameters varied in this experiment.

Table 2: Ranges of the process parameters varied in the process modelling.

Capsule filler speed (cycles/min)	Capsule filler tamping pressure (MPa)	Blender geometry (blade orientation)	Percentage starch (%)	Blender speed (rpm)
80 - 140	0.1 – 0.5	forward, straight, backward	20 – 60	41 – 136

The experimental procedure was as follows. First, the feeders were set to a desired mass flow rate. Next, the other process parameters were set as stated in the experimental design. If a process parameter of the feeder-blender unit (FBU) had to be adjusted, the FBU was roughly cleaned (i.e., with a vacuum cleaner). The product remaining in the capsule filler was removed as well to ensure that the results could be attributed correctly. However, if there was enough product remaining in the capsule filler additional experiments were executed before the rough cleaning. The mixture was therefore the same in these addition experiments but the process parameters of the capsule filler were altered. These experiments were included in the results and used for the model development purposes (Appendix A2, No. 25 – 33).

At the start of an experiment, the feeders were switched on and the blender was activated. Depending on the blender's geometry, it took some time to feed the powder into the capsule filler (i.e., time to establish the above-mentioned powder slope). Once the hopper (i.e., a buffer) was filled by 15 %, the capsule filler started. When the powder bed height in the capsule filler reached the set point (25 mm), the capsules were collected. The experiments were conducted in two days.

After all the runs were completed, the API amount was determined. For each run, 48 capsules were randomly chosen. The capsules' weights were measured using a XPE 204 (Mettler Toledo, Switzerland) and their X-ray absorption was assessed. With the help of the X-ray model, the amount of API located in the capsule was determined. This is ensured to be correct as the validation experiments (see below) provided an exact determination of the API inside the capsule for similar mixtures ratios (correction factors applied). Hence, the API content of each capsule is available for the process modelling.

4.3.2.3 Target Definition

Mean API mass (mg): This target represents the mean mass of API dosed into the capsule, calculated for the respective experimental run. The X-ray model was used to determine the mass. After the mass of API of each capsule was determined, the mean was calculated.

RSD of API mass (mg): In addition to the mean API mass, the RSD of the API amount is important. In a capsule filling process, the RSD of the filled weight indicates if the capsules are equally filled. However, a variation in the content uniformity cannot be detected solely based on the RSD of the capsule weight, especially for small amount of API (< 25 %). To that end, we investigated whether the capsules have the same API mass and if deviations occurred. For each run, the RSD of API mass was calculated to investigate the content uniformity.

RSD of weight (mg): A simple way to check the quality of a dosing process is to calculate the RSD of the capsule weight. For each run, the weight of the capsules was measured. The mean empty capsule weight (76 mg) was subtracted from each capsule weight and the RSD was calculated for each run.

4.4 Results and Discussion

4.4.1 Developed Detection Model

4.4.1.1 X-ray Modelling

Based on Experiments 1, three parameters were obtained for each capsule: the capsule weight, the amount of API inside the capsule and the signal received from the X-ray system. A linear regression was applied to the data (using Cornerstone 7.0, camLine, Germany), resulting in a very good model fit with an adjusted R^2 of 0.999. No transformation was applied, and the data were normally distributed.

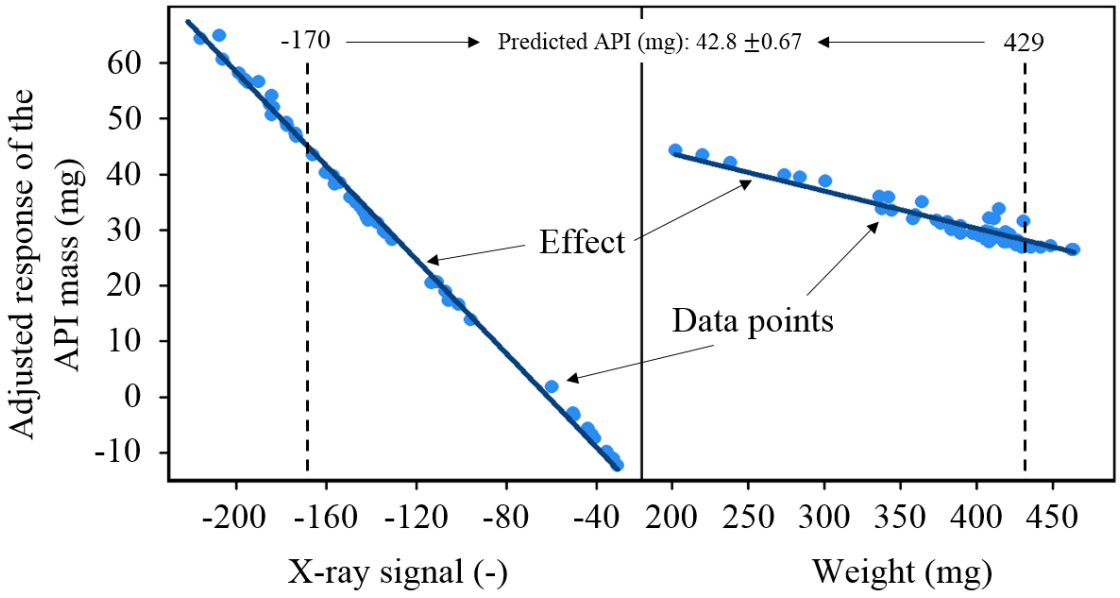

Figure 6: Adjusted response of the API mass as a function of the model predictors. Response data points were adjusted (recalculated: effects of other factors were averaged out) and the effect modelled for each factor is shown. The position of the mean capsule weight and the mean X-ray signal (dimensionless) produced in the subsequent experiment are drawn (dashed lines). Predictions for this point are given within a confidence interval of 95 %.

Figure 6 illustrates the adjusted response graph of the API mass. In the adjusted response graph, all response data points (i.e., API masses) are plotted against each parameter (X-ray

signal and weight). The drawn effect is the result of the regression. The graph is called adjusted response graph because the data points are recalculated. The modeled effect of the other process parameter is removed from the data points drawn for one parameter. Meaning that the effect of the modelled weight is not included in the data points drawn for the X-ray signal and vice versa. Therefore, the data points in each box illustrate not the real API masses but the recalculated ones. Only the deviation is visible which arises from noise or the effect of the displayed parameter. Based on this graph it is evident how the effect is modeled and how much noise remains inside the model. Obviously, these deviations (distances of the data points from the modelled effect) are very small, which demonstrates the superiority of the model fit.

The two parameters, i.e., the mean capsule weight and the X-ray signal (discussed in Chapter 3.1.1, Eq. 11) were successfully determined. Both parameters had a significant effect on the amount of the API. As expected, the effect of the X-ray signal is stronger than the effect of the total capsule mass (the amount of barium sulfate has a higher influence on the X-ray signal than on the total fill weight). The model used to calculate the mass of the API is given in Equation 12 (rounded values, detailed model is provided in the Appendix A3).

$$m_{API} = -\mathbf{0.067} * m_{tot} - \mathbf{0.421} * Signal \quad (12)$$

The following short assessment of the equation delivers a first validation. In an imaginary experiment the capsule weight should remain the same. If then a lower X-ray signal is measured (a lower negative signal equals a higher absorption) the composition of the capsule must have changed, i.e., it must contain more API. This matches the determined values of the equation, where a negative factor is calculated for the signal. Another experiment would be that there are two capsules, a light-weight and a heavy one, both showing the same X-ray absorption. The conclusion is that they must contain different material compositions. Again, this fits the equation. When the absorption signal is constant, the API amount decreases as the capsule weight increases.

To discuss the accuracy, a prediction was calculated (visible in Figure 6). In Cornerstone it is possible to calculate a confidence interval for a prediction. As the experimental data scatter around the determined effects the standard error can be calculated. By using the standard error and the t-distribution [18] it is possible to give an estimation in which area a predicted value probably falls, i.e., the confidence interval. The confidence interval depends on the certainty defined for the prediction, the confidence level. At a level of 95 %, 95 out of 100 experiments should lie within the calculated confidence interval. The model predicts for a signal of -170 and a total capsule weight of 429 mg an API mass of 42.9 mg (which is similar to the API amounts filled in the Experiments 2). The confidence interval is calculated to ±0.67 mg

(confidence level 95 %), corresponding to about ±1.56 % of the absolute filled API amount, which is considerably accurate.

4.4.1.2 Validation with Target Excipients

After the detection model was created, a validation of the model was executed. This ensures a reliable prediction of the API mass in the follow-up process development. The excipient used to create the detection model was lactose (Spherolac 100), chosen because of its good flowability. The excipients used in the continuous process however were starch and mannitol mixture. These excipients have slightly different attenuation coefficients (see above). Thus, the objective was to validate if the model could predict the API mass as accurately as it was possible in combination with lactose.

Table 3 shows six runs V1 – V6. The ratios of mannitol and starch were chosen similar to the ratios used in the continuous capsule-filling process. The ratio of 3.5 represents a mixture of 20 % of starch and 70 % of mannitol mixture. The ratio of 0.5 represents a mixture out of 60 % of starch and 30 % of mannitol mixture. To each mixture, three API concentrations were added: 8 %, 10 % and 12 %. For each experiment, 19.2 g were prepared and placed into a small vessel. After mixing the powder manually for 3 minutes in the vessel, 45 capsules were manually filled and weighed. The empty capsules were weighed before and a mean empty capsule weight of 76.1 mg was subtracted from the total capsule weight to calculate the mass filled into the capsules (powder filled). Afterwards the amount of API in each capsule was detected (using the x-ray detection model). The single API amounts were added up to get the whole amount of API located in all capsules (API detected). If the model is accurate (i.e., the amount of API is determined correctly), the detected API percentage (i.e., API detected divided by the powder filled) should equal the target one.

Table 3: Results for capsules filled with the two excipient mixtures used in the subsequent continuous capsule-filling process.

Run number	V1	V2	V3	V4	V5	V6
Ratio mannitol/starch	3.5	3.5	3.5	0.5	0.5	0.5
Target API %	8	10	12	8	10	12
Powder filled (mg)	18945.6	18824.6	18931.0	18667.5	18569.6	18727.9
API detected (mg)	1550.4	1925.4	2307.2	1592.3	1985.2	2362.3
Detected API %	8.18	10.23	12.19	8.53	10.69	12.61

The results in Table 3 (detected API percentage) indicate that the amount of API inside the capsules can be predicted. Yet the exact percentages are not reached (compare e.g.. V5,

10.69 % instead of 10 %). With these excipients a slightly higher API was predicted. As the amount of starch increases, the predicted API amount increases. This correlates to Equation (10). When the factor of a material p_2 (containing the attenuation coefficient of the excipients) is reduced the predicted API amount increases, which seems to be the explanation of the increased predicted API amount. The X-ray coefficient of lactose is higher than the coefficient of the mannitol mixture and the starch coefficient is the lowest one. To correct for the slightly higher amount (assigned to a different material composition), a correction factor was added to the calculation of the API amounts. For the subsequent analysis of the continuous capsule-filling process, a correction factor of 0.98 was applied to the API masses of the mixture containing 20 % starch. For the mixture using 60 % of starch a factor 0.94 was chosen. The factors were used in the creation of the continuous-process model. The API masses given in Appendix A2 were multiplied by these factors, the same was considered for the calculation of the RSD of API mass.

4.4.2 Analysis of the Continuous Capsule-Filling Process

With the help of an automated content check in the RAPD it is possible to detect the amount of the API within the capsule. This allowed the modelling of the mean API mass and the RSD of the API mass. Hereinafter details of the model creation are proposed and the influences of the CMAs and the CPPs are discussed based on the effects identified in the model.

The experiments to create the model were conducted for 2 days, after which the capsules were weighed and measured for API content using the X-ray system. A regression was performed in order to develop a process model (Cornerstone 7.0). A Box-Cox plot was used to check whether a transformation of the results was beneficial (Appendix A4). The mean API content remained untransformed, for the RSD of API a reciprocal square-root transformation was chosen. The residuals were then normal distributed. To model the targets, the significance level of each term was calculated. Several significant effects were identified. The significance levels for removing a term and bringing a term back were 0.025 and 0.075, respectively. No considerable lack of fit was detected. No outliers were detected.

4.4.2.1 Effects on the Mean API Mass

In Experiments 2, the range of mean API mass varied between 33.2 mg and 47.0 mg. The adjusted R^2 for the mean API mass was 0.42 indicating only a sub-optimal model fit. However, three significant effects were identified in the model. The equation for the mean API mass is provided in Appendix A3. A possible explanation for the model could be found in segregation of the API, especially in the blender. In this prototype of blender a gap exists between the

mixing blades and the casing (tube) of the blender along the transport and the mixing zone. This gap (about 5 mm) was used due to slack tolerances of the prototype design. Powder located in this area is not included in the mixing process, and is thus a possible area for segregation of the dense API. Especially in the beginning of the mixing process this gap has to be filled with powder and the dense API could be separated from the main mixture. Depending on the residence time of the blender, experimental order (time when mixture was produced in the blender) and the starch amount (preventing segregation, compare next chapter) different amount of API reaches the capsule. The result is a poor overall prediction as these factors influence the API content, especially at the start of the process. The model of the mean API mass showed reasonable effects, however, for an exact prediction of the API mass a different approach would be needed. One could be to assume a certain API content and to predict the content with the mean capsule weight. Another solution would be to reduce segregation to a minimum, thus adjust the design of the blender.

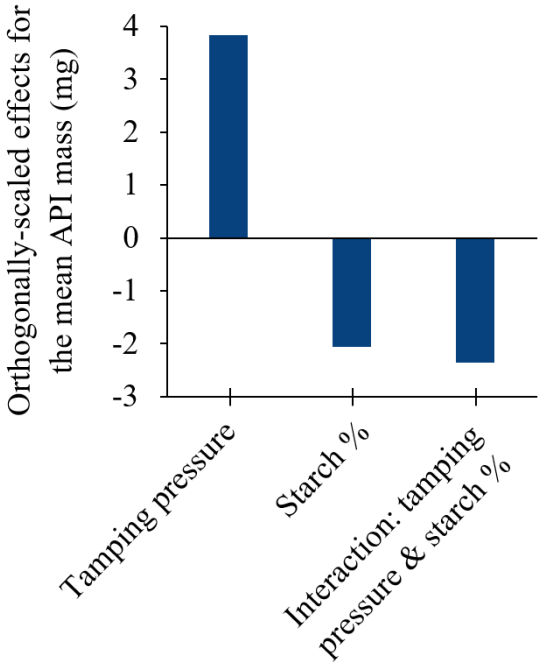

Figure 7: Orthogonally-scaled effects of the model terms onto the mean API mass.

Nevertheless, effects which show a high significance in the model could be identified, independent from the model prediction quality. Figure 7 shows the orthogonally-scaled effects for the mean API mass. Note that orthogonal scaling requires the factors to be in a range from -1 to 1 so that the scaled effects can be compared. With regard to the mean API mass, the pressure in the capsule filler (tamping pressure) was found to be significant. This is reasonable,

as it increases the amount of powder filled into the capsules and, consequently, the amount of API inside the capsule (compare Wagner et al. [1]). The linear effect of pressure within the range of 0.1 – 0.5 MPa was 3.8 mg.

The next effect in Figure 7 is the percentage of starch (starch %). When it is increased from 20 % to 60 %, the amount of API decreases (-2.1 mg), possibly due to a lower bulk density of starch. Since the mass percentage of API is kept constant and the excipient has a lower tapped density, the amount of API is reduced within the dosing volume (die-hole of the dosing disc). Another reason can be a change in the compaction behavior. As the amount of mannitol mixture increases, more magnesium stearate enters the product, changing its compressibility (compare Wagner et al. [1]).

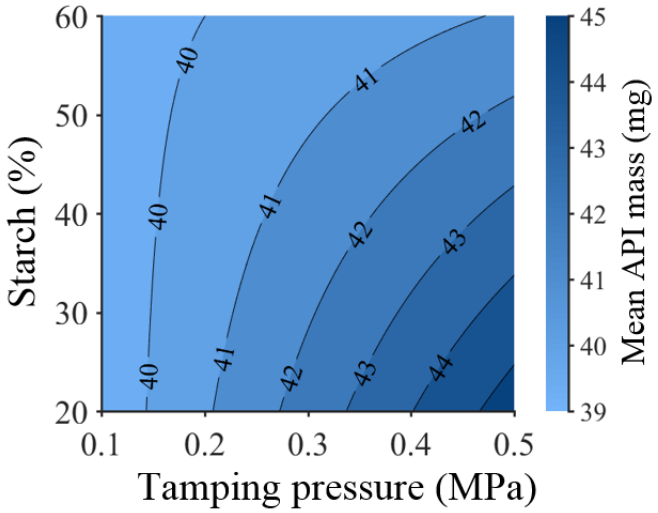

Figure 8: Contour plot of the mean API mass predicted by the three modelled effects: tamping pressure; amount of starch and the interaction between both. A high API mass is illustrated by a darker colour.

The third effect is the interaction of tamping pressure multiplied by the amount of starch (tamping pressure and starch %), which equals -2.4 mg. Lower amount of starch and higher tamping pressure lead to an increase of the API mass. Figure 8 provides an advanced view on this interaction. Illustrated are the three effects used in the model, the tamping pressure, the starch amount and the interaction of the two. Visible as a colored contour plot is the mean API mass. In combination with a low amount of starch, the tamping pressure leads to a higher fill weight (above 45 mg). When the amount of starch is increased the pressure has a smaller effect on the API mass (i.e., there is an interaction between both process parameters). A reason for this effect may be a different compaction behavior as mentioned above. Another explanation is

the fine particle size of the starch. In general, in between the tamping pins and the die-hole, in which the powder is densified, a small gap is needed due to manufacturing tolerances. When the tamping pin applies pressure on the powder inside the die-hole the powder is compressed and air escapes trough the gap. However, if a powder with a small particle size is filled, the air can entrain the powder out of this gap, i.e., out of the die-hole. This is an explanation for the reduced effect of a high tamping pressure in combination with a high amount of starch. With the increase of the pressure the powder is pushed out of the die hole and the densification does not increase as much as with a lower amount of starch.

4.4.2.2 Effects on the RSD of API Mass

The lowest and highest RSDs of the API mass were calculated to 2.4 % and 6.5 %, respectively. The mean RSD of API mass was 3.5 %. An average adjusted R^2 of 0.63 was obtained. Five significant terms were identified. The equation of the RSD of API mass can be found in detail in Appendix A3.

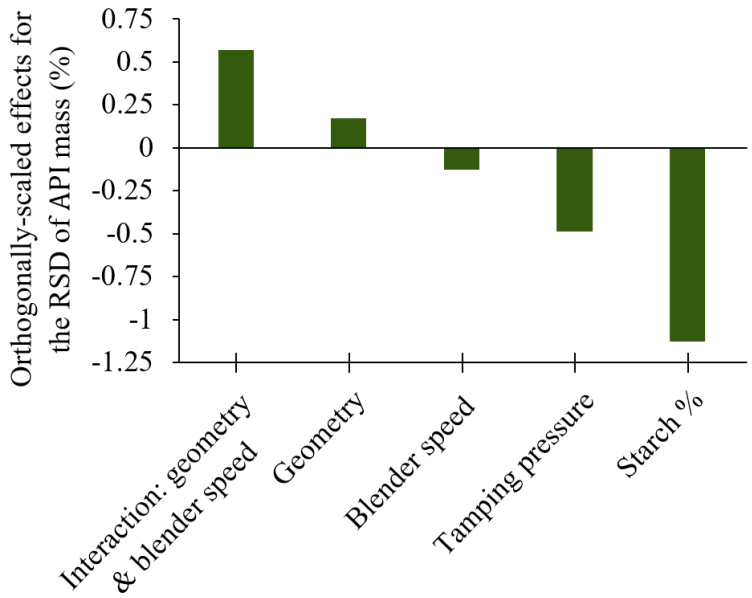

Figure 9: Orthogonally-scaled effects of the model terms for the RSD of API mass.

Visible in Figure 9 are the orthogonally-scaled effects for the RSD of API mass. The most relevant positive effect is an interaction between the blender geometry and the blender speed (interaction: geometry and blender speed). The effect is 0.57 %, indicating a negative influence on the RSD (i.e., an increase in the RSD of API mass). However, since the effect contains the categorical variable of the blender geometry, it is difficult to visualize it for the various geometry settings in one graph. Figure 10 helps to illustrate this interaction. Two

contour plots are shown, predicting the RSD of API mass as a function of the starch amount and the blender speed. The left plot is for the backward orientation of the blades, the plot on the right the forward orientation. The tamping pin pressure is maintained at 0.3 MPa.

Investigation of the plot on the left (Figure 10) leads to the conclusion that backward-transporting blades in combination with a high blender speed are beneficial. The reason may be that backward transport significantly increases the powder's residence time inside the blender. The amount of powder located in the blender (in a stable operation point) ranges from under 200 g (forward transport) to over 1000 g (backward transport). As the amount of powder increases, a higher blender speed (e.g., 135 rpm) becomes advantageous rather than a low speed (e.g., 40 rpm). The combination of a higher speed and a higher residence time seems to promote an equal distribution of the API throughout the mixture and positively affect the RSD of API mass inside the capsule. With a forward orientation of the blades a different effect is visible (right plot, Figure 10). A lower blender speed seems to be beneficial. In this setting the difference between the minimum and maximum blender speed is not very high. Contour lines are flatter compared to the plot on the left. A reason for this might be that with a forward orientation of the blades the product moves faster out of the blender. Residence time is reduced and with an increase of speed the separation of the API from the mixture may be enhanced. However, the effect is smaller and the blender speed has a greater effect with the backward orientation.

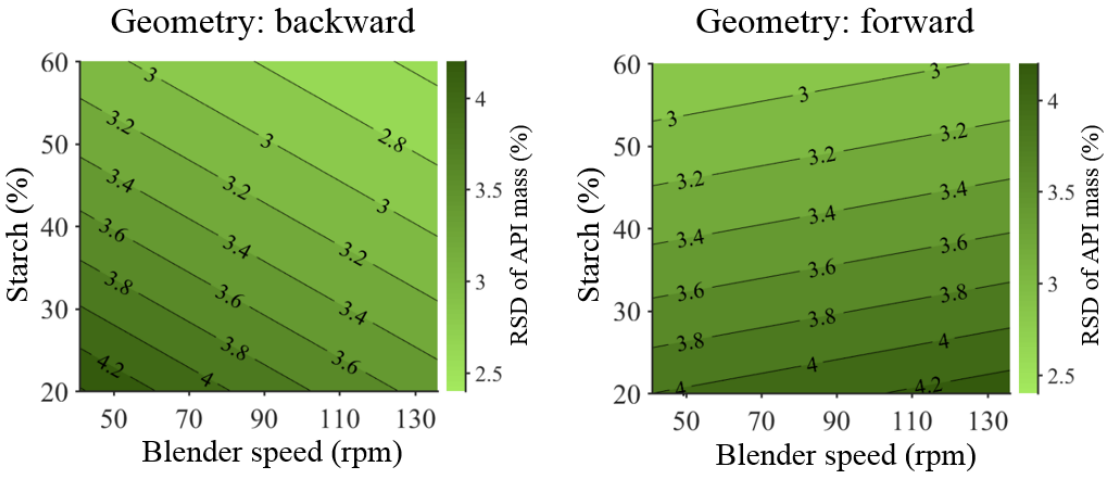

Figure 10: Contour plot of the RSD of API mass. A light colour indicate a low RSD. The tamping pressure was maintained at 0.3 MPa. On the left plot prediction is made based on the backward orientation of the blades. A high blender speed benefits the RSD of API. On the right plot prediction is made based on a forward orientation and a low blender speed is beneficial.

The next two effects in Figure 9 are blender geometry (geometry) and blender speed, showing a reasonable correlation (e.g., a higher blender speed leads to a more equal distribution). However, these are very small effects (effect on RSD <0.2 %), which were mainly used in the model to preserve its hierarchical structure (including all lower order terms). The pressure of capsule filler (tamping pressure) is also relevant for the RSD of API mass. The effect was about -0.49 %. A possible explanation may be that a higher pressure induces a more consistent compression in the dosing disc die-holes, leading to a lower RSD of weight and a lower RSD of API mass.

The fifth effect was the strongest one. The amount of starch influenced the RSD in a positive way (i.e., reduced RSD of API mass). Increasing the amount of starch from 20 % to 60 % resulted in a reduction in the RSD of -1.13 %, demonstrating the importance of material attributes for the mixing process. The API was much more equally distributed throughout the mixture, possibly since the fine, and thus cohesive, starch inhibits segregation in the mixture. Figure 11 illustrates two examples of capsules containing various percentages of starch.

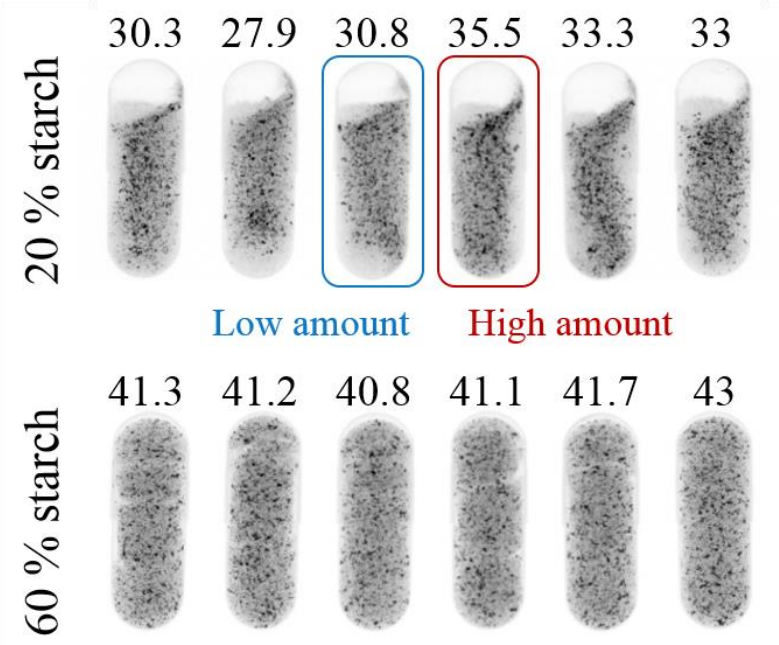

Figure 11: Capsules measured via the X-ray system containing a low (20 %) and a high (60 %) amount of starch. The API contents (mg) are shown above the capsules.

The amount of API (mg) determined via the X-ray system is indicated above the capsules. The capsules in the upper row were filled with a mixture containing 20 % of starch and 70 % of mannitol mixture. The capsules in the lower row were filled with a mixture containing 60 % of starch and 30 % of mannitol mixture. A visual inspection of the X-ray

images clearly shows a distinct difference in the API distribution inside the capsules. The capsules containing 20 % of starch have areas with a low amount of API (light areas), e.g., near the surface. Moreover, slight differences in the amount of the API in each capsule are noticeable. For example, a comparison between the third capsule (30.8 mg, low amount) and the fourth capsule (35.5 mg, high amount) clearly indicates differences in the API distribution, similar to segregation patterns.

Images in the lower row have a very different appearance from those in the upper one. First of all, there are no gaps in the powder inside the capsules due to the distribution of the powder initiated by the large amount of starch rather than by a different mean capsule weight, which is only slightly higher than that in the upper row (3.8 %). Inside a closed capsule, there is no more pressure acting on the powder, leading to a formation of a firm powder plug. Secondly, the API is equally distributed throughout the entire capsules and no bright areas with a reduced amount of API are visible. The coloring of the powder is consistently grey with distributed small darks spots of API. The API has not segregated or separated inside the capsules and is dispersed equally over the capsules (a maximum deviation of 2.2 mg is visible). The difference in the API amount is difficult to detect for a human eye. A comparison between the API distributions in the two sets indicates that the starch effect was modelled well.

4.4.2.3 RSD of Weight Compared to RSD of API Mass

After successfully modelling the mean API mass and the RSD of API mass, we modelled in addition the RSD of fill weight to compare the two RSDs (RSD of API mass and RSD of weight). To model the latter, the same significance parameters were chosen (i.e., the significance levels for removing a term and bringing a term back were 0.025 and 0.075, respectively). Reciprocal square root transformation was applied (Appendix A4, Box-Cox plot). Although the adjusted R^2 had poor predictability (0.33), significant effects were detected. Predictors that added significant terms to the model were: the amount of starch, the geometry of blender and the speed of capsule filler.

According to the model's prediction, increasing the amount of maize starch increases the RSD of weight. In Figure 12, the starch effect is plotted for the RSD of weight and the RSD of API mass. To achieve a one-dimensional diagram, the other parameters were set as follows: capsule filler speed: 130 rpm; geometry setting: backward; pressure: 0.3 MPa; and blender speed: 100 rpm. The predicted effect for the RSD of weight (gray line) begins at 0.87 % with a small amount of starch and reaches 1.33 % with a large amount of starch. The RSD of weight worsens about 0.46 % as the amount of starch increases. This agrees well with the previous studies that made a connection between a poorly flowing material and an increased RSD of

weight ([19], [20], [21]). An optimization algorithm modelling the weight and the RSD of weight would prompt to use a small amount of starch to achieve a low fill weight deviation and a low API deviation. However, the opposite is true in the case of RSD of API mass.

The RSD of API mass decreases with an increasing amount of starch. The RSD of API mass is calculated for the same process parameter setting (green line). The predictions for 20 % and 60 % of starch are 3.82 % and 2.73 %, respectively. To achieve a low API deviation, it would be reasonable to increase the amount of maize starch. Though the RSD of capsule weight increases, the overall RSD of API mass decreases since it benefits strongly from an equally-distributed API in the mixture.

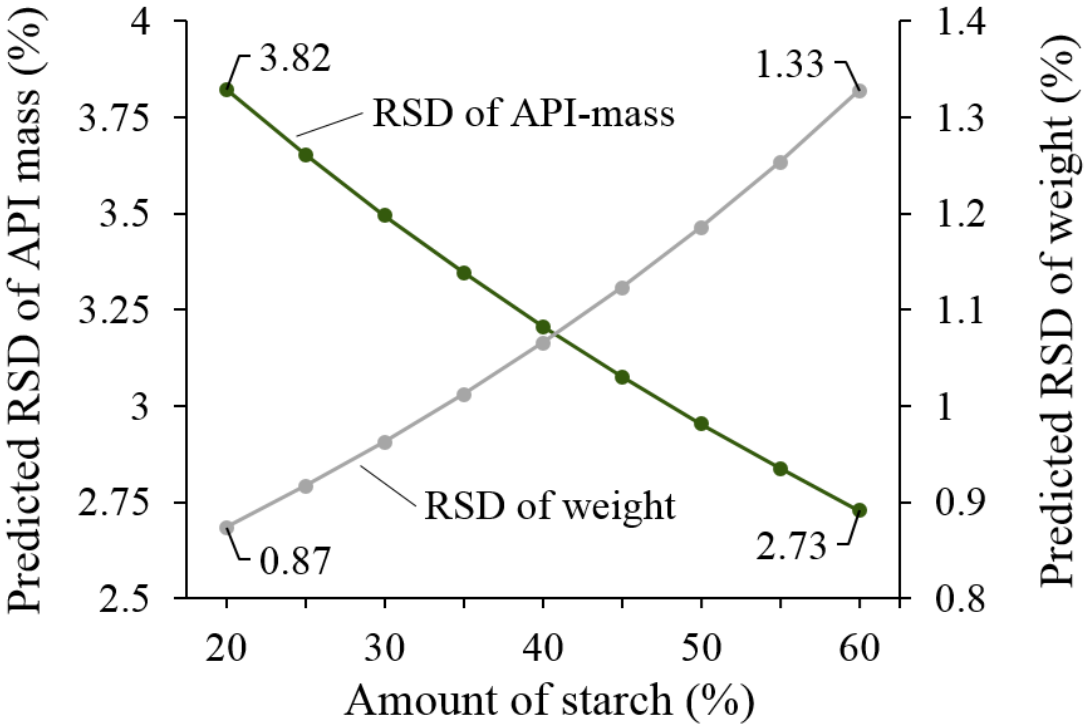

Figure 12: Predicted RSD of API mass and predicted RSD of weight calculated for various amounts of starch in the mixture. The other process parameters were: the capsule filler speed: 130 rpm; the geometry setting: backward; pressure: 0.3 MPa; and blender speed: 100 rpm.

Optimizing the RSD of API mass is a good example for the importance of the content check in the RAPD. Although modelling the process without analyzing the API content may be feasible, for products containing a small API amount it is reasonable to assess the API content since various interaction may influence the API content (blender speed, blender geometry, mixture composition, etc.). Without a modelled RSD of API mass (i.e., only examining the

capsule weight), an algorithm would optimize the RSD of mean fill weight without considering the RSD of API mass.

Moreover, assessing solely the mixture quality in the blender is insufficient. Additional experiments are required to determine which influences on the capsule filler may exist. A decision as to whether select a low amount of maize starch, which is beneficial for the capsule-filling process, or a high amount of starch, which is important for the blending process, is difficult to make by analyzing a single process step alone (e.g., the capsule filling or the blending process alone). As such, an evaluation should include not only the capsule filler but also the feeders and the blender in order to establish possible influences on the target.

4.5 Summery and Conclusion

In this study, we established an X-ray detection model, which allowed the precise determination of the barium sulfate inside hard gelatin capsules. The model had an excellent fit (adjusted R^2 of 0.999) and an accurate calculation of the mass of barium sulfate was achieved (confidence interval of ±0.6 mg at 42.9 mg). The automated X-ray system allowed a fast measurement of the entire capsule volume. Therefore, this system in an example for an automated content check system that is able to determine API content (barium sulfate) inside the capsules.

After modelling the X-ray detection, we applied the X-ray system as an automated content check in the RAPD of a continuous capsule-filling process. This way a model was developed for investigating influences on the mean API mass, the RSD of API mass and the RSD of weight during the continuous capsule-filling process.

With regard to the mean API mass, the tamping pressure of capsule filler, the starch amount and an interaction between the two were found to be significant. The amount of starch in the mixture had the highest influence on the RSD of API mass, followed by the blender geometry interacting with the blender speed. While comparing the results for the RSD of API mass and the RSD of weight, the amount of starch had the opposite influence. A high amount of starch in the mixture led to a greater deviation in the capsule fill weights. For the process as a whole, however, a high amount of starch is preferred since it is beneficial for the API distribution in the mixture and leads to an overall lower API variation.

In this work, we presented the advantages of including an automated content check in the RAPD. Especially for low-dosed drugs, it is worthwhile to detect the amount of API during the process development. The analysis of the API content is particularly important for the development of formulation composition and for establishing the blender's process parameters. Using our approach, the effects on the API content can be identified in a short time and with

reduced effort. The combination of automated experiments, automated content measurement and DoE offers a better understanding and optimization of the process, especially compared to approaches where offline content determination (e.g., HPLC), one-factor-at-a-time experiments or non-automated equipment is used.

Spectroscopic technologies play a key role in today's continuous manufacturing. They enable control strategies for single units (e.g., feeder, blender) or form the basis of real time release ([5], [6]). In the view of RAPD they are important and can help to achieve an automated content check. In summary, an automated content check is a valuable part of RAPD, independent of the technology (classic analytical or spectroscopic).

4.6 References

[1] Wagner B, Brinz T, Otterbach S, Khinast J. 2018. Rapid automated process development of a continuous capsule-filling process. Int J Pharm. 546:154–165.

[2] Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. 2014. Understanding pharmaceutical quality by design. AAPS J. 16:771–783.

[3] Saitoh S, Yoshimori T. 2008. Fully automated laboratory robotic system for automating sample preparation and analysis to reduce cost and time in drug development process. J Assoc Lab Autom. 13:265–274.

[4] FDA [Internet]. Guidance for Industry PAT – A Framework for Innovative Pharmaceutical Development, manufacturing, and Quality Assurance. 2004 [cited 2018 Nov 28]. Available from: http://www.fda.gov

[5] Rantanen J, Khinast J. 2015. The future of pharmaceutical manufacturing sciences. J Pharm Sci. 104:3612–3638.

[6] Fonteyne M, Vercruysse J, Leersnyder FD, Snick BV, Vervaet C, Remon JP, de Beer T. 2015. Process analytical technology for continuous manufacturing of solid-dosage forms. Trends Anal Chem. 67:159–166.

[7] Vanarase AU, Alcalà M, Jerez Rozo JI, Muzzio FJ, Romañach RJ. 2010. Real-time monitoring of drug concentration in a continuous powder mixing process using NIR spectroscopy. Chem Eng Sci. 65:5728–5733.

[8] Eliasson C, Macleod NA, Jayes LC, Clarke FC, Hammond SV, Smith MR, Matousek P. 2008. Non-invasive quantitative assessment of the content of pharmaceutical capsules using transmission Raman spectroscopy. J Pharm Biomed Anal. 47:221–229.

[9] Gao Y, Vanarase A, Muzzio F, Ierapetritou M. 2011. Characterizing continuous powder mixing using residence time distribution. Chem Eng Sci. 66:417–425.

[10] Weinekötter R, Reh L. 1995. Continuous mixing of fine particles. Part Part Syst Charact. 12:46–53.

[11] Meschede D. 2004. Gehrtsen Physik. Chapter 17, Die Elemente und die Chemie. Berlin: Springer-Verlag; p. 838–840.

[12] Murty RC. 1965. Effective atomic numbers of heterogeneous materials. Nature. 207:398–399.

[13] Sachtleben Minerals [Internet]. Schwerspat (Bariumsulfat, BaSO4). 2017 [cited 2017 Apr 30]. Available from: http://www.sachtleben-minerals.com/produkte/schwerspat

[14] Rowe RC. 2009. Handbook of pharmaceutical excipients. 6th edition. London: Pharmaceutical Press; p. 364–369, 424–428, 685–690.

[15] Vogt M, Beck M, Maga I. 2011. 100%-Inline-Qualitätskontrolle mit X-ray-Technologie. TechnoPharm. 1:60–67.

[16] Vogt M, Sternberger-Rützel E, Birke M, Jacobs C. 2012. Influence of X-ray radiation as PAT method on the model substances tramadol HCl and Nifedipine compared to the influence of UV–Vis radiation. TechnoPharm. 3:200–210.

[17] Eriksson L, Johansson E, Kettaneh-Wold N, Wikström C, Wold S. 2000a. Design of experiments principles and applications. Sweden, Umea: Umetrics AB; p. 213–220.

[18] Eriksson L, Johansson E, Kettaneh-Wold N, Wikström C, Wold S, 2000b. Design of experiments principles and applications. Sweden, Umea: Umetrics AB; p. 267–270.

[19] Podczeck F, Newton J. 1999. Powder filling into hard gelatine capsules on a tamp filling machine. Int J Pharm. 185:237–254.

[20] Podczeck F. 2001. The development of an instrumented tamp-filling capsule machine II, Investigations of plug development and tamping pressure at different filling stations. Eur J Pharm Sci. 12:515–521.

[21] Nair R, Vemuri M, Agrawala P, Kim S. 2004. Investigation of various factors affecting encapsulation on the in-cap automatic capsule-filling machine. AAPS Pharm Sci Technol. 5:E57.

4.7 Appendices

A1 - Dataset Experiments 1

Table 4: Experimental data for creation of the X-ray detection model

No.	Mass API (mg)	Capsule weight (mg)	X-ray Signal (-)	No.	Mass API (mg)	Capsule weight (mg)	X-ray Signal (-)
1	35.15	358.58	-143.3234	26	55.51	364.53	-184.2179
2	16.70	344.21	-95.8161	27	52.98	462.68	-198.7533
3	18.29	359.90	-101.4236	28	52.75	448.88	-196.3942
4	37.05	406.56	-154.1445	29	44.11	463.60	-177.7822
5	21.33	376.54	-112.3718	30	57.85	427.23	-206.3519
6	32.05	389.62	-141.9555	31	48.28	420.26	-184.229
7	61.93	430.87	-207.7544	32	30.81	435.86	-144.9162
8	40.62	427.93	-166.2875	33	33.10	425.91	-149.4512
9	54.08	421.86	-194.7763	34	26.20	417.06	-130.6959
10	45.02	412.41	-173.2406	35	20.68	383.76	-113.3864
11	30.23	408.32	-141.2822	36	18.67	389.50	-107.1157
12	27.97	411.42	-134.3540	37	29.74	429.73	-142.4924
13	21.00	381.08	-110.8133	38	34.47	337.73	-137.2408
14	47.40	406.03	-177.3752	39	19.79	373.71	-107.2516
15	28.65	397.61	-133.8649	40	16.24	401.77	-105.5035
16	36.86	406.21	-156.0893	41	0.00	202.30	-30.5622
17	33.46	406.82	-146.8502	42	0.00	220.10	-32.5381
18	38.41	404.92	-156.9660	43	0.00	274.29	-40.8172
19	38.13	418.19	-160.2074	44	0.00	301.15	-43.7169
20	49.82	419.28	-183.6968	45	0.00	336.42	-50.019
21	69.86	414.95	-221.5570	46	0.00	284.42	-41.8515
22	45.69	409.19	-173.7581	47	0.00	411.59	-59.8594
23	55.04	408.34	-190.1763	48	0.00	342.05	-50.2988
24	50.17	420.13	-184.9746	49	0.00	238.56	-35.4845
25	60.56	442.17	-215.8357				

A2 - Dataset Experiments 2

Table 5: Experimental data for creation of the capsule-filling process model

No	Speed filler (cycles/min)	Pressure (MPa)	Geometry (Type)	Starch (%)	Speed blender (rpm)	Mean API mass (mg)	RSD of API mass (%)	RSD of weight (%)
1	110	0.1	backward	20	41	41.9	5.02	1.44
2	80	0.3	backward	20	41	44.6	4.18	0.98
3	80	0.3	backward	20	136	41.9	4.53	1.07
4	140	0.5	backward	20	136	47.4	3.65	0.75
5	80	0.3	backward	60	41	41.4	2.82	0.99
6	140	0.5	backward	60	41	42.0	2.79	1.41
7	110	0.1	backward	60	136	40.1	2.37	0.66
8	80	0.3	backward	60	136	39.9	2.56	1.25
9	140	0.3	straight	20	41	46.0	3.27	0.72
10	80	0.5	straight	20	41	43.5	3.71	0.81
11	140	0.1	straight	20	136	33.4	6.52	1.43
12	110	0.5	straight	20	136	45.4	3.30	0.83
13	110	0.5	straight	60	41	41.1	2.73	1.48
14	140	0.1	straight	60	41	38.4	3.76	2.29
15	80	0.5	straight	60	136	40.8	2.67	0.85
16	140	0.3	straight	60	136	40.5	3.06	1.72
17	110	0.1	forward	20	41	40.7	4.55	1.44
18	140	0.5	forward	20	41	43.1	3.66	0.75
19	110	0.3	forward	20	136	36.2	4.78	1.05
20	80	0.1	forward	20	136	37.1	4.34	1.18
21	110	0.3	forward	60	41	40.5	2.54	0.92
22	80	0.1	forward	60	41	39.2	2.86	1.70
23	140	0.1	forward	60	136	39.9	3.15	1.12
24	110	0.5	forward	60	136	40.8	2.86	1.08
25	110	0.3	forward	20	136	44.6	3.86	1.10
26	80	0.3	forward	60	136	39.3	3.32	1.86
27	140	0.1	forward	60	41	40.0	3.54	1.60
28	140	0.3	backward	60	136	40.2	2.45	2.09
29	80	0.3	backward	20	136	47.0	3.03	0.80
30	140	0.5	backward	60	41	41.1	3.45	1.38
31	140	0.1	straight	20	41	40.7	3.91	1.00
32	140	0.5	backward	20	41	45.4	3.89	0.84
33	110	0.1	straight	60	136	40.3	2.53	1.13

A3 - Detailed equations for the detection model and for the process model

Equation of the API mass for the detection model, containing the X-ray signal and the total capsule weight.

$$\mathbf{m_{API}} = -0.0670030701024 * \mathbf{m_{tot}} - 0.4208800489938 * \mathbf{signal}$$

Equation of the mean API mass (MA), used in the process model

$$\mathbf{MA} = \text{const.} + a * \mathbf{tamping\ pressure} + b * \mathbf{starch}\ \% + c * \mathbf{tamping\ pressure} * \mathbf{starch}\ \%$$

Equation of the RSD of API mass (RA), used in the process model

$$\mathbf{RA} = 1/(\text{const.} + a * \mathbf{pressure} + b(\mathbf{geometry}) + c * \mathbf{starch}\ \% + d * \mathbf{blender\ speed} + e(\mathbf{geometry}) * \mathbf{blender\ speed})^2$$

Equation of the RSD of weight (RW), used in the process model

$$\mathbf{RW} = 1/(\text{const.} + a * \mathbf{capsule\ filler\ speed} + b(\mathbf{geometry}) + c * \mathbf{starch}\ \% + d(\mathbf{geometry}) * \mathbf{capsule\ filler\ speed} + e * \mathbf{blender\ speed} * \mathbf{starch}\ \%)^2$$

Table 6: Factors of for the equations used in the process model. The geometry setting are defined as: backward is 1, forward is 2 and straight is 3.

MW		**RA**		**RW**	
Variable	Factor	Variable	Factor	Variable	Factor
const.	37.03621563	const.	0.411160859	const.	0.706760952
a	21.37411715	a	0.100294055	a	0.003444525
b	0.037087347	b(1)	-0.03735789	b(1)	0.056003747
c	-0.29489218	b(2)	0.019924755	b(2)	-0.45183416
		b(3)	0.017433137	b(3)	0.395830409
		c	0.002344616	c	0.007663278
		d	0.000110262	d(1)	-0.00030775
		e(1)	0.000497104	d(2)	0.003749583
		e(2)	-0.00030601	d(3)	-0.00344183
		e(3)	-0.0001911	e	-0.000097744

A4 - Box-Cox plot and model transformations

A transformation was applied to the measured values of the RSD of API mass and the RSD of weight. The transformation was chosen based on the Box-Cox plot. The Box-Cox plot (Figure 12) compares the residual sums of squares (the error term) of different transformations (from $\lambda = -1$ to $\lambda = 2$). Transformations with a lower error term indicate a better fit. The significance line illustrates the border between transformations having a worse fit than the best fit (based on a likelihood-ratio test). For the mean API mass no transformation was chosen as the untransformed response had not a significantly worse fit than a square root transformation (both below significance line). The data of the RSD of API mass and the RSD of weight were both transformed using a reciprocal square root transformation.

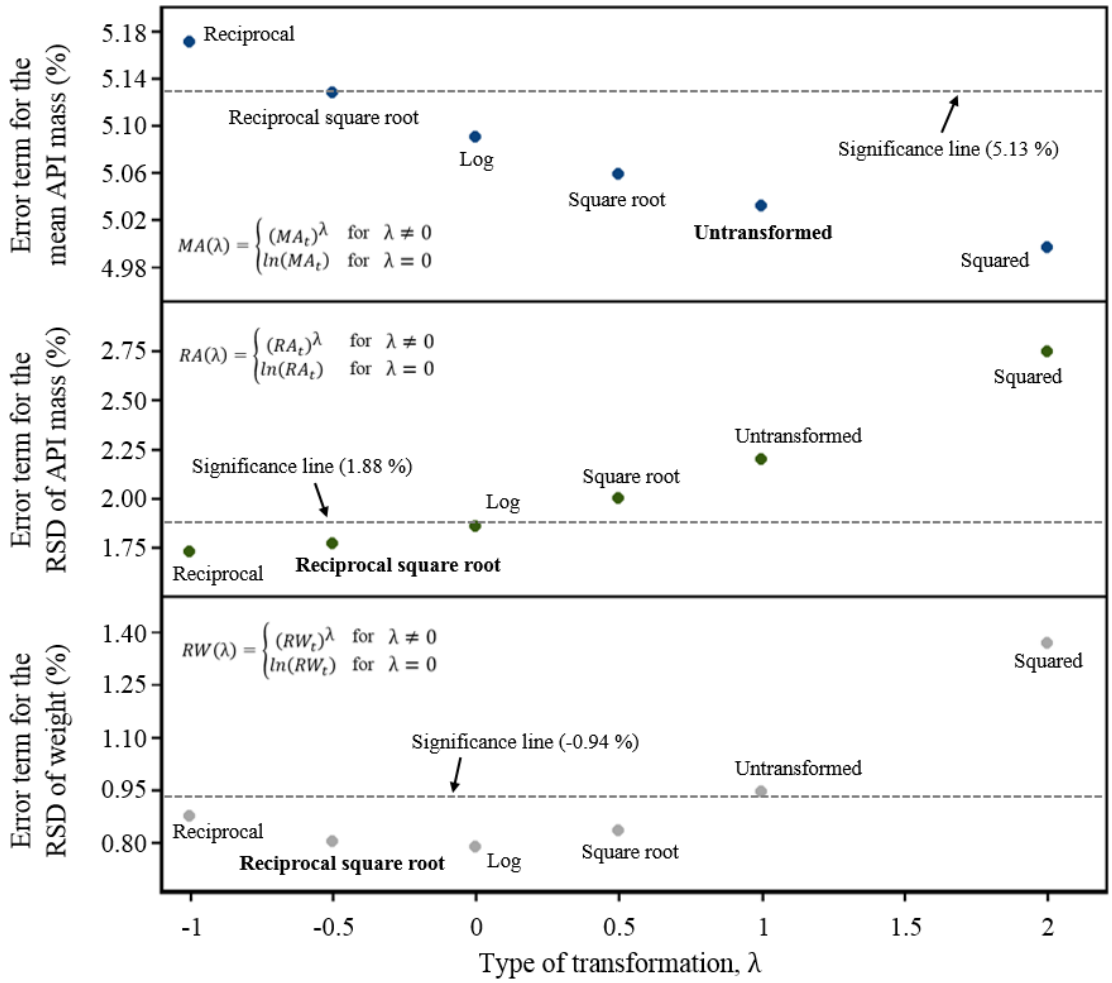

Figure 13: Box-Cox plot for the mean API mass (MA), the RSD of API mass (RA) and the RSD of weight (RW). Lower values indicate a better fit, points above the significance line result in a significantly worse fit than the best fit in the comparison.

5 Deriving Control Parameter Settings from Process Models to Control Capsule Fillers Integrated into Continuous Manufacturing

(This chapter is based on the publication Wagner B, Cheong SF, Brinz T, Khinast J, Deriving Control Parameter Settings from Process Models to Control Capsule Fillers Integrated into Continuous Manufacturing, Drug Development and Industrial Pharmacy, 2019 45:1523–1536.)

5.1 Introduction

5.1.1 Continuous Capsule Filling

Continuous production technology is constantly improving. New production methods are established, technology is commercially available (e.g., Xelum [2], Consigma [3] or Modcos [4]) and experience in the design and development of continuous production plants is growing [5]. Yet, to the best of our knowledge, only few studies have focused on continuous capsule filling (e.g., [6], [7], [1] and [8]). The application of control strategies for a continuous capsule filling processes have not been investigated in detail. However, a robust control is important, since it can help to achieve a stable process and improve the product quality. In general, a control strategy depends on the setup of the continuous process. A continuous capsule filling process can encompass several process steps: dosing, blending, lubrication, granulation, capsule filling and coating. A basic process is direct capsule filling (Figure 1, Wagner et al., 2018 [1]). Here, three gravimetric feeders, a horizontal blender and a capsule filler unit are used to directly fill powder from bulk into hard gelatin capsules.

To include a control option into the system, a gravimetric scale and a PAT sensor (Process Analytical Technology, [9]) for active pharmaceutical ingredient (API) content detection may be added to the process (Figure 1). The sensors form the basis to control the capsule filling process. A gravimetric scale allows an inline weight measurement, and thus, each capsule's weight is determined. A PAT sensor can detect the API concentration [10], which therefore can be used with the gravimetric weighing system to determine the amount of API inside the capsule. Nowadays, PAT sensors can be implemented in various locations of a process, e.g., on a tablet press ([11], [12], [13]), using either in-line, at-line or on-line implementations. In a capsule filling process, online measurement can be used: Capsules are separated after the filling process, and the API content can automatically be determined, e.g., via Raman transmission spectroscopy [14]. Other options are to measure the API content via NIR reflection spectroscopy from the surface of the open capsule, or to analyze the powder inside the bowl of the capsule filler.

In a capsule filling process, one of the priorities is to produce capsules that contain a precise amount of the API. The amount of API depends on the fill weight (i.e., the total weight of API and excipients). In a continuous process, the fill weight can be influenced by various process parameters. For example, a speed change of the feeders alters the mixture composition. This will lead to different API concentrations, and at the same time, to different fill weights in the capsules, as the density or the compressibility changes (Wagner et al. 2018, [1]). In addition, the critical process parameters of the capsule filler have an impact. In general, the dosing disc

principle (illustrated in Figure 2), which is the underlying mechanism of the capsule filler used in this study, has several parameters that have an influence on the fill weight. Thus, there are several options to control the amount of API inside the capsule (Wagner et al. 2018, [15]), based on fill weight and API content (high fill weight and low API concentration vs. lower fill weight with high API concentration).

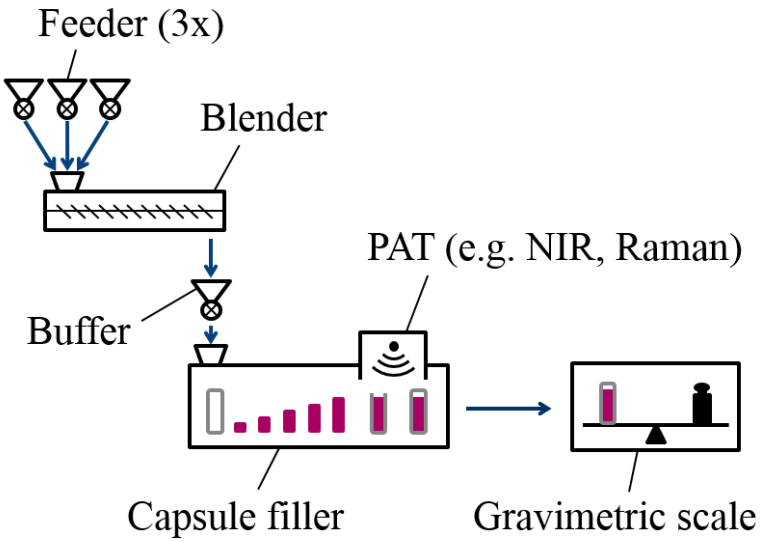

Figure 1: Schematic of a continuous capsule filling line. Three feeders dose the powder into a blender. After the blender, the product is transported through the buffer into the capsule filler. A PAT sensor inside the capsule filler determines the API content, after which the capsule is sent to a gravimetric scale that measures the capsule weight.

In a dosing-disc capsule filler, a powder bed is created in a bowl on top of the dosing disc that has multiple die holes (see Figure 2). The die holes are used to dose a defined amount of powder. There are two ways how the powder enters the dies. First, if it is a well flowing material, it enters by gravity supported by a stop-and-go movement of the dosing disc. Secondly, the powder is forced into the die by the tamping pins. The tamping stations move the tamping pins in and out of the dosing disc's die holes thereby pushing powder into the dies. In addition, the pins compress the powder inside the die holes to form a powder plug. The force used for the compression is determined by springs mounted above the tamping pins. Different type of springs (i.e., spring constants) lead to different compression forces. Thus, the fill weight can be influenced by the type of springs inside the tamping stations. As the dosing disc moves through its positions, the plug is transferred from station 1 (left) to station 6 (right). At station 6, the powder is finally transferred into a capsule. Beside the springs, there are other process parameters like the powder bed height, speed and immersion depth (Wagner et al. 2017, [15]),

which influence the fill weight. Clearly, since the capsule filler's parameters affect the mean weight, they can alter the amount of powder and API inside the capsules. However, compared to other process parameters (e.g., the rate of feeders), the process parameters of the capsule filler can be adjusted rather quickly (< 2 sec), for example the speed of the machine.

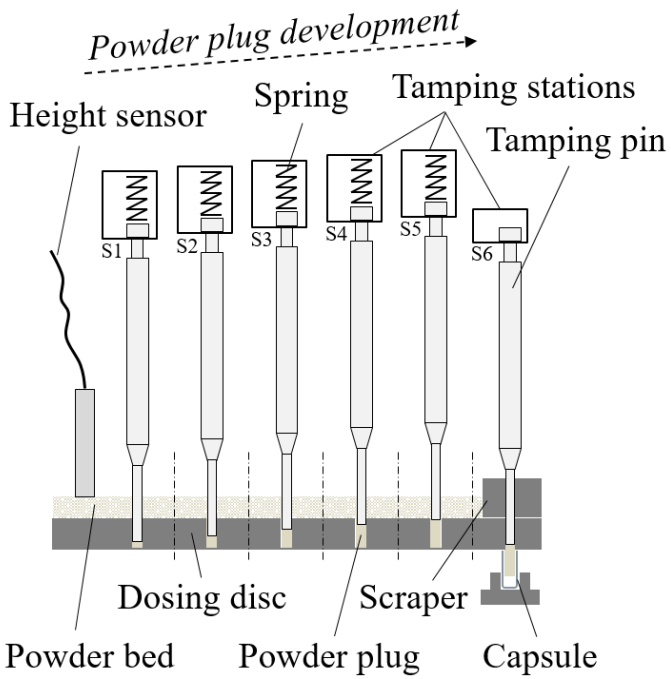

Figure 2: Schematic drawing of the tamping pin system. The powder enters the dosing disc where it is five times compressed (S1-S5). From station to station, more and more powder enters the die hole. The previously loose powder is compressed into a solid powder plug. At station S6, the plug is transferred into the capsule.

5.1.2 Rapid Automated Process Development

The rapid automated process development (RAPD) is an approach which was presented by Wagner et al. 2018 [1]. The RPDA allows a fast and efficient development of a continuous capsule-filling process, based on a high level of automation in combination with efficiently designed experiments. To develop a process it is vital to understand the process as a whole. The impact of critical process parameters (CPPs) and the critical material attributes (CMAs) on the critical quality attributes (CQAs) must be known (Yu et al. 2014, [16]). Interactions between the CPPs and the CMAs should be determined. The black box of the process must be understood to ensure an optimized and robust production process. A solution is to investigate the process, hence to create a model of the process. With a model, it is possible to understand the process and to optimize the same. The model describes, for example, which process parameter (CPP)

has an influence on the fill weight (CQA). Furthermore, it predicts how the process parameter must be adjusted to reach the desired fill weight. Then, the process can be optimized to fill the right amount of API into each capsule.

Nevertheless, a real process deviates to a certain degree from the theoretical model. There can be disturbances, which are not considered by the model. Consequently, a control system is needed to keep the CQAs within a demanded range. Today, it is state of the art to use control systems within a capsule filling process to maintain the fill weight. This is important if, for example, the density of a filled product slowly changes over the time. However, the implementation requires significant effort and the control system must be adapted for each process (compare chapter 3.1.2). In this study, we investigate whether it is possible to derive the control parameter settings from the process model (available from the RAPD), to reduce the effort and to ease the implementation of fill weight control into a continuous process.

5.1.3 Control Challenges within Continuous Capsule Filling

Continuous manufacturing has several advantages ([17], [18], [19]). One is the improvement of the product quality. In a continuous process it is possible to monitor the critical quality attributes. Technology like NIR, Raman or UV-Vis spectroscopy (Fontaine et al. 2015, [9]) can be applied. The result is a better process understanding and an opportunity to control precisely the critical process parameters. Other advantages are, for example, a much smaller production area or a faster supply chain of the final drug. Nevertheless, there are still challenges ([20]). Unstable powder feeding ([21], [22], [23]) and variable material attributes ([24], [25], [26], [27]) are some of them.

5.1.3.1 Unstable Powder Feeding

A critical part of any continuous process is the feeding of powders. While in a batch process, the dose is established via weight (where reliable technology exist to measure weight), in a continuous process feeders (typically screw feeders) are used constantly. Here, a defined mass flow rate needs to be maintained. Direct measurement of the mass flow rate of powders is not possible with today's technology. Thus, derived quantities, i.e., the weight loss over time, are used to determine the mass flow rate.

However, even so-called "loss-in-weight" feeders are not without problems, e.g., for adhesive/sticky powders or when the wrong screw is selected for a specific powder [28]. In addition, the feeder cannot be physically manipulated during feeding, since this would disturb the weight signal. Even hopper refilling is critical [29] since the feeder is not operated with a weight signal during a time, where the powder density at the screw inlet changes rapidly, and

thus, the feed rate changes in an unknown manner for approximately 5-10 % of the feeding time. Feed factors have been used to predict screw speed (i.e., the smart refilling approaches) but there is still a level of uncertainty. Feeder cleaning is not feasible during the process, although a cleaning step may be required if powder adheres to the outlet of the feeder (see example in Figure 3). If the powder deposits reach a critical mass, they may break off and momentarily increase the respective component's mass fraction in a mixture. This is especially problematic for highly potent APIs. In general, significant deviations in the API concentration should be avoided. Small deviations might be acceptable if a control loop adjusts the API content inside the capsule. Clearly, the extent of acceptable deviations has to be investigated for each process individually.

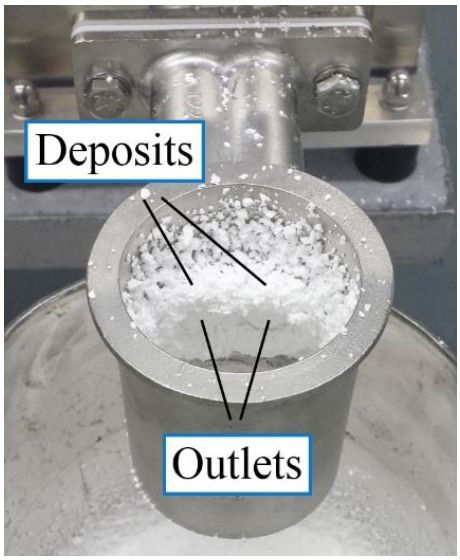

Figure 3: Example of powder deposits on the feeder. The powder is transported by two screws through the outlets. Some of the powder does not fall down and sticks to the outlet of the feeder (powder deposits). The deposits can grow over time and avalanche down into the blender.

5.1.3.2 Variable Material Attributes

Another issue is associated with excipients (i.e., with their material attributes). In general, excipients have certain specification limits. Within these limits properties are likely to vary. The following example illustrates this issue: An excipient is used as a diluent for a highly potent API. When the density of this excipient changes, the amount of API inside the capsule changes as well. The mass flow from the feeders will remain the same since feeders commonly operate in the gravimetric mode. The capsule filler, however, uses a volumetric dosing principle, and the amount of API will thus change if the density of the mixture changes. This is not as critical in a batch process as it is in a continuous process. In the former case, only slow changes are

likely to occur since a large amount of product is blended at once and the capsule filler is adjusted to the batch. In contrast, in a continuous system, a switch to a new batch of excipients may result in a sudden change in the filled weight.

5.1.3.3 Solution: Capsule Weight Control

Both challenges above lead to a deviation of the API inside the capsules. A solution is to control the fill weight of the capsule. By taking the information from gravimetric scales (e.g., KKE) and a PAT sensor (e.g., using Raman spectroscopy) it is possible to determine which capsule weight is needed to achieve the right amount of API inside the capsules. Certainly, there are weight control systems available for capsule fillers. A feedback controller is used in combination with a scale to correct the filled weight. Yet, these weight control systems are designed for batch processes. For a continuous system, a different development approach is needed and different controller types may be beneficial.

In a batch process, it is sufficient that the controller reacts within several minutes (5 to 20 minutes, standard on a gelatin capsule filler like the GKF 702, Robert Bosch Packaging Technology) and only a minor weight adjustment is typically needed (e.g., due to a drift in the compressibility/density of the material). In a continuous process with a narrow RTD and a short average residence time, changes can occur much faster (e.g., increase of capsule filling speed for buffer emptying) and the necessary correction may be larger. The demand on the controller behavior is significantly different. This has an impact on the development of the controller.

The development of a batch controller is more straightforward compared to a controller used for a continuous process. A slow response is sufficient and a small values (i.e., parameters K_{PC}, T_I; compare chapter 3.1.1) can be chosen. These values fit a wider range of products and can be empirically adjusted, even by an inexperienced operator. The system (i.e., controller and plant) is executed at an over-damping condition ([30]) and no critical oscillations occur.

The setup of a continuous controller is inherently different. In order to provide a fast and stable control option it is important to have well-optimized controller. Typically, experts (e.g., control engineers) are needed to analyze, modify and to optimize the control. This however is connected with additional effort, which is yet another obstacle for the continuous process development. Hence, a new approach for developing a weight control system of a continuous process is valuable and information about the control options is interesting.

In this study, we evaluated capsule weight control for a specific capsule filler (GKF 702, Robert Bosch Packaging Technology) combined with a gravimetric scale (KKE 2500, Robert Bosch Packaging Technology). The control parameter settings have to match the process to

ensure a stable and fast control. Based on the principle of RAPD, we instigated how to derive the control parameter settings from process models in order to achieve optimal control for each process. Furthermore, we analyzed how quickly the capsule filler could react to possible disturbances, illustrating its capability to handle possible challenges inside a continuous manufacturing process.

5.2 Materials

Three pharmaceutical excipients with different material attributes (Table 1) were used: maltodextrin (GLUCIDEX IT 19, Roquette Pharma, Lestrem, France) mixed with 1 % magnesium stearate (Nutri Mag ST-v, Calmags GmbH Lüneburg), microcrystalline cellulose (VIVAPUR 200, JRS Pharma, Rosenberg, Germany) and maize starch (Maize Starch Extra White, Roquette Pharma, Lestrem, France). All measurements were performed in triplicate.

First, after dispersing the dry powders with compressed air, the particle size distribution was assessed via laser diffraction (HELOS BR, Sympatec, Germany). Maize starch had the smallest particle size (x_{50} of 15 µm). Maltodextrin mixture and microcrystalline cellulose had a significant bigger particle size, x_{50} of 200 µm and x_{50} of 195 µm, respectively. Obviously, there is a huge difference between the powders, at least in the view of the particle size.

Table 1: Material attributes.

Material	x_{10} (µm)	x_{50} (µm)	x_{90} (µm)	Span $(x_{90}-x_{10})/x_{50}$	BD (g/ml)	TD (g/ml)	CI (%)
Maltodextrin mixture	19.63 ± 0.10	200.77 ± 1.07	354.11 ± 1.51	1.67 ± 0.00	0.457 ± 0.002	0.510 ± 0.005	10.37 ± 0.69
Microcrystalline cellulose	57.91 ± 0.23	194.97 ± 0.84	333.74 ± 1.12	1.41 ± 0.00	0.370 ± 0.010	0.466 ± 0.010	20.40 ± 3.81
Maize Starch	8.44 ± 0.04	15.33 ± 0.01	22.78 ± 0.03	0.94 ± 0.01	0.535 ± 0.003	0.708 ± 0.006	24.42 ± 0.99

Second, the Carr Index (CI, [31]), which quantifies the relative difference between bulk and tapped densities, was evaluated using a jolting volumeter (JEL STAV II, J. Engelsmann, Germany). After filling a certain quantity of powder into a 250 ml graduated cylinder and determining the bulk density (BD), the powder sample was mechanically tapped 2,500 times to establish the tapped density (TD). The CI indicates the compressibility of materials. Starch had the highest compressibility (CI about 24 %), followed by MCC. The maltodextrin mixture had the lowest CI value of about 10 %. Hence, also for the CI there is a great difference between the powders.

The excipients were filled into hard gelatin capsules size 1 (CAPSUGEL). To investigate each excipient, a new package of capsules was used and the mean empty capsule weight was determined based on 7000 capsules. The mean empty capsule weights ranged

between 76.5 mg and 77.8 mg. The relative standard deviation (RSD) was 1.9 %. The empty weight was subtracted from the data that we used for generating the process models and from the input signal given to the controller to ensure that the weight in this study is the net weight of powder filled into the capsules.

5.3 Fundamentals

5.3.1 Control of the Capsule Fill Weight

A capsule filler has several process parameters that influence the capsule weight. All of them can be used - in theory - to control the mean fill weight. Some researchers (Podczeck and Newton, 1999 [32]) suggested using the spring constant to change the density of the powder plug. Replacing mechanical springs with pneumatic ones allows using air pressure to control the fill weight. This option works well for most products since the density in the die holes can be adjusted in such a way. We used an automated capsule filler setup (Wagner et al., 2017 [15]) with pneumatic springs at tamping stations 1-5 (6^{th} station is the transfer station into the capsule) to control the fill weight. In the following, pressures A and B refer to the pressure inside tamping stations 1-3 and stations 4-5, respectively. Pressure B was used in this study to control the fill weight as it has the greatest influence on the fill weight (Podcheck, [32]). Pressure A was only varied to generate the process model (chapter 4.2.1).

To implement a weight control there are different options. One option is to use a feedback control. A feedback control is commonly used on a capsule filler as it easy to implement, especially for slow changing processes. With a KKE (online gravimetric scale) behind the GKF (hard gelatin capsule filler), the fill weight can be measured and thus controlled. Another option is to use feedforward control. This type of control however requires a deeper process understanding. A model of the process is needed which describes the dependency between the manipulated variable and the controlled variable (fill weight).

5.3.1.1 Feedback Control (Standard Application)

A control model for the mean fill weight ($\bar{m}$) is illustrated in Figure 4. The control loop consists of a feedback controller and a plant. The plant represents the combination of the GKF and the KKE. The GKF is modeled by a proportional element (K_{PP}) and a first order lag element (T_1). The proportional element represents the gain, that is, the relationship between pressure (p) and fill weight. The lag element represents the lag inside the GKF. If for example a new pressure is set, it takes some cycles of the machine until the final weight is reached. The pressure in the stations must be increased and the compression of the powder plug must be executed. In

addition, between the output of the GKF and the gravimetric weighing there is a delay. This delay is caused on the one hand by the capsule transport from the GKF to KKE and, on the other hand, by the alignment of the capsules, until they reach the scale pans inside the KKE. A dead-time element (T_{DT}) was added to simulate this delay. Finally the transfer function of the plant $G_P(s)$ can be written as described in Equation 1 (Laplace transformed, [33]).

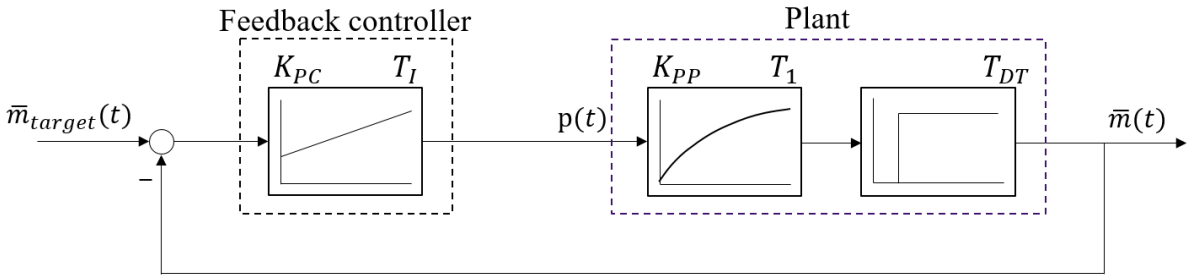

Figure 4: Illustrates a standard control solution, which uses a feedback controller. The measured mean fill weight ($\overline{m}$) is subtracted from the target mean fill weight ($\overline{m}_{target}$) and is given to the feedback controller. Values for the plant are (determined for a model material) a gain K_{PP} of 30.0 mg/MPa, a time constant T_1 of 2.0 sec and a dead-time T_{DT} of 11.5 sec.

$$G_P(s) = \frac{K_{PP}}{T_1 * s} * e^{-sT_{DT}} \quad (1)$$

$$G_C(s) = K_{PC}\left[1 + \frac{1}{T_I * s}\right] \quad (2)$$

The controller (shown as box to the right in Fig. 4) is designed as a PI controller [34], containing a proportional and integrating part. No derivative part is included, since the process is rather slow, especially with the dead time caused by the capsule transport. The transfer function of the controller $G_C(s)$ is described in Equation 2. The parameter K_{PC} is the proportional gain of the controller and T_I the reset time (integrating time constant) of the controller. To establish a fast and robust control of the system, the controller parameters (K_{PC}, T_I) must fit the plant parameters (K_{PP}, T_1, T_{DT}).

In general, there are different methods to obtain the control parameters. One method uses experiments to first identify the plant parameters. A step response is recorded from the system and in a subsequent step a simulation model is created. After a model is available, the controller parameters can be optimized inside the simulation and afterwards transferred to the real system. Another method is to use tuning rules, for example, after Ziegler and Nichols or Chien, Hrones and Reswick (Wendt, [35]). These rules can be used to avoid the time-consuming

analysis of the plant and the subsequent modeling of the plant. Nevertheless, these tuning rules require experiments to find the correct control parameters. Therefore, independent of the method significant effort is required, and operators with a control engineering background have to tune the controller parameters.

In order to determine a first set of plant values, this effort was made in the beginning of this study. A model material (corn flour) was used to characterize the system. A step response was recorded and the parameters of the plant were determined. The dead time (T_{DT}) was about 11.5 seconds, the time constant T_1 was 2.0 sec and the gain (K_{PP}) was determined to 30.0 mg/MPa. After the values of system were known, a simulation model was created using Simulink (MATLAB 2017b, The MathWorks). The controller parameters were optimized (data not shown) and the following controller settings were chosen for the model material: K_{PC} of $9.0 * 10^{-3}$ MPa/mg and T_I of 4.3 sec.

Indeed, the parameters were successfully determined for the model material, however for an efficient process development this approach is not suitable. To receive these values considerably effort was needed: product, time and expert knowledge. Furthermore, these values are only valid for this specific material (compare chapter 3.1.2). For a new product, the same effort is needed again. Within our study, we show (chapter 4.1.1) how to derive the parameters for the feedback control from the existing process model, which is a much more efficient approach.

5.3.1.2 Unsuitable Controller Settings

Depending on the filled material, different controller settings are required to achieve a fast and accurate control. If the settings are not chosen properly, weight oscillations or a very slow response may be observed, leading to a deviation from the defined target mean weight. Figure 5 illustrates these two issues. In experiment (a) microcrystalline cellulose (MCC) was filled with the controller setting of maize starch; in experiment (b) with setting of the maltodextrin mixture. The controller parameter settings are provided in chapter 5.

Both the filled-capsule weights (blue dots, mean empty capsule weights subtracted) and pressure B of the capsule filler (purple line) are shown. The grey area and the two dashed lines (upper and lower limit) show the target mean fill weight, which is changed after 70s to a lower set point. The limits used in this study were defined separately for each material and were determined as following. The respective product was run at a stable set point (no disturbances, fixed process parameters) and the distribution of the fill weights was observed. The limits were than defined, such that most of the capsules (>95 %) were within the limits (so-called normal

range). Therefore, for a stable operation, only a few capsules are out of the range. The normal range was for the maltodextrin mixture ±9 mg, for MCC ±8 mg and ±7 mg for Maize starch. These limits were only used to investigate the controller performance. Without a doubt, for the final process with API, the limits of the process have to be defined differently (e.g., according to the relevant pharmacopeia).

Note that the delay in the capsule transport (T_{DT}) was removed in all diagrams showing the weight and pressure signal (such as Figure 5) to illustrate the weight at the end of the capsule filler. The feedback controller, however, has to account for the dead time.

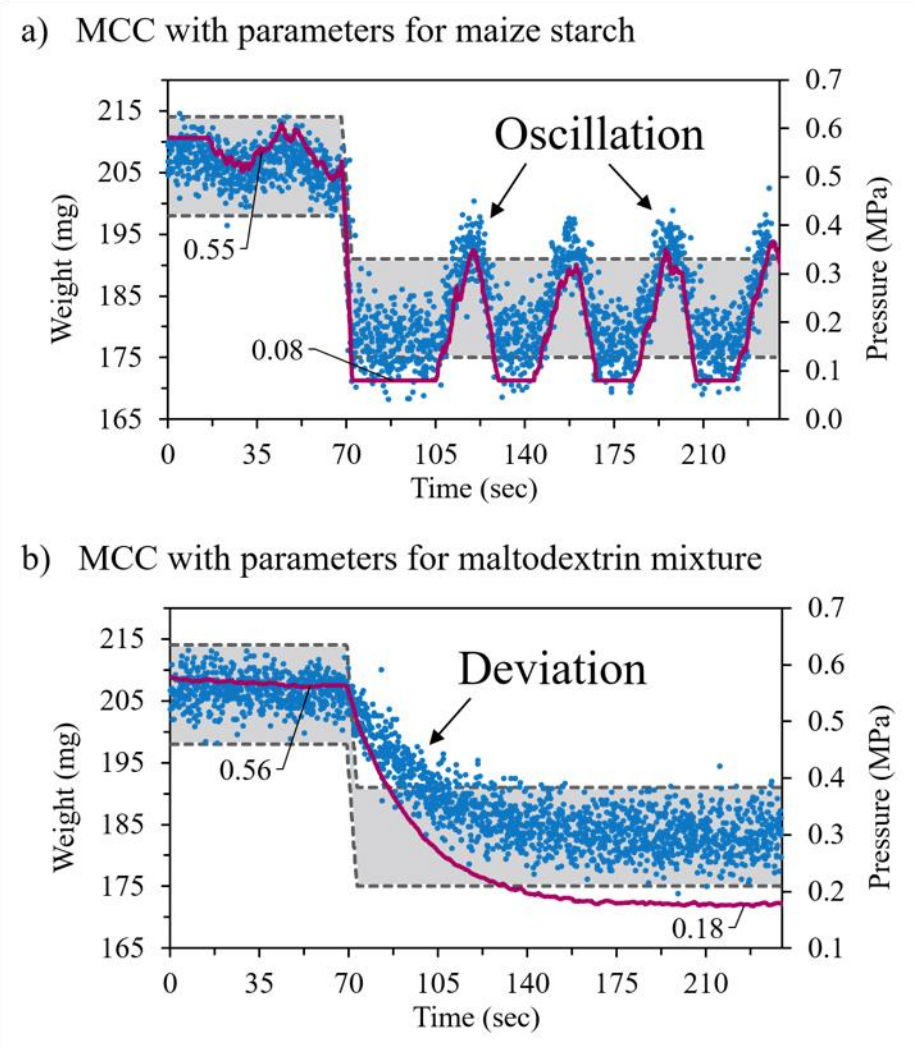

Figure 5: Two set point changes were performed with unsuited controller parameters. The blue dots and the purple line represent the weight and pressure B, respectively. After about 70 seconds the target fill weight changed from 206 mg to 183 mg within 4 seconds.

The two cases in Figure 5 show that the control settings are unsuitable for this material. Before a change was made (< 70 sec), the target mean weight was within the normal range.

After the target weight abruptly changed (206 mg to 183 mg), the feedback controller tried to adjust the weight in both experiments. In experiment (a), the controller first reduced the pressure from 0.5 MPa to 0.08 MPa (lowest possible value for the pneumatic hardware). After some time the controller recognized that this pressure setting was too low. The mean weight was below 183 mg and the controller increased the pressure above 0.3 MPa. This setting is too high and the pressure is reduced again. The adjustments led to a continuous oscillation that resulted in many capsules being outside the normal range. In experiment (b), the controller decreased the pressure too slowly, yielding many capsules outside of the specification limits.

Overall, these examples demonstrate that if the feedback control settings are unsuitable, the adjustment of mean fill weight is either unstable or too slow, resulting in deviations from the target fill weight. Thus, it is important to match the controller parameters to the specific filled product.

5.3.2 Automation Technology

Today's automation technology offers several opportunities for developing and operating a process. A capsule filler has several process parameters (compare chapter 1.1). The parameters are adjusted to reach the target quality for a wide range of different material attributes (i.e., different powders). This is done during the development of the process. Historically the process is manually developed. That means simple experiments (experimental design: one-factor-at-time [36]) were executed. The process parameters were manually adjusted. The CQA were measured offline, for example, on a laboratory scale.

A much better method is presented by the RAPD. Beside the design of experiments, a key element is a high automation level. During the experiments, the process parameters are automatically adjusted (Wagner et al. [1]). At the same time, the results are measured online (e.g., the mean capsule weight is measured by an online gravimetric scale, KKE). Finally, it is possible to investigate the process in a very short time. The experiments used to create a model of a capsule filling process typically need less than 1.5 hour (30 experiments). After this time, the effects and interactions of the process are known and a process model is available.

Built-in into the capsule filler is a programmable logic controller (PLC). The PLC controls the process parameters of the capsule filler. The PLC is able to communicate with other systems of the continuous manufacturing line, including the KKE or a PAT sensor system. Using the mean weight signal from the KKE, a controller was programmed into the PLC. The parameters of this controller are adjustable. The controller had two different modes of operation. One mode using only the standard feedback controller and another mode, where the feedback control is combined with a feedforward controller (chapter 4.1.2). The parameters of

the controller were adjusted dependent on the parameters determined for each material. In the case of the feedforward control, the mathematical function was used that describes the dependency between the mean capsule weight and the tamping pressure.

5.4 Methods

5.4.1 Deriving Control Parameter Settings from Process Models

5.4.1.1 Feedback Controller Settings

$G_{CP}(s)$ is the system transfer function for the open-loop system calculated by multiplying the controller transfer function $G_C(s)$ with the plant transfer function $G_P(s)$ (Equation 3, [37]). The system transfer function $G_{CP}(s)$ describes the behavior of the system (i.e., relationship between the control error and controlled variable). If the system transfer function remains the same ($G_{CP}(s) = const.$), the closed-loop behavior of the system stays the same and likewise does the control performance. When a new product is filled, primarily one parameter changes in the transfer function of the plant, that is, the proportional gain K_{PP}. The other parameters like the lag time T_1 or the delay T_{DT} stay nearly constant. This is reasonable as, for example, the GKF uses always the same amount of strokes to produce the capsules and the transport time from the GKF to the KKE nearly stays the same. Of course, this is an approximation, but the results of this study support this assumption.

The main approach is to maintain the system transfer function ($G_{CP}(s) = const.$), when there is a new K_{PP}. If the K_{PP} of the new material is known the gain of the controller K_{PC} can be adjusted. Hence, the relationship between K_{PC} and K_{PP} has to be constant (Equation 4). The relationship itself has to be defined only once when the controller settings are optimized for the first time, like executed in chapter 3.1.1. Here the relationship between the gain of the plant filing the model material $K_{PP_{model}}$ and the controller gain $K_{PC_{model}}$ was determined, as well as the non-material-specific parameters: T_I, T_1, T_{DT}. Subsequently, it is possible to calculate the new controller gain $K_{PC_{new}}$ from $K_{PC_{model}}$, $K_{PP_{model}}$ and $K_{PP_{new}}$ (Equation 5). The only remaining unknown parameter is $K_{PP_{new}}$, which is determined from the process model of the RAPD.

$$G_{CP}(s) = G_C(s) * G_P(s) = K_{PC}\left[1 + \frac{1}{T_I * s}\right] * \frac{K_{PP}}{T_1 * s} * e^{-sT_{DT}} \quad (3)$$

$$K_{PC} * K_{PP} = const \quad (4)$$

$$K_{PC_{new}} = \frac{(K_{PC_{model}} * K_{PP_{model}})}{K_{PP_{new}}} \quad (5)$$

Figure 6 describes the basic principle how the controller setting K_{PC} is determined. First, a process model MW is created by executing experiments on the plant (RAPD). The process model describes the effects of the CPPs onto the mean fill weight with a polynomial function; one of the CPPs is pressure B. With the help of the process model, it is possible to calculate $K_{PP_{new}}$ for a certain process set point. The critical process parameters are set as desired (e.g., a certain machine speed is chosen). Pressure B is adjusted, first to a low setting, then to a high setting. Subsequently, the model predicts two different mean weights. With these weights, the plant gain ($K_{PP_{new}}$) is calculated from the relation of the mean weight increase divided by the pressure increase. Now the gain for this process set point is available. This approach is important, as there can be interactions between the effect of the pressure B and other process parameters onto the fill weight (not described in the equation of Figure 6).

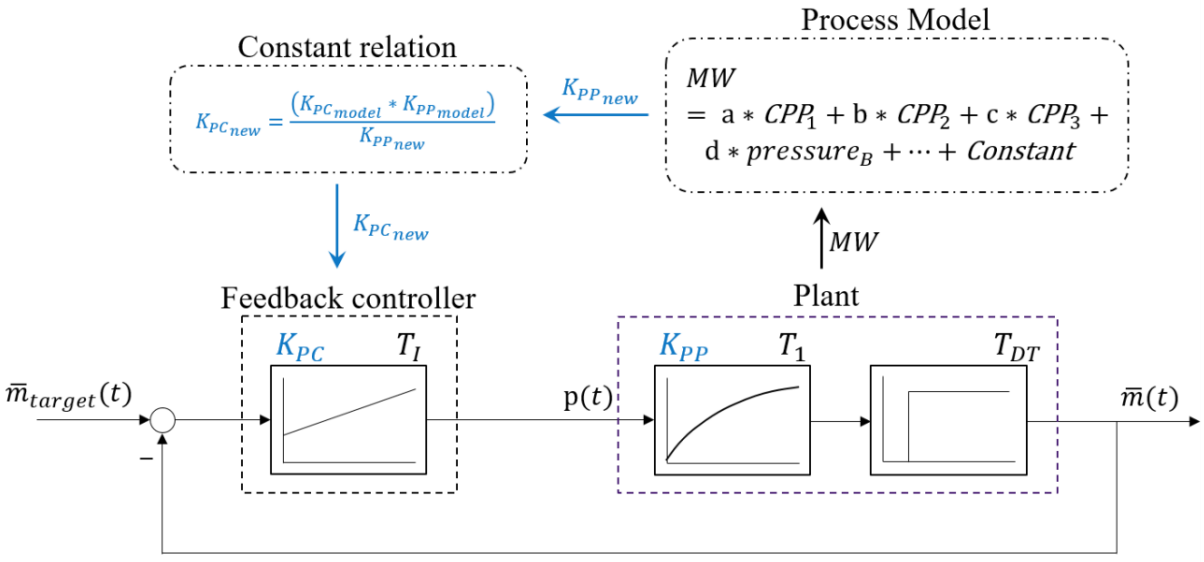

Figure 6: Derivation of the feedback controller settings. The process model is used to determine $K_{PP_{new}}$. With the help of the previously determined parameters $K_{PC_{model}}$ and $K_{PP_{model}}$ (model material corn flour), the gain of the plant $K_{PC_{new}}$ can be calculated.

With the help of $K_{PP_{new}}$ it is now possible to calculate $K_{PC_{new}}$ using the optimal settings from the model material ($K_{PC_{model}}$ of $9.0 * 10^{-3}$ MPa/mg, $K_{PP_{model}}$ of 30.0 mg/MPa). $K_{PC_{new}}$ is given to the controller, the transfer function of the system remains the constant and likewise the previously optimized close-loop behavior stays the same. As a result, the optimal

control setting is established for the new material. Of course, effort is needed to create the process model from the plant, but the idea is that the model is already available from the previous RAPD.

In this study, the feedback controller settings were calculated for the three materials: maltodextrin mixture, MCC and starch. The feasibility of this method was tested (discussed in the Results Section). The parameters for the feedback control were calculated based on the process model created for each material. In each case, two predicted weights at a pressure level of 0.1 MPa and 0.7 MPa were used to calculate the gain of plant $K_{PP_{new}}$.

5.4.1.2 Feedforward Control Settings

Beside the option to use a feedback control, there is the option to use a feedforward control. Figure 7 illustrates the implementation of the feedforward controller and how the parameter settings can be derived. The feedforward controller is used in combination with the feedback controller. A combination of the two controllers is reasonable, since the feedforward control cannot correct any external disturbances or errors that are not described in the model. If only a feedforward control would be used and the mean weight is somehow off the target, no correction is applied and the deviation will remain inside the process.

However, a combination of the two controllers can be challenging. When both react at the same time to a new target setting, a change in the manipulated variable (pressure) can be too significant. Moreover, a substantial overshoot may be induced since the adjusted capsules have not reached the KKE yet. A solution is to reduce the effect of the feedback controller by choosing a smaller K_{PC}. The optimal setting depends on the accuracy of the process model. If the process model fits the reality well, no feedback control is required. If its accuracy is poor, the effect of the feedback control has to be increased. Otherwise, the system would react too slowly to the target adjustment. In the Simulink simulation, we expected a deviation between the process models to be no greater than ±20 % (based on experience with previous process models, [1]). As an outcome, we chose a $K_{PC_{model}}$ of $1.2 * 10^{-3}$ MPa/mg. This parameter is used to derive the feedback controller settings, when used in combination with the feedforward controller. The derivation of the feedback controller settings out of the model is illustrated by blue arrows in Figure 7.

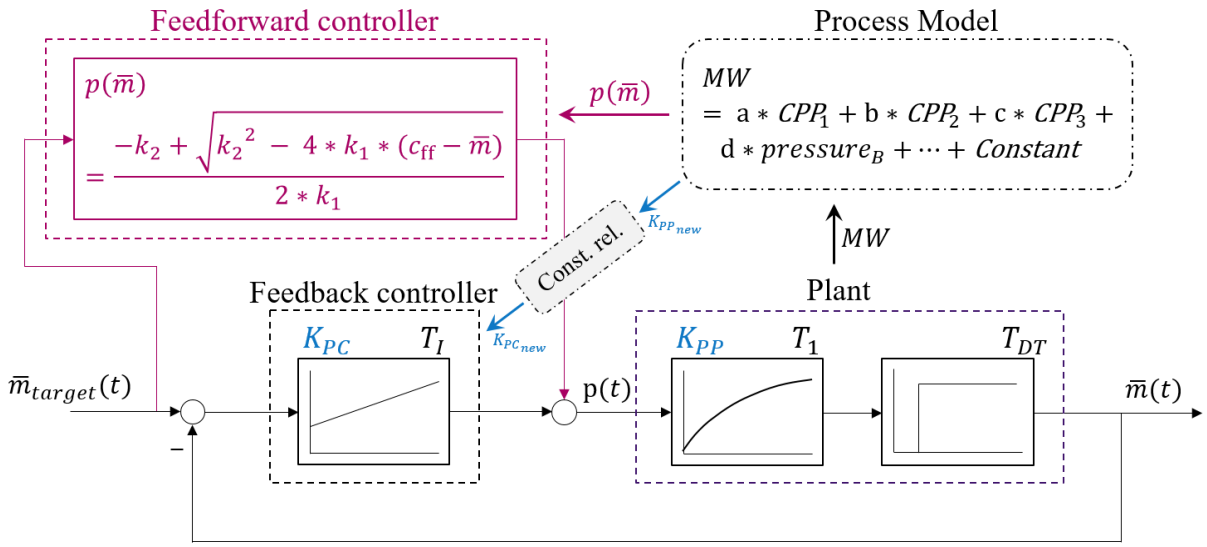

Figure 7: Implementation of the feedforward controller in combination with the feedback controller. The feedback controller parameters were derived from the model as described in the previous chapter (constant relation). However, a smaller gain ($K_{PC_{model}}$ of $1.2 * 10^{-3}$ MPa/mg) was used.

The feedforward controller is shown in purple color. The feedforward controller takes the target mean weight ($\bar{m}_{target}$) and calculates a pressure which is directly added to the pressure calculated by the feedback controller. The sum of both controllers is then provided to the plant. In general, the feedforward controller could be designed via an inverse process model (MW^{-1}) using the variable pressure B. However, to ease the implementation in the PLC a simpler function was used. A quadratic regression was fitted to predictions made from the process model MW (within the range 0.1 MPa to 0.7 MPa). The inverse function of this regression was calculated ($p(\bar{m})$) and used in the feedforward controller. There are two factors, k_1 (if there is a quadratic dependency), k_2 (linear dependency) and a constant c_{ff}. Consequently, the feedforward controller is derived from the process model of the RAPD and is able to calculate the pressure needed for a certain set point. In the following experiments, the three parameters were calculated for each tested material and used to control the fill weight.

5.4.2 Experimental Design

5.4.2.1 Process Model Development

Normally, the process model is already available from a RAPD. For this study, no such development was previously executed. Therefore, a small RAPD (changing only critical process parameters of the capsule filler) was executed to model each material. Cornerstone 7.0

(camLine) was used to plan the experiments. 16 runs (see Appendix A) were executed using a D-optimal design [38]. Three critical process parameters were varied: the speed of the capsule filler (90 to 120 rpm), pressure A (0.1 – 0.7 MPa) and pressure B (0.1 – 0.7 MPa). The model contained linear terms, interactions (one-way) and quadratic terms. After the runs, a regression was performed on the data. The significance level of each term was calculated and insignificant terms were identified. The significance levels for removing a term and bringing a term back were 0.1 and 0.05, respectively. The obtained process models are discussed in the result section of each material.

5.4.2.2 Controller Evaluation

Two types of control, feedback and the combination of feedback and feedforward were tested for their reaction to a target weight set-point change. At first, the process was set to an initial target weight (a weight with pressure B near 0.55 MPa estimated based on the process model). After the weight was reached (stable weight signal), the target weight was reduced to a lower target set point (a weight produced near 0.2 MPa). The exact targets are provided in the results. This approach was taken to simulate an appropriate target weight change when an increased API percentage is detected via a PAT sensor and the weight has to be reduced to maintain a stable API content in the capsules.

To investigate the behavior of the controller, three different changes were chosen: fast (4 sec), mid (30 sec) and slow (90 sec). Within these three periods, the target weight is linear reduced to the new target weight (illustrated by the adjustment of the limits, drawn in the diagrams below). To maintain the capsule weight, the controllers adjusted pressure B. The rest of the process parameters were held constant: speed at 105 rpm, pressure A at 0.1 MPa, immersion depth of stations 1-3 at 13.9 mm, depth of stations 4-5 at 13.4 mm and powder bed height at 22.5 mm.

5.5 Results and Discussion

5.5.1 Maltodextrin Mixture

The first material tested was the maltodextrin mixture. A process model was generated (experimental data provided in Appendix A). The process model is also provided in Equation 6 (rounded values). The model had a good fit, with an adjusted R^2 of 0.995. No significant lack of fit and no outliers were detected. Apparently, both pressures A and B affect the mean weight (78.65 mg/MPa, 56.44 mg/MPa). Since the influence of speed was insignificant (possibly due to the flowability), it was removed from the model. Even at low filling speeds, the powder was

distributed well on the dosing disc. Between pressure A and pressure B a negative interaction was identified (-110.07 mg/MPa²), which is expected. When pressure A and pressure B increased, the influence of single process parameters declined, meaning that when pressure A decreases pressure B has a greater influence on the weight and vice versa. In addition, pressure B has a quadratic effect (78.50 mg/MPa²) on the target weight.

$$\boldsymbol{m_{capsule}} = 233.30 + \boldsymbol{pressure\ A} * 78.65 + \boldsymbol{pressure\ B} * 56.44 + \boldsymbol{pressure\ A} * \boldsymbol{pressure\ B} * -110.07 + \boldsymbol{pressure\ B^2} * 78.50 \quad (6)$$

After the model was developed, $K_{PS_{new}}$ was determined for this product. The weight predicted by the model at 0.1 MPa was 246.5 mg and at 0.7 MPa it was 311.4 mg. Thus, $K_{PP_{new}}$ is 108.2 mg/MPa. Compared to the model material ($K_{PP_{model}}$ of 30.0 mg/MPa), the weight of the maltodextrin is a much stronger function of the pressure at the tamping stations. Subsequently, smaller parameters for the feedback control were calculated (Table 2).

Table 2: Control parameters calculated for the maltodextrin mixture.

Type of control	K_{PC} (MPa/mg)	k_1 (mg/MPa²)	k_2 (mg/MPa)	c_{ff} (mg)
Feedback	$2.50 * 10^{-3}$	–	–	–
Feedback & feedforward	$0.33 * 10^{-3}$	78.27	45.58	241.16

After calculating the parameters for both control options, the controllers were tested. For the maltodextrin mixture, a 40 mg change in the target was chosen (from 295 mg to 255 mg). Figure 8 (a) illustrates the reaction of feedback control to a fast target change. The controller reduced the pressure signal immediately when the new target weight was set. The capsule weights changed abruptly but did not remain within the normal range (grey box). After 30 seconds, a minor overshoot in the average capsule weight was observed. After a slight oscillation, the weights returned to the normal range. This behavior (i.e., minor overshoot) is desired for the feedback control. A larger overshoot would amplify the oscillation and lead to more out-of-spec-capsules (OOS, capsules outside the limits). Overall, the feedback controller performed as expected, confirming the method of adaptive adjustment of controller parameters. Nevertheless, run (a) had a high number of OOS (183).

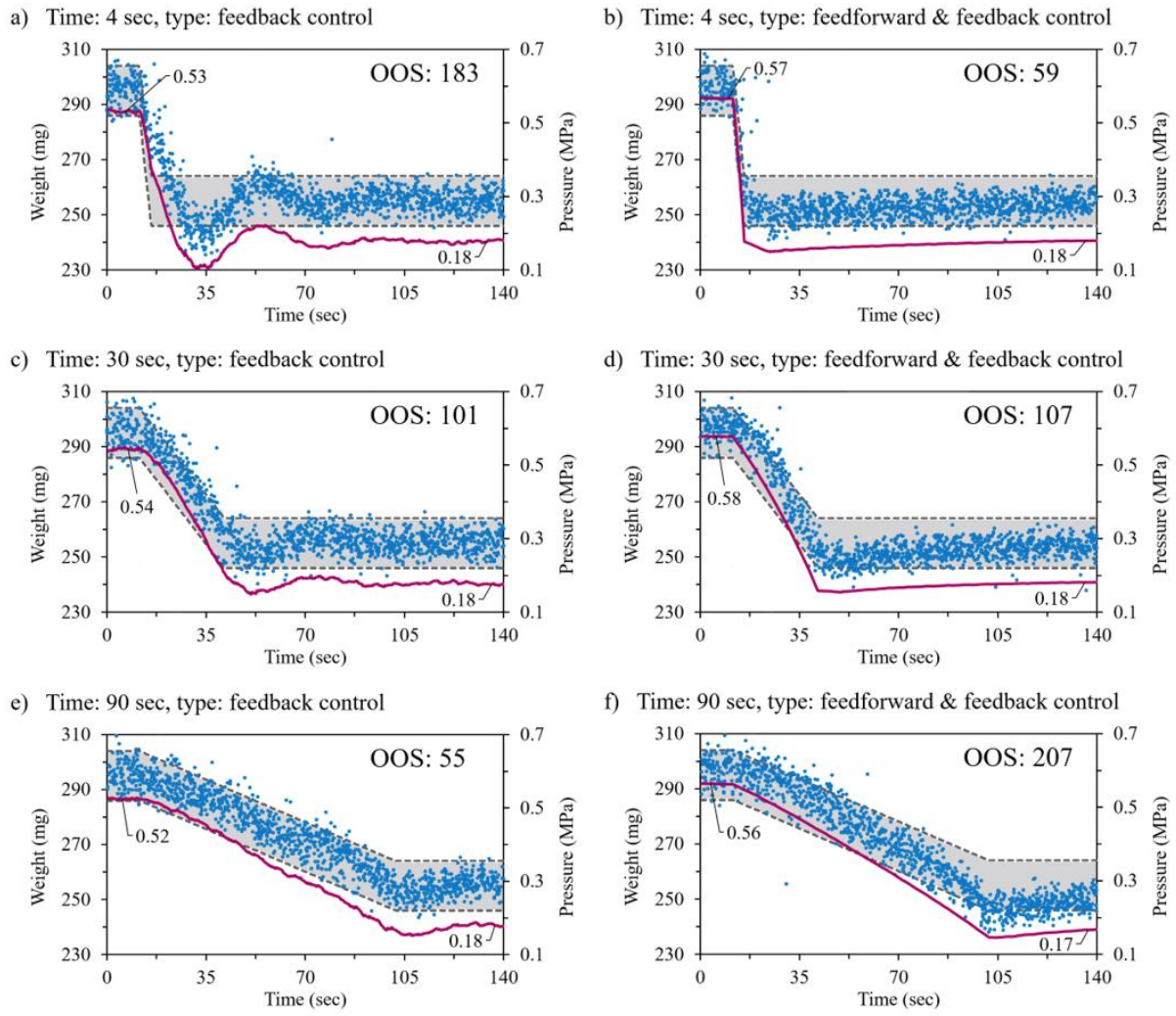

Figure 8: Responses of the weight control system. Six experiments were executed for the maltodextrin mixture. The target weight was adjusted in three time settings. Two control strategies (feedback and a combination of feedback and feedforward) were compared. The normal range for this product (grey box) was defined as ±9 mg.

Compared to the feedback control, the combination of feedback and feedforward control (b) had fewer OOS. In the beginning, the weights changed instantaneously together with the requested target weight and stayed within the normal range. Only some capsules were out-of-spec since the model is not 100 % accurate. After the target changed, the pressure was a little too low (about 0.03 MPa) and had to be adjusted via the feedback control. At the end, the same pressure of 0.18 MPa was achieved. Only 59 OOS were detected. Given this fast target change, the combination with the feedforward was faster and less OOS occurred.

When the target weight adjustment was executed over a longer time, the benefits of the combination of feedback and feedforward control decreased, and the control performance even worsened. For a change within 30 sec, both types of control had nearly the similar number of

OOS (101 and 107). The feedback control still produced some delay and a minor oscillation at the end that yielded some OOS. Yet (c) produced a better result than (a). The result for the feedforward and feedback (d) was poorer than that of (b). In the beginning, the mean weight did not decrease as fast as required. One reason for this is that the selected pressure from the feedforward control was too high in the beginning (0.58 MPa). When the target weight started to decrease the mean weight was above the normal range, which leads to some OOS. At the end of the target weight adjustment also OOS occurred. While the target weight was decreased, the integrating part of the feedback controller reduced the pressure in addition to the feedforward control and it took time until the weights reached again the target. This behavior illustrates the tradeoff that has to be made for the feedback controller gain. If the gain of the feedback controller is increased, a higher overshoot will be visible. On the other side, if the gain is reduced it takes a longer time until the weights reach the target mean, because the feedforward model is not 100 % correct and still OOS will occur.

Finally, when a slow change (90 sec) was executed, the feedback control performed better (Figure 8 (e)). Only 55 capsule were out of range. The feedback controller was able to accurately follow the weight signal with a minor oscillation at the end. The combination with the feedforward control yielded a poorer result (f) with 207 OOS since the feedback control failed to correct fast enough for deviation from the target. Again, an increase in the feedback control would not be beneficial since a higher overshoot would occur at the end due to a delayed signal from the KKE.

5.5.2 Microcrystalline Cellulose

The second material that was tested was MCC. The runs performed are listed in Appendix B. Similar to the maltodextrin mixture, a very good model was achieved. The adjusted R^2 was calculated to be 0.978, indicating a good fit. No outliers or lack of fit were detected. Equation 7 shows the model obtained via regression. Both pressure A and pressure B had a significant impact on the capsule weight (66.19 mg/MPa, 69.08 mg/MPa). Once again, a negative interaction between pressure A and pressure B (-95.84 mg/MPa²) was observed. Unlike in the case of maltodextrin mixture, an influence of speed was modelled. The linear effect of speed (2.42 mg/rpm) was coupled with a quadratic effect (-0.01 mg/rpm²).

$$\boldsymbol{m_{capsule}} = 40.34 + \boldsymbol{speed} * 2.42 + \boldsymbol{pressure\ A} * 66.19 + \boldsymbol{pressure\ B} * 69.08 + \boldsymbol{pressure\ A} * \boldsymbol{pressure\ B} * -95.84 + \boldsymbol{speed^2} * -0.01 \quad (7)$$

With the help of the model, two weight settings were predicted: 180.7 mg at 0.1 MPa and 216.4 mg at 0.7 MPa. The result is a $K_{PP_{new}}$ of 59.5 mg/MPa, which is slightly higher than the gain for the model material. The parameters for the control were adjusted as shown in Table 3.

Table 3: Control parameters calculated for MCC.

Type of control	K_{PC} (MPa/mg)	k_1 (mg/MPa²)	k_2 (mg/MPa)	c_{ff} (mg)
Feedback	$4.54 * 10^{-3}$	–	–	–
Feedback & feedforward	$0.61 * 10^{-3}$	–	59.50	174.75

Figure 9 presents the results for the target weight changes. The target weight was initially 206 mg and changed to 183 mg (23 mg difference). Diagram (a) shows the result of the feedback control for a fast weight adjustment. When the target weight changed, the pressure was modified and the new set point was reached. Similar to the maltodextrin mixture, the controller performed as desired. A minor overshoot occurred and after 70 seconds the target weight was reached. Consequently, the control parameters were successfully determined for this material. For this fast change, the feedback control had OOS (83) since it failed to exactly follow the target weight. The feedback control had less OOS than the combination with the feedforward control (b). The feedback control in (b) needed time to change the pressure of the model, cancelling the benefit of swift adjustment by the feedforward control. Even after a longer time period (130 sec), the target weight was not in the middle of the normal range.

As the time for the target weight adjustment increased, the feedback control performed better. When the target changed within 30 sec (c), the OOS were reduced to 29. With a slow change of 90 seconds (e), there were only 5 OOS. Although the amount of OOS for the combination with the feedforward control decreased, the feedback control still yielded a better result. The model of the feedforward was clearly not accurate enough. In both cases (d) and (f), the feedback control part has to correct the pressure to reach the demanded target. This took time and increased the number of OOS.

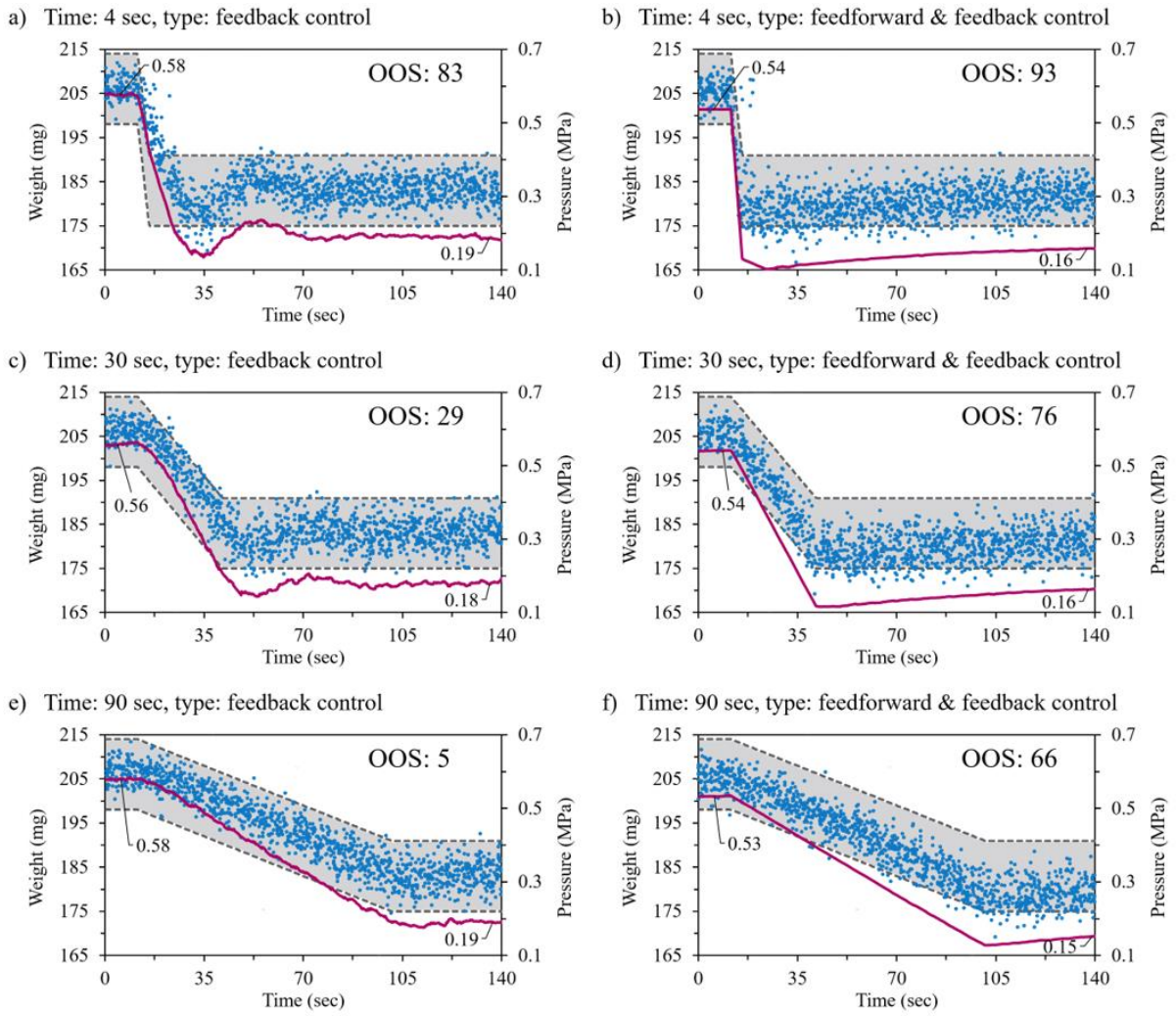

Figure 9: Responses of the weight control system. Six experiments were executed for microcrystalline cellulose. The target weight was adjusted in three time settings. Two control strategies (feedback and a combination of feedback and feedforward) were compared. The normal range for this product (grey box) was defined as ±8 mg.

5.5.3 Maize Starch

Finally, maize starch was tested. Data used for process modeling is provided in Appendix C. A model with a good fit was created (adjusted R^2 of 0.962). Once again, no lack of fit or outliers were detected. The modeled effects are described in Equation 8. All three parameters, speed (0.16 mg/rpm), pressure A (2.26 mg/MPa) and pressure B (32.60 mg/MPa) affected the filled weight. In addition to the negative influence of interaction between pressure A and pressure B (-8.00 mg/MPa²), an interaction between the speed and pressure B was significant (-0.13 mg/rpm/MPa). The reason could be as follows: At a slow speed, the powder piles up before the scraper at Station 6. As a result, the effect of pressure B increases (more powder to compress above the die holes at Stations 4 and 5). The effect decreases when the speed increases

and the powder is distributed more equally over the dosing disc.

$$\boldsymbol{m_{capsule}} = 284.10 + \boldsymbol{speed} * 0.16 + \boldsymbol{pressure\ A} * 2.26 + \boldsymbol{pressure\ B} * 32.60 + \boldsymbol{speed} * \boldsymbol{pressure\ B} * -0.13 + \boldsymbol{pressure\ A} * \boldsymbol{pressure\ B} * -8.00 \quad (8)$$

The predicted weights of 0.1 MPa and 0.7 MPa were 302.4 mg and 313.4 mg, respectively. The gain of the plant ($K_{PP_{new}}$) was calculated to be 18.3 mg/MPa (much lower than for the other materials). When the gains of materials are compared to the compressibility (compare CI), maize starch had the highest CI value of about 24 % but the lowest gain. The maltodextrin mixture had the lowest compressibility (CI of about 10 %) but the highest gain of 108.2 mg/MPa. With a maximum mean weight of above 300 mg (at 0.7 MPa), the relative influence of pressure is much lower for maize starch than for the maltodextrin mixture. As such, the materials attributes provided cannot be used to determine the control parameters. The adaptive adjustment of control parameters based on the process model offers a much better solution. Table 4 shows the calculated process parameter settings. The gain K_{PC} is much higher than the gain used for the maltodextrin mixture.

Table 4: Control parameters calculated for maize starch.

Type of control	K_{PC} (MPa/mg)	k_1 (mg/MPa²)	k_2 (mg/MPa)	c_{ff} (mg)
Feedback	$14.73 * 10^{-3}$	–	–	–
Feedback & feedforward	$1.97 * 10^{-3}$	–	18.30	300.60

The results of the experiments are shown in Figure 10. The target weight was adjusted from 308 mg to 304 mg. Because of the low $K_{PP_{new}}$, a target change of only 4 mg was selected. In all experiments, there were only few OOS, probably since the target change was small compared to the normal range. In general, when the ramp time increased, there were fewer OOS for both type of controllers. Comparing the two types of control is difficult. Both maintained the capsule weight well within the normal range. In experiment (c), the number of OOS was noticeably higher since a deviation occurred when the feedback control was still adjusted to the initial target (308 mg). Overall, the feedback control maintained the weights within the range. The designed control behavior (small overshoot) is only barely visible: compare (a) and (b). The weight change is too small compared to the standard deviation. Despite the exact control behavior, the derivation of control parameters once again yielded to the correct parameters. In general, maize starch had a very low plant gain and the control parameters needed to be greatly adjusted.

The pressure signal of feedforward control was overall smoother and the adjustments executed via the feedback control were smaller (compared to the previous materials). At the same time, the pressure took much longer to reach its final value. Interestingly, the final pressure in each diagram varied. In diagram (f) the pressure ended at about 0.28 MPa, while in diagram (b) it was at 0.36 MPa, indicating that the model fit was sometimes excellent and sometimes not. The reason for this (not investigated further) could be either the changed material attributes or the deposits that accumulate during the capsule-filling process. Nevertheless, the two controllers were able to maintain the filled weight.

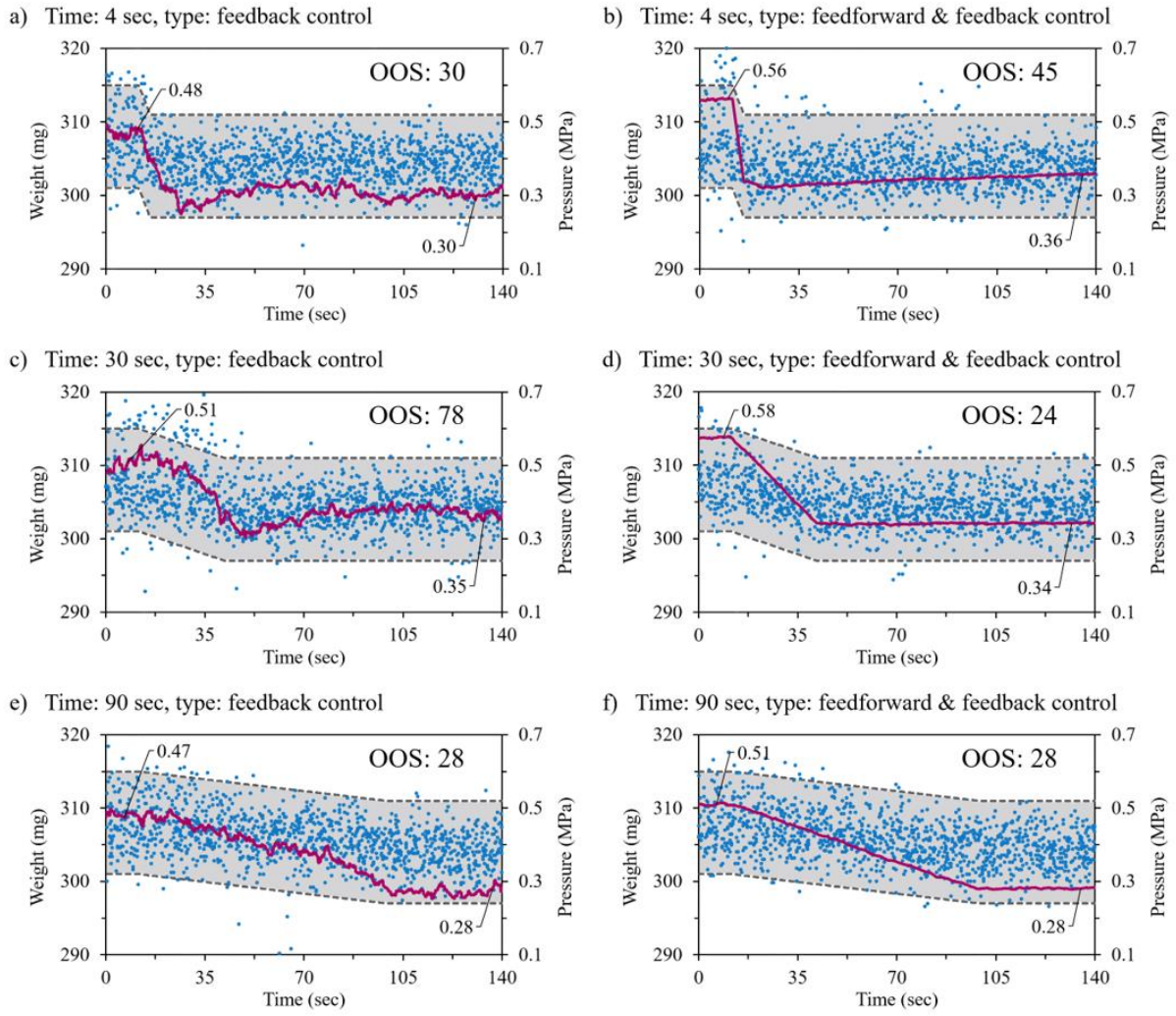

Figure 10: Responses of the weight control system. Six experiments were executed for maize starch. The target weight was adjusted in three time settings. Two control strategies (feedback and a combination of feedback and feedforward) were compared. The normal range for this product (grey box) was defined to be ±7 mg.

5.6 Summary and Conclusions

In our work, the control parameters for two types of controllers (feedback and a combination of feedforward and feedback) were adapted to three different materials. After a process model (for each material) was established, the control parameters were derived from the model. For each material, stable and dynamic control behavior was achieved, proving that the derivation of process parameters is feasible. When an accurate process model is available, for a fast target weight change (within 4 sec) the combination of feedforward and the feedback control yielded the best results. It reacted faster to the target weight change, e.g., in the case of maltodextrin mixture, than the pure feedback control and produced fewer OOS.

In the absence of an accurate process model, the feedback control is a better option. A properly adjusted feedback control can react to various disturbances and target demands. In our experiments, it responded well to changes that took longer than 30 sec. If the change (determined by the continuous process) takes longer, the feedback control option is a robust solution, and the proposed solution for the GKF and the KKE could be used. A clear benefit of feedback control is easy handling of a change of material attributes. In this study, although the process models did not always fit the reality, the feedback control performed well and the deviations were evened out.

Yet, both types of controllers have their advantages. For a final process, it has to be investigated (considering the entire continuous production process) which type of control has to be preferred and what the actual requirements for a successful process control are. In our process, we defined a normal range, which contained not more than 5 % OOS in a stable set point. When the control was activated, in most of the experiments the OOS were below 8 % (in each experiment about 1200 capsules were produced). These runs are considered successful, because the control parameters determined by a classic optimization (compare chapter 3.1.1) will not lead to significant better results. Concerning a final process, normally the limits are even wider and not near the mean weight distribution of the capsules' mean weights. With this consideration, it is likely, that processes using the excipients and the control strategies above, produce even without any OOS.

Overall, we were able to derive the control parameters for each material using the process models. Effectively, no oscillation occurred and the process behaved as desired (i.e., a small overshoot provides the lowest number of OOS, being the best compromise between an oscillation and too slow control behavior). In addition, we illustrate how fast and accurate a control of a capsule fill process can become. Changes within 4 sec are achievable with the combination of feedback and feedforward control; with an optimized PID control, changes

within 30 seconds are definitely possible. This control ability helps to achieve robust and efficient continuous processes.

Challenges, which arise from irregular feeding or variable material attributes, can be addressed. If a PAT sensor is used to determine the amount of API at the end of the process (i.e., inside the capsule or inside the powder bowl of the capsule filler), the API amount can be corrected by the filled weight. Prerequisite is a fast control of the filled weight. In consequence, the weight control helps to solve content uniformity problems. The system could be used to improve the quality of the product by optimizing the content uniformity.

Once more, this study highlights the benefits of an RAPD. With the help of a fully automated capsule filler, a process model can easily be established (it took us less than 40 min to create a process model for each material), providing good process understanding. Various control strategy options can be evaluated, e.g., developing the product mixture to influence the effect of a control parameter, such as the tamping pin pressure. Based on the model, it is possible to optimize the control parameter settings. In summary, the RAPD can be used to enhance and ease the controller implementation within a continuous capsule filling system, and thus, improve the overall process and product quality.

5.7 References

[1] Wagner B, Brinz T, Otterbach S, et al. Rapid automated process development of a continuous capsule-filling process. Int J Pharm. 2018;546:154–165.

[2] Boschpharma-blog.com [Internet]. Germany, Waiblingen: Robert Bosch Packaging Technology GmbH; [cited 2017 Oct 6]. Available from: http://boschpharma-blog.com/

[3] gea.com [Internet]. Germany, Düsseldorf: GEA AG; [cited 2019 Mar 29]. Available from: https://www.gea.com/

[4] glatt.com [Internet]. Germany, Binzen: Glatt GmbH; [cited 2019 Mar 29]. Available from: https://www.glatt.com/

[5] Rantanen J, Khinast J. The Future of Pharmaceutical Manufacturing Sciences. J Pharm Sci. 2015;104:3612–3638.

[6] Kruisz J, Rehrl J, Faulhammer E, et al. Material tracking in a continuous direct capsule-filling process via residence time distribution measurements. International Journal of Pharmaceutics. 2018;550:347–358.

[7] Kruisz J, Faulhammer E, Rehrl J, et al. Residence time distribution of a continuously-operated capsule filling machine: Development of a measurement technique and comparison of three volume-reducing inserts. International Journal of Pharmaceutics. 2018;550:180–189.

[8] Wagner B, Brinz T, Khinast J. Using online content uniformity measurements for rapid automated process development exemplified via an X-ray system. Pharm Dev Technol. 2019;24:775–787.

[9] Fonteyne M, Vercruysse J, Leersnyder FD, Snick BV, Vervaet C, Remon JP, de Beer T. Process Analytical Technology for continuous manufacturing of solid-dosage forms. Trends Anal Chem. 2015;67:159–166.

[10] Siew A. Analyzing Content Uniformity. Pharm Tech. 2018;42(2):16–22.

[11] Wahl PR, Fruhmann G, Sacher S, et al. PAT for tableting: Inline monitoring of API and excipients via NIR spectroscopy. Eur J Pharm Biopharm. 2014;87:271–278.

[12] Järvinen K, Hoehe W, Järvinen M, et al. In-line monitoring of the drug content of powder mixtures and tablets by near-infrared spectroscopy during the continuous direct compression tableting process. Eur J Pharm Sci. 2013;48:680–688.

[13] Karande AD, Heng PWS, Liew CV. In-line quantification of micronized drug and excipients in tablets by near infrared (NIR) spectroscopy: Real time monitoring of tabletting process. Int J Pharm. 2010;396:63–74.

[14] Matousek P, Parker AW. Non-invasive probing of pharmaceutical capsules using transmission Raman spectroscopy. J Raman Spectrosc. 2007;38:563–567.

[15] Wagner B, Brinz T, Otterbach S, et al. Automation of a dosing-disc capsule filler from the perspective of reliability and safety. Drug Dev Ind Pharm. 2018;44:502–510.

[16] Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, Woodcock J. Understanding pharmaceutical quality by design. AAPS J. 2014;16:771–783.

[17] Plumb K. Continuous Processing in the Pharmaceutical Industry. Chemical Engineering Research and Design. 2005;83:730–738.

[18] Kleinebudde P, Khinast J, Rantanen J, editors. Continuous Manufacturing of Pharmaceuticals. Chichester, UK: John Wiley & Sons, Ltd; 2017. p.8–11.

[19] Lee SL, O'Connor TF, Yang X, et al. Modernizing Pharmaceutical Manufacturing: from Batch to Continuous Production. J Pharm Innov. 2015;10:191–199.

[20] Byrn S, Futran M, Thomas H, et al. Achieving Continuous Manufacturing for Final Dosage Formation: Challenges and How to Meet Them May 20-21 2014 Continuous Manufacturing Symposium. Journal of Pharmaceutical Sciences. 2015;104:792–802.

[21] Engisch WE, Muzzio FJ. Feedrate deviations caused by hopper refill of loss-in-weight feeders. Powder Technology. 2015;283:389–400.

[22] Engisch WE, Muzzio FJ. Method for characterization of loss-in-weight feeder equipment. Powder Technology. 2012;228:395–403.

[23] Hanson J. Control of a system of loss-in-weight feeders for drug product continuous manufacturing. Powder Technology. 2018;331:236–243.

[24] Stauffer F, Vanhoorne V, Pilcer G, et al. Raw material variability of an active pharmaceutical ingredient and its relevance for processability in secondary continuous pharmaceutical manufacturing. Eur J Pharm Biopharm. 2018;127:92–103.

[25] Dave VS, Saoji SD, Raut NA, et al. Excipient variability and its impact on dosage form functionality. Journal of Pharmaceutical Sciences. 2015;104:906–915.

[26] Hagsten A, Casper Larsen C, Møller Sonnergaard J, et al. Identifying sources of batch to batch variation in processability. Powder Technology. 2008;183:213–219.

[27] Fonteyne M, Wickström H, Peeters E, et al. Influence of raw material properties upon critical quality attributes of continuously produced granules and tablets. Eur J Pharm Biopharm. 2014;87:252–263.

[28] Wang Y, Li T, Muzzio FJ, et al. Predicting feeder performance based on material flow properties. Powder Technology. 2017;308:135–148.

[29] Nowak S. Improving Feeder Performance in Continuous Pharmaceutical Operations. Pharm Tech. 2016;40(10):68–73

[30] Lutz H, Wendt W. Taschenbuch der Regelungstechnik. Chapter 4.5. Frankfurt am Main und Thun (Germany): Verlag Harri Deutsch; 2007. p.115–118.

[31] Carr RL. Evaluating flow properties of solids. Chem Eng. 1965;72:163–168.

[32] Podczeck F. The development of an instrumented tamp-filling capsule machine II Investigations of plug development and tamping pressure at different filling stations. Eur J Pharm Sci. 2001;12:515–521.

[33] Lutz H, Wendt W. Taschenbuch der Regelungstechnik. Chapter 3.5. Frankfurt am Main und Thun (Germany): Verlag Harri Deutsch; 2007. p.79–94.

[34] Lutz H, Wendt W. Taschenbuch der Regelungstechnik. Chapter 4.5. Frankfurt am Main und Thun (Germany): Verlag Harri Deutsch; 2007. p.156–157.

[35] Lutz H, Wendt W. Taschenbuch der Regelungstechnik. Chapter 10.3. Frankfurt am Main und Thun (Germany): Verlag Harri Deutsch; 2007. p.436–438.

[36] Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wikström, C., Wold, S. Design of Experiments Principles and Applications. Umetrics AB, Sweden, Umea; 2000. p.2–4.

[37] Lutz H, Wendt W. Taschenbuch der Regelungstechnik. Chapter 4.5. Frankfurt am Main und Thun (Germany): Verlag Harri Deutsch; 2007. p.187–188.

[38] Eriksson, L., Johansson, E., Kettaneh-Wold, N., Wikström, C., Wold, S. Design of Experiments Principles and Applications. Umetrics AB, Sweden, Umea; 2000. p.213–220.

5.8 Appendices

Appendix A: Experiments for the maltodextrin mixture.

No.	Speed (rpm)	Pressure A (MPa)	Pressure B (MPa)	Mean filled weight (mg)
1	90	0.7	0.7	312.2
2	120	0.1	0.1	243.3
3	90	0.4	0.7	313.5
4	120	0.4	0.4	279.6
5	105	0.4	0.1	270.9
6	90	0.1	0.7	309.0
7	120	0.1	0.7	309.7
8	90	0.7	0.4	296.0
9	120	0.7	0.1	285.4
10	90	0.7	0.1	293.1
11	105	0.7	0.7	314.0
12	90	0.1	0.1	244.2
13	105	0.7	0.1	284.2
14	120	0.7	0.7	313.6
15	105	0.1	0.4	280.1
16	120	0.7	0.4	283.8

Appendix B: Experiments for microcrystalline cellulose

No.	Speed (rpm)	Pressure A (MPa)	Pressure B (MPa)	Mean filled weight (mg)
1	90	0.7	0.7	213.9
2	120	0.1	0.1	178.5
3	90	0.4	0.7	211.7
4	120	0.4	0.4	201.3
5	105	0.4	0.1	200.5
6	90	0.1	0.7	214.5
7	120	0.1	0.7	214.6
8	90	0.7	0.4	212.8
9	120	0.7	0.1	212.6
10	90	0.7	0.1	212.6
11	105	0.7	0.7	214.6
12	90	0.1	0.1	177.0
13	105	0.7	0.1	212.7
14	120	0.7	0.7	215.4
15	105	0.1	0.4	199.0
16	120	0.7	0.4	213.2

Appendix C: Experiments for maize starch.

No.	Speed (rpm)	Pressure A (MPa)	Pressure B (MPa)	Mean filled weight (mg)
1	120	0.1	0.1	305.0
2	120	0.7	0.1	306.1
3	120	0.7	0.7	312.6
4	90	0.1	0.7	313.2
5	105	0.7	0.1	301.8
6	105	0.1	0.4	307.7
7	120	0.4	0.4	309.7
8	120	0.7	0.4	308.3
9	90	0.7	0.4	306.5
10	105	0.7	0.7	311.7
11	120	0.1	0.7	314.3
12	105	0.4	0.1	302.4
13	90	0.4	0.7	310.3
14	90	0.7	0.1	302.1
15	90	0.7	0.7	310.5
16	90	0.1	0.1	300.1

6 Summary and Conclusion

Chapter 1 introduced the challenges for the pharmaceutical process development. Today *Quality by Design* is more important than ever. Other industries like the electronic industry or the automotive industry have optimized their processes to a great level. Six sigma processes are common here, which means 99.99966 % of the products are free of defects. They developed it on their own, free to optimize the processes to a maximum to be competitive among each other. The pharmaceutical industry is far away from these numbers. However, as described in this chapter, the pharmaceutical process development is about to change. The FDA demands an improvement. New regularities let new technologies arise, which help to improve the overall quality. Continuous manufacturing is stated as a key technology. Great advantages can be achieved. Clearly connected with challenges but at the same time with great opportunities.

Chapter 2 investigated the automation of a dosing disc capsule filler. It was possible to automate all the identified critical process parameters. With the automation of a process parameter and a control loop, it was possible to fill successfully a critical product on the capsule filler with a low powder bed height. A low powder bed height is beneficial as it reduces the residence time inside the capsule filler, which is desired in a continuous process. An integration of a force transducer into the capsule filler let it run at a safe and stable set point. Within a continuous system, this is an important prerequisite. Especially for the process development (where different CPP and CMA are varied), it is important to have a monitored machine. In conclusion, an automated capsule filler can be seen as a solid and basic element in the development of a continuous process. Several modifications were presented which show how a capsule filler can be adapted to work within a continuous system.

Utilizing the automated capsule filler from the Chapter 2, Chapter 3 presented an innovative method to develop a continuous production process: the rapid automated process development. With the use of this method, a capsule filling process was developed in a tremendous speed (2 days). The formulation of the drug was optimized as well as the process parameters. The rapid automated process development provides a solution for the challenge, described at the beginning of this thesis. It is now possible to develop the process as a whole and at the same time in an efficient and applicable way. In general, the method consist out of two main elements. The first element is represented by a high automation level. All critical process parameters must be automatically adjustable. With an automated acquisition of the critical quality attributes at the end of the process, experiments can be executed easily and efficiently. The second element is the creation of a statistical process model. Statistical optimized experiments are planned, executed and at the end, the model is created. This model

contains all the important information of the process. The black box of the process is now defined and understood. Finally, this technique showed its feasibility, thus an important tool for developing a continuous capsule filling process efficiently is available. It is now possible to develop a process on a continuous capsule filling system straightforward.

Chapter 4 concerned the content and the content uniformity. Previously in the rapid automated process development, the mean weight and the weight deviation were the target of the development. In this chapter, it is revealed what could be achieved, when the content is measured at the end of the capsule filler. In general, the technology is available and the rapid automated process development could be enhanced with the targets: content and content uniformity. By utilizing this information, it is possible to enhance the process development. To illustrate the benefits, a process was developed for a selected material, which could be detected by an X-ray system. The X-ray system determined the amount of the target material; hence, it was possible to determine the content uniformity. In comparison with the mean capsule weight, the content uniformity was influenced by different process parameters. An optimization of the content uniformity demands a different composition of the formulation. Regarding the importance of the content uniformity, it can be said that online content uniformity is useful for the process development. Especially in the combination with the rapid automated process development, it is an important option, which should be taken into account when a continuous capsule filling process is developed.

Looking at the implementation of a capsule filler into a continuous production system, the control of the fill weight is an important task. The capsule filler can adjust the fill weight at the end of the production line; thus, influence how much API is filled into the capsule. If there is a deviation in the API content (e.g., induced by the feeders), the capsule filler is able to correct it. Prerequisite however is that the control of the capsule filler is fast enough to react to the disturbances. This dynamic of the control depends on the controller settings. In the development of the process, the controller parameters must match to the filled product. In summary, chapter 5 investigated this topic and proposes a solution how the controller parameters could be derived from a previously build model of the rapid automated process development. With this new strategy, it is possible to determine the controller parameters in the process development of the system. In addition, the study illustrates, for three different materials, how fast two different types of controllers can react onto disturbances. Therefore, important information is gathered on how a capsule filler could benefit the process stability; hence benefit the entire continuous system.

Finally, a continuous capsule filling process can of course pose a challenge for the process development. It is a continuous manufacturing process and effort is needed to develop the process. However, with the right techniques and methods it is possible to overcome this challenge. Furthermore, it is possible to achieve great benefits when the process is developed on a continuous capsule filling system. Compared to batch processes (which also have their problems); there is the great opportunity to achieve a very efficient development. The system can be investigated as a single unit. This provides a great understanding of the process and in the end helps to reach the goals of *Quality by Design*. With this work a collection of knowledge is provided, which helps to develop future continuous capsule filling processes. Challenges can be recognized early and conceivable solution approaches are available.

7 Outlook

In this thesis, a high automation level was used to execute the needed experiments efficiently. The capsule filler was modified so that all the critical process parameters were adjustable. Yet there are some process parameters which are not automated. Some process parameters of the blender were only manually adjustable. This takes time, as the process has to be stopped. For example, the blender must be emptied to a certain level and blades with a different orientation have to be mounted manually. A second issue is that the blender has to be cleaned by hand between the different mixture experiments. If the old mixture is not removed, it is unknown how long it takes until the new mixture reaches the tamping pin process. Thus product is wasted and a lot of time is needed (compared to the other adjustments in the DoE) to switch to a new mixture. As a conclusion, it is difficult to run experiments on the plant efficiently. A future goal would be to investigate the blending process. It must be investigated whether it is possible to automate the critical process parameters of the blender. An efficient cleaning strategy would be helpful to speed up the experiments. Beside a continuous horizontal blender, there might be different blending processes, which work better in combination with the DoE. One example could be a vertical mini-batch blender. Small batches could be continuously produced and the mixtures could then be tested on the capsule filler. Thus, two studies should be executed. One should be an optimized blender design for the rapid automated process development and another study investigates if there is a benefit using a mini-batch or horizontal blender (which empties by gravity).

The residence time distribution was mentioned several times in this work. It is an important part of the continuous process development. The residence time must be known, for example, to evaluate the demands on the fill weight control. When a new batch of excipients is brought to the feeder, the residence time distribution determines how fast a control of the fill weight must reacted to keep the process in a stable condition. Despite of its importance, the residence time was not investigated in detail within these studies. As already mentioned, there are some studies available which investigate the residence time distribution of the capsule filler. However, it is still a challenging task and the residence time distribution can change, for example, for altered material attributes. Looking at process development and at the same time at the rapid automated process development, the target “residence time” was not integrated yet. An interesting study would be how to integrate the residence time distribution into the automated process development. With an additional target in the DoE, it might be possible to determine easily the main influences on the residence time distribution. By modelling the same, it might be possible to optimize the residence time distribution to a desired behavior.

The study, utilizing an X-ray system, showed promising results. The investigation of the content and the content uniformity inside the capsule is a great option. As mentioned, technology to measure content inside the capsule is available. Nevertheless, there is still work to do and these systems are not very common yet. Further experiments with real process developments would lead to much more experience in this area. One important part would be to connect the capsule filler with the detection system. In case of the X-ray system, the capsules could be measured inline after the capsule filling process. Other detection systems, which use for example Raman spectroscopy, need a longer time to execute the measurement. Hence, the detection must be executed at least online near the production. Looking at the process development it is important to highlight the need for automation. A study which uses an automated measurement of the content and content uniformity of real active pharmaceutical ingredients, would further enlighten the benefits of the automated process development. New experiences are likely to be made where new and unknown design modifications or process parameter settings which influence the product quality could be found. Thus, this effort would be a valuable investment to improve future process development. Prerequisite is a high automation and integration of the respective measurement technology.

For the control of the API content inside the capsule filler, an integrated PAT sensor is needed. In place of a tablet press there are several solution presented where a PAT sensor could be installed (e.g. in the feeder, in the punches or directly before the powder is compressed). In consequence, more research has to be done for the capsule filler. Perchance it is possible to integrate a PAT sensor inside the machine. The closer a PAT sensor gets to the actual filling process of the capsule filler, the faster the reaction is for controlling the fill weight. Interesting options might be locations near the transfer station. A study comparing the different locations would deliver essential data.

During this work, the approach was to develop the process before the final production was started. In contrast to this, there is another interesting option. This option would be to develop the process while the actual process is running. Small variations could be added to the process parameters. These variations of course should stay in the predicted stable range that a high product quality is still ensured. However, the influence of these small variations could be used to improve the first developed model continuously. With this technique, the model gets better and better as long as the process is running. The process is developed and refined during the production. Another option would be to use a certain percentage of the production to improve the process from time to time. Of course, this is a challenging approach but this could lead to a continuous adaption and improvement of the process. It would be interesting to

investigate how such an online process development could be applied. Especially, when it is combined with a model, previously developed by the rapid automated process development. An important prerequisite of such a study would be again a high automation level of the critical process parameters (to adjust them during the process) and a continuously monitoring of the critical quality attributes.

8 Appendix

8.1 Publications

Research Papers

Wagner B, Brinz T, Otterbach S, Khinast J. Automation of a dosing-disc capsule filler from the perspective of reliability and safety.

Journal: Drug Development and Industrial Pharmacy, 2018;44:502–510.

Received: 20 July 2017; *Accepted*: 30 October 2017

Wagner B, Brinz T, Otterbach S, Khinast J. Rapid automated process development of a continuous capsule-filling process.

Journal: International Journal of Pharmaceutics, 2018;546:154–165.

Received: 24 January 2018; *Accepted*: 05 May 2018

Wagner B, Brinz T, Khinast J. Using online content uniformity measurements for rapid automated process development exemplified via an X-ray system.

Journal: Pharmaceutical Development and Technology, 2019;24:775–787.

Received: 23 June 2018; *Accepted*: 12 March 2019

Wagner B, Cheong SF, Brinz T, Khinast J. Deriving Control Parameter Settings from Process Models to Control Capsule Fillers Integrated into Continuous Manufacturing.

Journal: Drug Development and Industrial Pharmacy, 2019;45:1523–1536

Received: 13 April 2019; *Accepted*: 12 June 2019

Talks and Poster

Talk: Wagner B, Brinz T, Khinast J: Use of Sensors to Monitor Hard-gelatin Capsule-filling Processes in the Context of Quality by Design

Location: ICPE 2016 – 7th International Congress on Pharmaceutical Engineering, Graz, Austria

Talk: Wagner B, Brinz T, Khinast J: Process Development Approach for Continuous Capsule-Filling

Location: 14th Minisymposium Chemical and Process Engineering and 5th Austrian Particle Forum, Linz, April 2018

Talk: Wagner B, Brinz T: Automated start-up of a powder station to fill hard gelatin capsules

Location: ACHEMA Congress 2018, Frankfurt (Main), Germany, June 2018

Poster: Wagner B, Brinz T, Khinast J: DoE Combined with Process Automation: a New Approach to Support Quality by Design

Location: 3rd European Conference on Pharmaceutics, Bologna, Italy, March 2019

8.2 Academic Development

2015 – 2019	Graz University of Technology, Doctoral School of Chemical and Process Engineering, Institute of Process and Particle Engineering, Austria
2011 – 2014	Friedrich-Alexander University Erlangen-Nuremberg, Mechanical Engineering, Master of Science, Institute for Factory Automation and Production Systems, Germany
2007 – 2011	University of Applied Sciences Esslingen, Mechanical Engineering, Bachelor of Engineering, Germany