Continuous twin-screw granulation with vibrated fluidised-bed drying

Inaugural-Dissertation

zur Erlangung des Doktorgrades
der Mathematisch-Naturwissenschaftlichen Fakultät
der Heinrich-Heine-Universität Düsseldorf

vorgelegt von

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Düsseldorf, Oktober 2024

Für meine Familie

„Wenn du es dir vorstellen kannst, kannst du es auch machen.“
Walt Disney

Aus dem Institut für Pharmazeutische Technologie und Biopharmazie
der Heinrich-Heine-Universität Düsseldorf

Gedruckt mit der Genehmigung der
Mathematisch-Naturwissenschaftlichen Fakultät der
Heinrich-Heine-Universität Düsseldorf

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Tag der mündlichen Prüfung: 18. Dezember 2024

Table of content

List of publications and contributions

Published manuscripts

K. Kiricenko & P. Kleinebudde, Drying behavior of a horizontal vibrated fluidized bed dryer for continuous manufacturing, Pharmaceutical Development and Technology, 28 (2023) 440–451.

K. Kiricenko, F. Hartmann, A. Altmeyer, P. Kleinebudde, Loss-on-drying prediction for a vibrated fluidised bed dryer by means of mass and energy balances, Journal of Pharmaceutical Innovation, 18 (2023) 2429–2446.

K. Kiricenko, S. Klinken, P. Kleinebudde, Proof of a LOD prediction model with orthogonal PAT methods in continuous wet granulation and drying, Journal of Pharmaceutical Sciences, 114 (2025) 176-184.

K. Kiricenko, R. Meier, P. Kleinebudde, Systematic investigation of the impact of screw elements in continuous wet granulation, International Journal of Pharmaceutics: X, 8 (2024) 100273.

Conference contribution

K. Kiricenko & P. Kleinebudde, Temperature profiles of the QbCon® 1 during continuous drying. Poster presentation, 13th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Rotterdam, Netherlands, 2022.

K. Kiricenko & P. Kleinebudde, Influence of drying parameters using the QbCon® 1 continuous dryer. Poster presentation 4th European Conference on Pharmaceutics, Marseille, 2023.

K. Kiricenko & P. Kleinebudde, Studies on continuous drying. Oral presentation, 4th APV Continuous Manufacturing Conference, Lisbon, Portugal, 2023.

K. Kiricenko & P. Kleinebudde, Drying behaviour using the QbCon® 1 continuous dryer. Poster presentation, 10th International Granulation Workshop – Granulation Conference, Sheffield, United Kingdom, 2023.

K. Kiricenko, F. Hartmann, S. Klinken, P. Kleinebudde, Application of mass balance for LOD determination in continuous wet granulation and drying. Poster presentation, 14th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Vienna, Austria, 2024.

List of abbreviations

API	Active Pharmaceutical Ingredient
CE	Conveying element
CM	Continuous Manufacturing
CQA	Critical Quality Attribute
DME	Distributive mixing element
DoE	Design of Experiment
FBG	Fluidised-bed granulation
FBD	Fluidised-bed dryer
FDA	United States Food and Drug Administration
HS	High-shear granulation
ICH	International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
KE	Kneading element
L/D	Length-to-diameter ratio
L/S	Liquid-to-solid
LOD	Loss-on-drying
MCC	Microcrystalline cellulose
MCS	Manufacturing Classification System
MEB	Mass and energy balances
NIR	Near-infrared
PAT	Process analytical technology
PVP	Polyvinylpyrrolidone, Povidone
QbD	Quality by Design
RMSE	Root mean square error
RTD	Residence time distribution
RTRT	Real-time-release-testing
TME	Tooth mixing element
TSG	Twin-screw wet granulation
VFBD	Vibrated fluidised-bed dryer

1 Introduction

1.1 Progress in continuous manufacturing

1.1.1 Batch versus continuous manufacturing

Batch manufacturing of oral solid dosage forms is the standard production approach and remains predominantly applied in the pharmaceutical industry. The complete process consists of single unit operations, such as blending, wet granulation, drying, sizing, tableting and coating. At each step, intermediates are produced, stored and then further processed, ultimately resulting in the final product. The manufacturing of the raw materials such as active pharmaceutical ingredient (API) and excipients is called primary manufacturing while secondary manufacturing describes the production of the final dosage forms [1]. Figure 1 visualises an example of a wet granulation process with coated tablets as the final dosage form, comparing batch to a continuous processing. The raw material is added into the first unit and the process is conducted under validated conditions until the endpoint of the single unit is reached. After each unit, the intermediate material is discharged. The quality of the material is usually determined off-line as an intermediate control and stored before the next unit is available for processing. Testing the quality between each unit allows the intermediates to be discarded if the specifications are not within the set limits and thus the quality is not met [2, 3]. The production of the final product can take weeks to months as the intermediates are usually stored and tested before further processing. Depending on the available equipment at the site, the intermediates might be shipped to another manufacturing facility. Thus, long supply chains are typically for batch manufacturing processes and in combination with the required storage capacity, the production costs are increased [1, 2, 4].

The automotive, food and consumer industry have used the continuous manufacturing (CM) approach successfully for many years, achieving high manufacturing efficacy and reduced costs [5]. In the CM process, the material is continuously fed into the system, transformed, and continuously removed as the finished product from the process [3, 6]. CM approach can be used for several or all unit operations. For example, some unit operations can operate in a batch mode, semi-continuously and others operates full continuously. As displayed in Figure 1, the different units are connected to each other and the process and material flow operate without interruption. The implementation of process analytical technology (PAT) tools allows the measurement of critical quality attributes (CQAs), such as blending uniformity, in-line.

Furthermore, the implementation of process control systems promises to enable real-time release testing (RTRT). Thus, the production within the CM approach can take days [2]. Additionally, either the secondary or primary manufacturing can operate in a continuous mode or the combination of both describe an end-to-end manufacturing process [6]. Mascia et al. and Domokos et al. presented an end-to-end CM approach starting either from chemical intermediate [7] or using flow synthesis [8]. Domokos et al. produced acetylsalicylic acid tablets involving synthesis, crystallisation and filtration followed by blending the API with microcrystalline cellulose (MCC) and finally direct compression into tablets. They implemented an in-line real time analysis using near-infrared (NIR) spectroscopy for blending homogeneity, as well as off-line determination of the API content [8]. This thesis focuses on secondary manufacturing, thus the downstream processing, as illustrated in Figure 1.

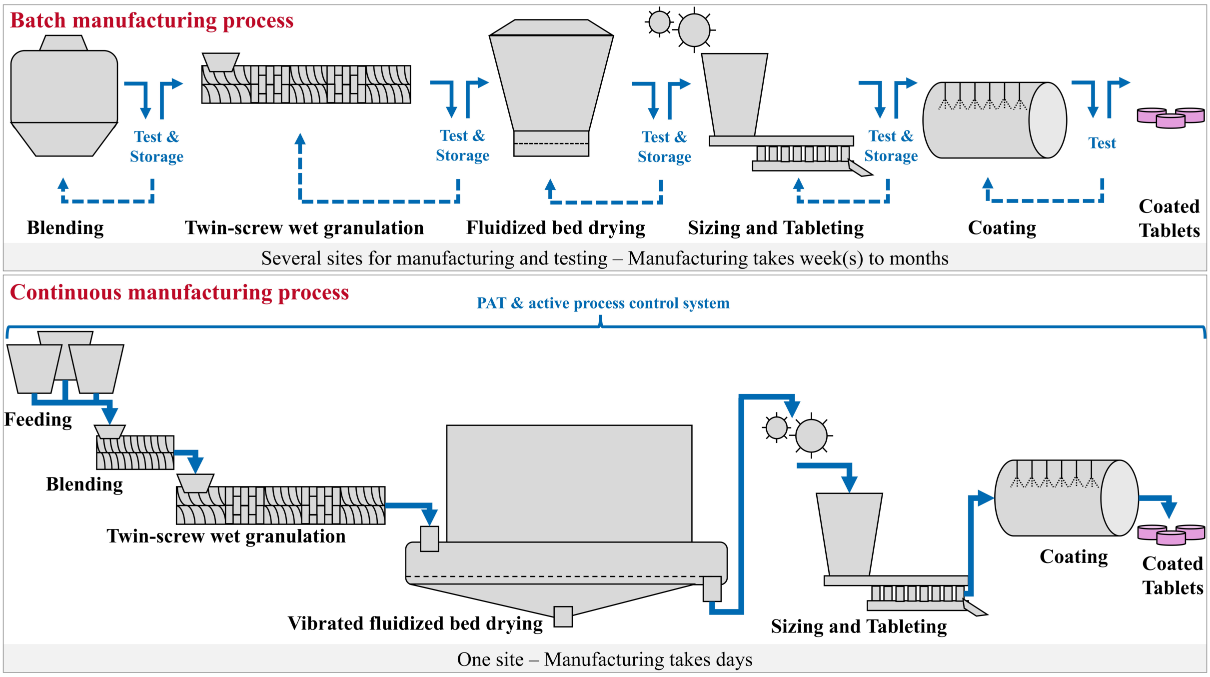

Figure 1. Schematical overview of the production of coated tablets demonstrated using batch manufacturing and continuous manufacturing process. (Figure is adapted from [2] and [9]).

Several pharmaceutical companies, such as Johnson & Johnson (Janssen), Eli Lilly, GlaxoSmithKline, Pfizer, Vertex Pharmaceuticals and Novartis have committed resources to the development of pharmaceutics using CM processes [9]. Some drug products manufactured using CM have been authorised by regulatory authorities. Although the trend to switch from batch to continuous manufacturing is growing, it remains expandable. Vertex Pharmaceuticals was the first company to gain approval for a CM drug product in 2015, with Orkambi® (lumacaftor/ivacaftor) for the treatment of cystic fibrosis. This product combines both APIs in tablets produced continuously [3, 9]. In 2018, the company received for a second CM product, Symdeko® (tezacaftor/ivacaftor) tablets, followed by approval for Trikafta® or Kaftrio® (elaxacaftor/ivacaftor/tezacaftor) in 2019 for the same indication [10]. Janssen switched from batch manufacturing to CM for Prezista® (darunavir) tablets for the treatment of HIV-1 infections and received approval in 2016. Other known approved CM drug products were Verzenio® (abemaciclib) by Eli Lilly in 2017 for the treatment of breast cancer, Pflizer's lung cancer drug Lorbrena® (lorlatinib) and Daurismo® (glasdegib) for myeloid leukaemia, both approved in 2018. Johnson and Johnson received approval for the treatment of chronic non-cancer pain with Tramacet® (tramadol hydrochloride/acetaminophen) [3, 9].

1.1.2 Regulatory considerations

The International Council of Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) provided the quality requirements for pharmaceutical processes in the quidelines: good manufacturing practice (Q7) [11], pharmaceutical development (Q8(R2)) [12], quality risk management (Q9) [13] and pharmaceutical quality system (Q10) [14] which should be considered for CM. Further quality considerations for CM processes are described in the guideline for continuous manufacturing of drug substances and drug products (Q13) [6]. Previously, the draft guidance for industry: quality considerations for continuous manufacturing was published in 2019 by the United States Food and Drug Administration (FDA) [15].

To ensure and maintain the quality of the product during CM, an adequate and robust control strategy is required. Therefore, the Quality by Design (QbD) approach, which is a more scientific and risk-based, was introduced for pharmaceutical development. The aim of the approach is to integrate considerations on quality from the beginning of the development phase throughout the entire process instead of end-product testing [12, 16]. Thus, the development and implementation of a control strategy is part of the QbD approach. The aim of the control strategy is to ensure that the product consistently meets quality and regulatory requirements. To achieve this, the strategy involves real-time process monitoring and control during manufacturing. Therefore, PAT tools are implemented to monitor the quality attributes of the material. To control variabilities in raw materials and process disturbances that may affect the final product, a feedback or feedforward control system can be applied. Alternatively, a combination of both systems can also be used. Feedback control takes action after disturbances affect the product properties, while feedforward control takes action before the disturbance impact the product characteristics. To maintain the product within the desired specification, even when disturbances occur, process and product understanding are required. The understanding and knowledge of how the product is influenced by these variabilities allows for a realisation of RTRT and helps to minimise end-product testing [9, 17].

To establish process and material understanding, the following steps can be applied: (1) identification of all process parameters and material attributes, (2) identification of potentially high-risk parameters and attributes, (3) determination of ranges for these parameters and attributes, (4) conduction of Design of Experiments (DoE), followed by (5) analysing the obtained data and determining of scalability for process parameters as well as applying first principle models for identification of critical process parameters and attributes, and lastly (6) development of a control strategy and outlining acceptable ranges or design space [16]. DoEs allow the screening of key effects and interactions between process parameters and material or product attributes. Consequently, the influence of such variables, whether process-related or material-related, on the final product can be identified. Furthermore, predictive models can be developed, that may be used as a control strategy for the manufacturing process, integrated in control loops as mentioned previously. DoEs can also be applied to define a design space and optimize a certain process [2, 18-20].

Based on the good manufacturing practise and product recalls, the definiton of a batch is also necessary in CM processes according to the regulatory guideline [2, 3, 6]. The batch size in CM processes can be defined as the quantity of the output material, the quantity of input material or the run time/period at a defined mass flow rate according to the ICH guideline Q13 [6]. Vanhoorne and Vervaet introduced further examples to specify a batch in CM as the amount of material manufactured within a time period, batch size of the used API or the duration of the operator's shift [3].

Another aspect that needs to be considered for the CM process is the knowledge of the process dynamics. This involves understanding how the material flows through the process to ensure material traceability in case of nonconforming material or product recall. Tracking the raw material and intermediates is essential to understand the distribution of the material and the effect of material and process variations. Additionally, precise process control, RTRT of the product or diverting out-of-specification material are only achievable if the residence time distribution (RTD) is known [9, 21]. RTD according to ICH Q13 is "a measure of the range of residence times experienced by material passing through a specific process evironment/vessel/unit operation" [6]. An adequate and well established approach for material traceability, process monitoring and material diversion allows that nonconfirming material due to start-up, shutdown or temporary process disturbances can be discharged without affecting the remainder of the batch [15, 22].

The implementation of RTRT is encouraged by regulatory authorities but is not mandatory for the implementation of a CM process. The application of PAT tools, which provide real-time data of the process and CQAs can support RTRT. When RTRT is part of the control strategy, further considerations regarding the sampling strategy are required. Therefore, in-process online, at-line and/or in-line sampling need to be included. An appropriate sample size and frequency, that represent the batch, need to be chosen and justified using a suitable statistical approach. The calculations of RTRT must consider the variance in CQA over the batch variability. Another important aspect is the establishment of a plan for potential error in the PAT data due to sensor failure [6, 15].

1.1.3 Advantages and challenges of Continuous Manufacturing

The adaption of a CM offers a range of advantages over traditional batch-wise manufacturing, but also presents several challenges that the pharmaceutical industry must overcome. The use of medium-sized equipment in the CM line provides benefits, as the same equipment can be used for development, pilot research, manufacturing of clinical trial samples and finally commercial production by varying the production time based on the required amount of drug product. This approach might accelerate the development of drug products, reduce scale-up issues commonly associated with batch manufacturing and consequently lower the machine footprint [2, 3, 9]. Furthermore, after the initial investment reduced costs are major benefits, which are achieved through the smaller footprint and improved usage of equipment, lower production costs and personnel requirements. The application of process monitoring and control using PAT tools and control loops lead to improved product properties and reliability [23, 24]. Furthermore, material that is out-of-specification for example due to process disturbances can be withdrawn by the knowledge of the RTD. This might reduce the number of product recalls and improve the product availability as drug shortages due to manufacturing problems can be avoided [3, 25]. Moreover, production using the CM process takes less time and requires less space as demonstrated by the company Janssen. The production time for their previous batch-wise process of Prezista®, which used seven rooms and took two weeks, was reduced to one week and two rooms after switching to the CM process [9].

Besides the quality considerations for CM provided by the FDA, that are also listed in the ICH Guideline Q13 [6], additional hurdles must be balanced against the benefits of implementing

CM process for pharmaceuticals. Companies that already possess equipment and facilities for batch manufacturing need to invest in new equipment and adopt CM. Particularly for contract manufacturers, implementing CM poses a challenge because they produce multiple drug products in batches using the same equipment for various pharmaceutical companies, requiring them to maintain flexibility. Furthermore, to realize end-to-end processing, the manufacturing of API and drug product needs to be in at least one facility, however, in reality, production is often distributed across different countries or locations within one country. Another challenge is the incorporation of suitable PAT tools for process monitoring and control which requires in-depth expertise not only in this field, but also in statistics, modelling, QbD processes and understanding the influence of process parameters and material attributes on the CQA and final product. The implementation of a process control needs to ensure that disturbances are detected and the process is adapted to maintain the product quality or to overcome material variability [6, 26]. As the implementation of CM requires experience for adaptation, it should be noted that there is also limited experience regarding the submission both within the companies but also within the regulatory authorities, especially the EMA (European Medicines Agency), MHRA (Medicines and Healthcare products Regulatory Agency, United Kingdom) and PMDA (Pharmaceuticals and Medical Devices Agency, Japan) [9].

1.1.4 Continuous Manufacturing of solid dosage forms

There are different manufacturing routes available to produce solid oral dosage forms. Leane et al. introduced a proposal for the Manufacturing Classification System (MCS) for solids. The MCS is divided in four categories: (1) direct compression, (2) dry granulation, (3) wet granulation and (4) other technologies such as melt extrusion. The classification within the MCS is based on the properties of the API, such as particle size, surface area, shape, modification, density, flowability and segregation tendencies for deciding the suitable manufacturing mode. Categories 1 to 3 are the main manufacturing routes for solid oral dosage forms. The higher the class, the greater the complexity of the process [27, 28].

Figure 2 summarises the main manufacturing routes for solid drug products, including capsule filling either directly from the blend or after granulation. The most favourable and simplest manufacturing route for tablets is direct compression, as it involves only blending and compression of the powder into tablets. According to Leane et al., difficulties such as segregation tendency or poor flowability require a granulation step prior to tableting in batch manufacturing. However, in continuous direct compression, these issues are mitigated due to the continuous feeding and blending, which reduce the risk of segregation [29].

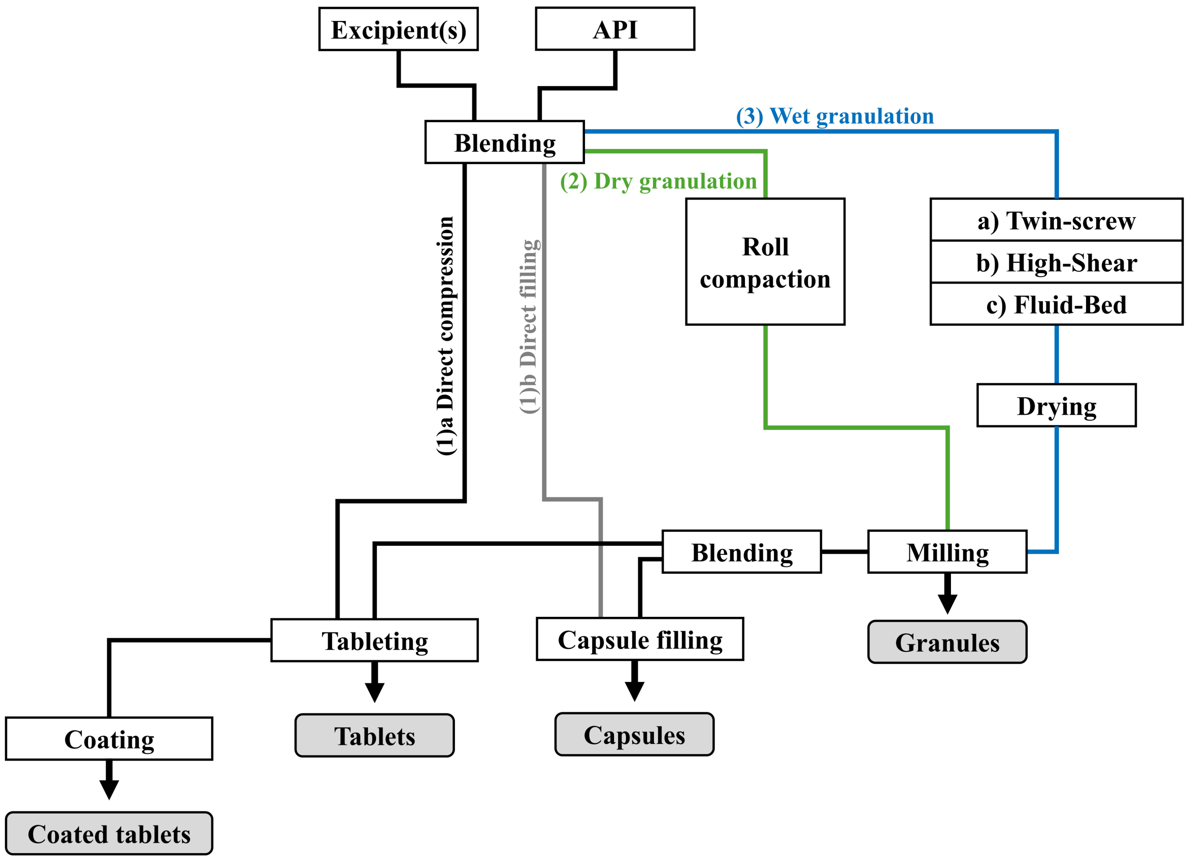

Figure 2. Overview of the main manufacturing routes for solid oral dosage forms. (Figure adapted from [28] and [30]).

Granulation is a size enlargement technique that produces agglomerates from powder through different methods. It can either be used before tableting or as a single process where the final dosage forms are granules or filled capsules. Granulation is applied to increase the flowability, reduce the dust generation during manufacturing and improve the API distribution and thus the API dosing [31].

The implementation of dry granulation within a tableting CM line is feasible by establishing a roll compaction/dry granulation unit between the blending and tableting step. The powder is compacted between two counter-rotating rolls, forming dense ribbons, which are then milled into granules. Continuous dry granulation is useful if the powder is not suitable for direct compression due to poor flowability or is sensitive to heat or moisture [32].

If the API and excipients are not sensitive to moisture or heat, wet granulation and drying step might be an option. Soluble binders are either added to the powder mixture in a dry state with water typically used as the granulation liquid. Alternatively, a binder solution can be applied directly as the granulation liquid. Different wet granulation processes are possible: the most popular are high-shear (HS), fluidised-bed (FBG) or twin-screw wet (TSG) granulation. In HS a mixing or granulator bowl is used. First, the dry powder is mixed followed by the addition of the granulation liquid at a slower impeller and chopper speed. The wet mass is then mixed at higher impeller and chopper speeds to enhance the liquid distribution and mixing, while the chopper is used to reduce coarse granules. The speed of both the impeller and chopper directly influences granule growth, breakage and densification [33]. Granules produced with HS typically have a high fraction of oversized granules, reduced porosity and higher strength due to the high densification. Therefore, reduced tabletability of HS granules has been observed in the literature [34-36]. Advantages of HS techniques include good mixing, short processing times, and the ability to handle high drug loads [33]. FBG allows both granulation and drying within one equipment. In this process, dry powder is fluidised by an upward airflow, while a granulation liquid is sprayed through a nozzle, promoting the formation of granules. Granules are less densified and usually narrow and monomodal granule size distributions (GSDs) are obtained resulted in good tabletability with sufficient tensile strength [34].

In particular, TSG is intrinsically continuous. Although wet granulation and drying before tableting is a more complex process, this method was the most popular choice, as Leane at al. reported in 2018 [27].

1.2 Twin-screw wet granulation

1.2.1 General

Twin-screw granulation, well established in the food [37] and plastic industries for decades, has been adapted for the production of pharmaceutical granules. Firstly, the production of paracetamol extrudates was demonstrated by Gamlen and Eardley [38] using a single-screw extruder. Lindberg et al. produced effervescent granules using a twin-screw extruder [39].

Since then, numerous studies have investigated the use of twin-screw granulators to continuously manufacture granules without a die plate at the outlet of the screws, as was originally applied [40, 41]. The granulator consists of two co-rotating intermeshing screws located in a barrel. The screws can be variably constructed with different elements mounted onto a shaft. The barrel is typically divided in several zones along the length, with each zone capable of being heated or cooled individually.

The length-to-diameter ratio (L/D) determined by the total barrel length and screw diameter allows a dimensionless description of the granulator independent of the manufacturer [42]. Figure 3 illustrates the typical parts of the TSG process. Blended powder is fed through a feeder, while the granulation liquid is introduced via a pump into the barrel. The wet mass is transported and mixed along the barrel through various screw elements. Inside the barrel three key mechanisms occur: (1) wetting/nucleation, (2) consolidation/coalescence and (3) attrition/breakage. Thus, wet granules exit the granulator and a drying step is required.

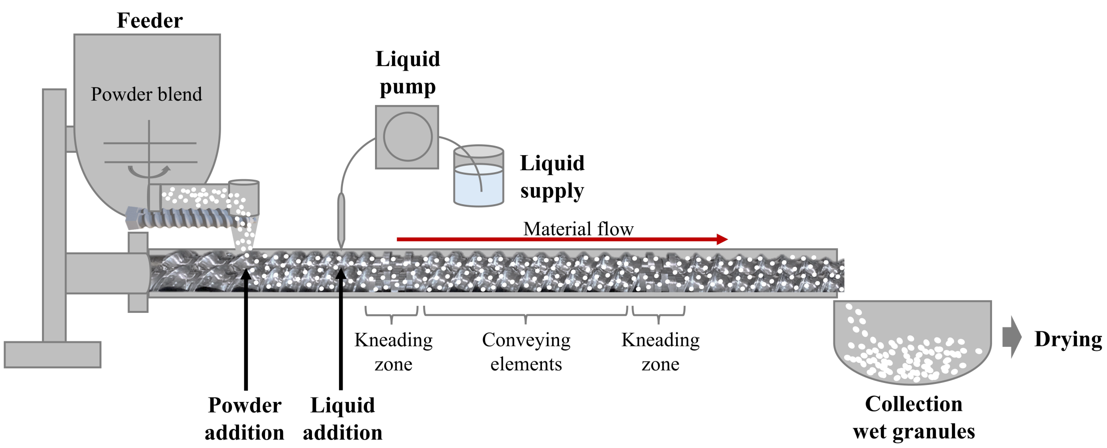

Figure 3: Schematic representation of twin-screw wet granulation process.

1.2.2 Screw configuration

1.2.2.1.1 Overview

The screw configuration can be individually constructed using different types of screw elements at different positions along the barrel to obtain specific granule attributes. Usually, the screw is longer than the barrel thus exceeds the barrel which facilitates the discharge of the wet granules. The available screw elements can be divided into conveying elements (CEs), kneading elements (KEs) and mixing elements.

1.2.2.2 Conveying elements

CEs are applied for the transportation of the material along the barrel and impart low mechanical energy. They exert low shear force compared to other elements [43, 44]. CEs exhibit a helical shape and can differ in their flight-pitch. The flight-pitch is the axial distance between two adjacent flights and the flight lead defines the distance a flight traverses axially for one turn. Figure 4 shows exemplary CEs with different flight pitches. From left to right, the pitch decreases and thus the transport capacity (Fig 4) [42, 44].

Figure 4: Exemplary conveying elements with different pitch and length.

Researchers investigated the impact of the screw configuration. As Dhenge et al. and Djuric and Kleinebudde examined, CEs are sufficient for the formation of granules [45, 46]. A mixture of lactose monohydrate, MCC and croscarmellose [45], as well as pure lactose monohydrate [46] with water as granulation liquid were capable for the production of granules. The use of only CEs led to a bimodal GSD [44, 47-49] independent of the viscosity of the binder solution [50]. Djuric and Kleinebudde found that the pitch impacted the granule properties. Using a higher pitch led to a higher yield fraction, a lower proportion of fines, lower porosity and friability of the granules and higher granule strength. The authors explained that the wet material is more densified due to the increased free chamber volume inside the barrel when using larger pitches resulting in a lower fraction of fines. Involving KEs in the screw configuration improved granule properties regarding the fines, porosity and granule strength

[46]. Rahimi et al. contributed to this by obtaining highly porous and loosely packed agglomerates when granulating with only CEs compared to the addition of KEs [51].

1.2.2.3 Kneading elements

KEs are single discs which can be combined to form a kneading block. Either ready-to-use kneading blocks are available or the kneading block can be individually build. Kneading blocks represent the mixing zone in a screw configuration. Compared to CEs the free chamber volume is decreased, thereby imparting high mechanical energy and producing high shear force [43]. Thus, the wet material is densified and agglomerated using KEs. The thickness of the KE can be varied as illustrated in Figure 5A. The angle between the KEs can be varied, defining the offset angle in a kneading block, which influences the conveying capacity. Figure 5B displays exemplary kneading blocks with the typical off-set angle 30°, 60° and 90° as ready-to-use block (left to right). Lee at al. postulated that the residence time of the granules inside the granulator grew with increased offset angle at constant process parameters, indicating that the conveying capacity was reduced [52]. Thompson and Sun emphasised that with a higher offset angle, the mixing capacity improved as the applied shear force also increased. 90° kneading blocks have no conveying capacity, as the forward transportation is pressure dependent [44]. Influence of the offset angle described in the literature is different. Kumar et al. found a significant influence of the offset angle on the fraction of fines and oversized granules. Higher angle resulted in decreased fraction of oversized granules (> 1400 µm) and consequently more fines (< 150 µm) [53]. In comparison, Thompson and Sun obtained an influence of the angle while granulation with high filling degree [44] and Vercruysse et al. reported even no impact of the angle in the conducted factor space [54].

Figure 5: Kneading discs with increased thickness from left to right (A) and kneading blocks with 30°, 60° and 90° offset angle (B).

KEs can be differentiated not only with different offset angles but also with different transport directions, such as forward and reverse, which change the flow of the material due to barriers in the case of reverse direction. Li et al. [47] and El Hagrasy and Litster [49] observed larger granules and improved liquid distribution while using the reverse direction, independent of the angle. The reverse movement of the wet material raised the pressure in the kneading zone, leading to a forward push. Thus, the material is more densified using the reverse direction, resulting in coarser granules due to improved liquid distribution [49]. According to the available literature, mostly forward kneading zones are used [53, 55, 56].

Since the kneading block can be set individually, the number of KEs is an additional variable. With a constant KE thickness, using more KEs resulted in a longer mixing zone inside the barrel. Similar effects of the number of KEs have been postulated in the literature. More KEs led to higher torque and residence time inside the barrel, resulting in a greater fraction of oversized granules and fewer fines, as the shear and compaction forces acting on the wet mass were amplified [53, 54, 57]. Vercruysse et al. also mentioned higher bulk- and tapped density if more KEs are involved in the kneading block. Furthermore, the increased granule density affected the resulted tablets, leading to a higher disintegration time and slower drug release. They assumed and argued that denser granules with a smaller fraction of fines resulted in impaired percolation of the liquid inside the granules [54]. As more KEs improved granule growth and densification, granule porosity decreased as reported by Rahimi et al. and Djuric and Kleinebudde, which led to a decrease in the tensile strength of the obtained tablets [46, 51].

Furthermore, the thickness of the applied KEs had an impact of the granulation process and granule properties. Van Melkebeke et al. and Portier et al. found that thinner KEs led to higher friability and reduced granule size that affected the flowability in further processing [58, 59]. Thicker KEs resulted in a similar effect as using more KEs as they raised friction against the wall and screw, resulting in higher torque values [18, 53]. The kneading zone offers many variations in the screw configuration, that might influence the granule and tablet attributes and will be focused further. The influence of screw configuration is depending on the barrel fill level, which differ depending on the set process parameters.

1.2.2.4 Mixing elements

Distributive mixing elements (DMEs), also named comb mixer elements in the literature [42, 46, 60], feature a distinct design of the flight tip based on the CEs geometry (Figure 6A). These screw elements cause more backflow compared to CEs and exhibit both conveying and mixing functions [48, 61]. The use of DMEs resulted in decreased granule size, especially when DMEs are included after the kneading zone [48, 51]. Furthermore, Rahimi et al. observed increased granule porosity when DMEs were used instead of a kneading zone with an offset angle of 90° [51]. Vercruysse et al. noted a higher yield fraction (150 µm – 1400 µm) by implementing DMEs in the screw configuration, as oversized granules were reduced. Additionally, a low and stable torque was observed indicating the low mechanical shear of these elements [48].

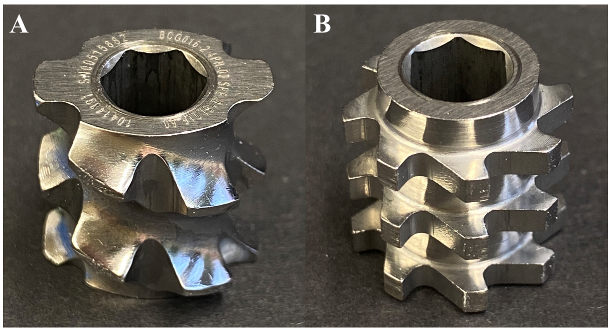

Figure 6: Sizing elements with exemplary distributive mixing element (A) and tooth mixing element (B).

Tooth mixing elements (TMEs, Figure 6B) are another type of mixing elements that can consist of narrow and wide discs. These elements exhibit no conveying function and result in higher torque values as material hold-up rises, indicated by longer residence time. This causes higher pressure, especially when these elements are placed at the outlet of the configuration leading to further agglomeration. Thus, TMEs impart shear stress to the material resulting in a decreased fraction of fines [48, 62].

1.2.3 Process parameters

During TSG various process parameters can be adjusted, affecting the properties of granules and tablets. Among these the liquid-to-solid (L/S) ratio is one of the most critical and influential parameters and has been extensively analysed by researchers [18, 57, 63-65]. A higher L/S ratio results in a larger granule size with a higher fraction of oversized granules and fewer fines. At higher L/S ratios, more liquid is available, thus more surface wetting of granules results in further granule growth. El Hagrasy et al. [66] reported bimodal granule size distribution consisting of lumps as well as un-granulated powder during granulation with low L/S ratio. The granule shape was found to be elongated and became more spherical at higher L/S ratio, that also shifted the granule size distribution to larger granules resulting in a monomodal distribution [63, 65, 66]. It should be considered that lumps are insufficient for tableting and therefore a milling step is necessary, if high L/S ratio is required [63, 66]. Furthermore, a higher L/S ratio led to a longer residence time and greater torque due to the change in consistency, as the material became pasty [18, 53, 65, 67, 68]. Dhenge et al. [65] observed increased granule strength by applying a higher L/S ratio. More liquid bridges were formed, resulting in stronger granules. A decrease in porosity was also observed by El Hagrasy et al. [66] and Shirazian et al. [67]. Some authors postulated an influence on tablet tensile strength [18, 69].

The material throughput, adjusted by the powder feed rate, as well as the screw speed are parameters that change the barrel fill level and therefore should be considered together [70]. At low screw speed, higher throughput results in a higher fill level with greater shear force on the material [55, 64]. At high throughput, the fill level is decreased with increased screw speed [71]. Sufficient liquid distribution for granule formation might require longer residence time [53]. Typically, the residence time for a TSG process is below one minute, often only a few seconds [56, 72]. A longer residence time is observed with higher barrel filling, which is obtained either by higher throughput or lower screw speed [18, 55]. Higher feed rates lead to plug causing faster material transport along the barrel. The torque, which indicates compaction inside the barrel, rises with higher throughput or lower screw speed. Granule size grows due to increased shear force associated with greater barrel filling and higher throughput [56, 65]. Meier et al. explained that larger granule size at higher fill levels result from more consolidation and growth leading to increased particle contacts [55]. Dhenge et al. contributed to this by showing that higher feed rates enhanced granule strength, indicating greater compaction inside the barrel [65]. The fraction of fines is reduced and oversize increased with higher fill level through greater throughput [19, 53, 64]. However, the impact of the screw speed on the amount of fines or oversized granules varies depending on throughput [19] and L/S ratios [18, 64], as these factors affect the fill level and the availability of the granulation liquid. In contrast, Vercruysse et al. reported no impact of throughput and screw speed on the fraction of fines and oversized granules within the studied design space [54].

The effect of the fill level, throughput and screw speed on tablets were investigated in the literature. Liu et al. reported reduced tablet tensile strength with increased screw speed or throughput, as higher throughput thus greater fill level led to denser and less porous granules [19]. Meier et al. found an optimum for the specific feed load used as surrogate for the barrel fill level. They observed that both too high and too low fill levels resulted in low tensile strength, likely due to granule size. They further reported that a medium specific feed load, thus fill level, combined with high screw speed resulted in favourable tablet properties [55].

Barrel temperature is a process parameter that can be adjusted to change the granule properties. Vercruysse et al. found that the proportion of fines was reduced and the amount of oversized increased by applying a higher barrel temperature during granulation for a formulation consisting of theophylline as a hydrophobic API and alpha-lactose. This is due to the enhanced solubility of the powder in the granulation liquid, which allows for the formation of more solid bridges and thus results in stronger granules [54]. Meng et al. [73] and Vanhoorne et al. [68] also studied the effect of enhanced solubility by raising the barrel temperature. Furthermore, Ito and Kleinebudde observed a similar reduction in the fraction of fines with higher barrel temperature, as well as a shift to a monomodal GSD [74].

In conclusion many variables in the TSG process can be adjusted to optimise the quality of granules and tablets. As highlighted previously, screw configuration and process parameters significantly impact the attributes of the granules. Moreover, the interaction between the chosen screw configuration and the process parameters is crucial, making a thorough understanding of the process essential.

1.3 Drying

1.3.1 General

Drying is a crucial step following wet granulation to remove the granulation liquid, in most cases water, from the granules, making them suitable for further processing or storage. Typically, wet granules are dried using a fluidised-bed dryer (FBD) in batch manufacturing.

The drying process in a batchwise FBD for porous materials is divided into three main phases: heating of the particles, first drying period (also known as primary drying) and the second drying period (also known as secondary drying) [75]. In the heating phase, the wet particles are first heated to the saturation temperature. In the first drying stage, unbound free water from the particle surface and within large pores is removed through evaporation at a constant drying rate. In this stage, the moisture content of the solids decreases linearly and the rate of drying is limited by the amount of heat supplied. The drying rate is influenced by the external conditions of the dryer, such as temperature, relative humidity, pressure and air flow rate. The solids remain in this stage until they reach the critical moisture content, that marks the transition between the first and second drying stage. After this point, the second drying stage begins, characterised by the removal of more tightly bound water at a continuously decreasing drying rate, also known as the falling rate. During this stage, the path for diffusion increases while the drying rate decreases over time [75, 76].

1.3.2 Continuous drying

Mostly, segmented FBDs are implemented in (semi-)continuous manufacturing lines after wet granulation [77-80]. These segmented FBDs consist of six or ten separate, identical drying chambers. In the segmented dryer from the company GEA (GEA Pharma Systems, Belgium), the wet granules are filled into the chamber via a rotary valve from the top of the dryer. Each of the segments can be filled, dried and emptied in parallel. The fill mass in each segment is defined by the fill time and mass flow rate [79]. In comparison, the Glatt dryer (Glatt GmbH, Germany) uses a star-shaped rotor in the drying chamber, resulting in ten rotating drying segments. At the bottom of the star-shaped rotor, a sieve plate is placed to allow air stream to pass from below. The segments are rotated clockwise to the outlet while the granules inside each segment are dried under the set drying conditions. Thus, one segment is continuously filled, then moved clockwise to fill the next one, and after a full rotation, each segment is discharged at the outlet port. Therefore, the drying time is defined by the rotational speed [77].

These segmented FBDs were implemented into the ConsiGma® system by the GEA company and the MODCOS concept available in different scales from Glatt. Both companies offer a lab scale (ConsiGma®-1, MODCOS S), which consists of only one drying chamber and a production scale (ConsiGma®-25 or MODCOS M or L) utilising the segmented FBDs [71, 79, 81]. A number of studies has focused on the application of these dryers [71, 79, 81-83]. Vercruysse et al. investigated and successfully achieved the transfer from batch to the continuous ConsiGma® system, from powder to tablet, involving wet granulation and drying as intermediate steps [83]. Furthermore, Vercruysse et al. evaluated the repeatability using ConsiGma®-25 by running the process for 1 hour at constant process settings and compared the granule and tablet quality to the products obtained with the lab scale ConsiGma®-1. Comparable tablet qualities were observed, although the granule size distribution and flowability differed between both systems [79]. Extensive breakage and attrition of granules were observed during the transfer of wet granules to the dryer and the exit of dried granules using pneumatic transfer. This was even more pronounced when a horizonal setup of the ConsiGma®-25 was used as reported by De Leersnyder et al. [80] and Ryckaert et al. [84]. The temperature difference was analysed in the individual chambers. For the Glatt dryer Pauli et al. found a comparable drying performance and temperatures of the granules, as well as inlet, outlet air and air humidity [77]. The moisture content can be reduced by increasing drying time, inlet air temperature or air flow [80]. Other studies focused on the process monitoring during drying [85, 86], the implementation of a mass and energy balance [77, 87, 88] to determine moisture content and the application of dynamic process models to predict the granule moisture and temperature inside each drying chamber [82].

Since the introduction of the segmented fluid dryer, other companies focused on continuous dryers. Freund-Vector introduced the Granuformer® (Freund-Vector Corporation, USA), including a spiral dryer following the twin-screw granulator unit. Unfortunately, the application and drying performance has not yet been investigated in the literature [89]. Additionally, the company Lödige has implemented a horizontal fluid bed dryer that can be used in the continuous granulation line GRANUCON® (Gebrüder Lödige Maschinenbau GmbH, Germany). This dryer consists of a screw conveyor inside the drying chamber, facilitating transportation with low shear stress exposure [9, 90]. Zhang et al. demonstrated that the required air flow for fluidisation can be reduced by increasing the screw rotation. Furthermore, the driving forces for the solid flow are screw rotation and air flow rate, also influencing the residence time of the granules inside the dryer [90].

Adapted from the food industry, where vibrated fluidised-bed dryers (VFBDs) are widely used [91] as for drying root crop [92], grain [93] wheat [94] or paddy rice [95], these systems have become of interest to the pharmaceutical industry. Han et al. highlighted the enhanced mass and heat transfer, easier fluidisation due to the destruction of agglomerates by the applied vibration and better control of the RTD with VFBD compared to conventional FBDs [94]. Studies on mathematical and empirical models describing VFBDs and drying kinetics were set [93, 96-100]. Palzer identified drying temperature and mean residence time as primary parameters influencing drying kinetics and moisture content [98]. The drying of granules was demonstrated using a prototype of a VFBD developed by Quick (Quick 2000, Hungary). This dryer is divided into four drying zones: the first three zones are used for heating with heated air supplied, while the fourth zone is dedicated to cooling through conditioning [101, 102]. Fülöp et al. found out that only the inlet air temperature influenced the moisture content of the residual granules significant [102].

L.B. Bohle introduced the VFBD, equipped with a TSG for lab-scale use, named QbCon® 1 (L.B. Bohle Maschinen + Verfahren GmbH, Germany). Additionally, the QbCon® 25 powder-to-tablet production line is available, which allows the option to integrate TSG and a production scale VFBD as intermediate steps within the line. The function of both VFBD scales is the same. QbCon® 1 and the function principle of the dryer are illustrated in Figure 7. Wet granules fall from the outlet of the twin-screw granulator into the drying chamber onto a sieve plate. Through the meshed sieve plate heated air enters the system, passes the granules and exit the drying chamber through the exhaust filters. Vibration is used to transport the wet granules from the inlet to the outlet. As the granules travel along the drying chamber and are exposed to hot, dry air, this leads to drying. The incoming air from below causes minimal fluidisation of the granules [103, 104].

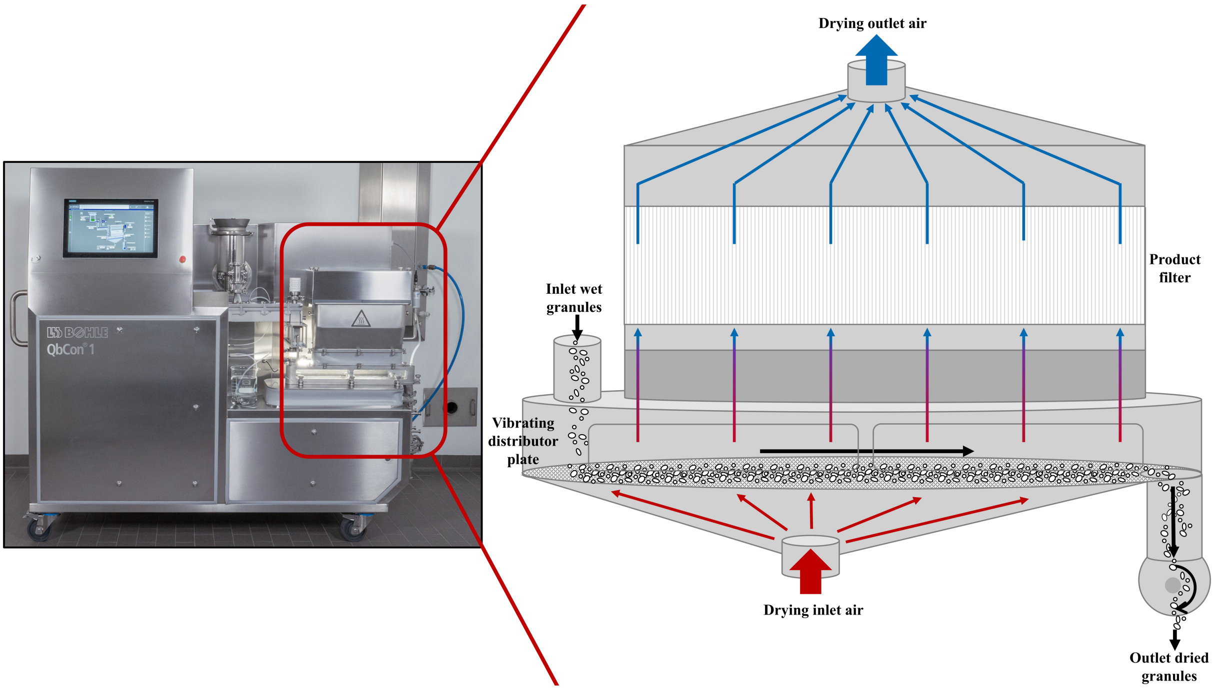

Figure 7: Picture of QbCon® 1(left, with courtesy of L.B. Bohle Maschinen + Verfahren) and a schematic illustration (right) of the working principle of the implemented VFBD.

Meier and Emanuele demonstrated stable and reproducible loss-on-drying (LOD) and GSD over a drying process time of 2.5 h [103]. Furthermore, Meier et al. pointed out that the LOD of the resulting granules is significantly reduced with increased air flow, higher drying temperature or reduced vibration acceleration. They conducted a full-factorial DoE with eleven runs over approximately 4 h, providing benefits in the research and development phase. They showed narrow RTD curves (20 – 30 s) and depending on the process parameters, mean residence times between 22 to 114 seconds were obtained, which can be adapted quickly with changes in vibration acceleration [104]. Elkhashap et al. introduced a grey-box model for the VFBD to predict the moisture content [99, 105] and RTD [106] combining Gaussian Process Regression and physical state modelling, which demonstrated a suitable quality control approach.

Besides these studies, the application of this continuous system, particularly the drying of granules with the VFBD, requires further investigation. This thesis aims to provide additional process insights.

1.3.3 Moisture content

Moisture content of granules is one of the CQAs that need to be monitored and controlled as part of in-process control, since it significantly impacts the quality of the final product. High moisture content in powders or granules can reduce flowability, leading to greater mass variation and potential content uniformity issues [107, 108]. Additionally, increased moisture content may cause sticking during tablet compression [109]. Therefore, the amount of residual water in the granules after the drying process, defined as LOD, needs to be investigated. Karl Fischer titration and LOD measurement are common methods based on different measurement principles. Karl Fischer titration is an analytical method that determines water content through the reaction of water with sulfur dioxide and iodine [110]. In LOD measurement, the sample is heated using for example an infrared light source causing evaporation and the weight-loss is measured once a steady-state is reached, resulting in the LOD value [111]. However, neither method allows real-time observation of the moisture content.

For this purpose, especially in continuous processes, PAT systems are used to monitor and control CQAs, such as LOD, in real-time to ensure consistent product quality. Commonly used PAT tools for drying systems, as reported in the literature, included NIR spectroscopy and microwave resonance technology. Both methods offer a fast, non-destructive measurement without sample preparation and can be implemented in-line within the drying process [112, 113].

Buschmüller et al. were the first to adapt microwave resonance technology as an in-line method for monitoring granule moisture during FBD. They demonstrated good agreement with the reference LOD measurement and Karl Fisher titration [113]. Peters at al. used the microwave resonance technology for the moisture monitoring in both FBG [114] and FBD [115]. They used a semi-continuous FBD and found that NIR spectroscopy and microwave resonance technology showed good agreement [115].

NIR spectroscopy is the preferred tool for in-line moisture monitoring as investigated by many researchers for FBDs [101, 115-117]. A disadvantage of both NIR spectroscopy and microwave resonance technology is the need for calibration with an additional method, such as LOD measurement [77]. Calibration for these methods typically requires multivariate analysis, for example partial least square [87, 112] or multiple linear regression [114, 115].

The LOD can be predicted using mass and energy balances (MEB) which are based on thermodynamics. The advantages of this approach not requiring additional installation and validation of a sensor for measuring the moisture content of the product and the prediction is material independent. MEB facilitates prediction using real-time process data from sensors already installed in the dryers. Therefore, temperature, pressure and humidity of incoming and outgoing air during drying are used. Additionally, the mass of wet granules entering the dryer is required for the prediction of LOD [77]. MEB has already been implemented in six segmented FBD [87, 88] as well as in ten segmented FBD [77]. Furthermore, Pauli et al. demonstrated the parallel use of MEB and NIR spectroscopy providing an orthogonal and redundant PAT system. This setup allows for more accurate monitoring and process control addressing potential sensor issues [77]. The application of PAT systems has not yet been shown for pharmaceutical VFBD.

1.4 Aim of the thesis

Since wet granulation is a favourable manufacturing route for solid oral dosage forms, numerous studies have contributed to the understanding of this process, particularly with respect to the continuous approach of TSG. For the complete implementation of TSG into a CM line, whether the granules are used as final dosage forms, filled into capsules or compressed into tablets, a drying step, preferably using a continuous mode, is required. While many studies have explored the use of segmented FBDs, only a few have investigated horizontal VFBD, adapted from the food industry to the pharmaceutical industry since 2018.

Therefore, a special focus will be put on the application of the VFBD, which, along with a twin-screw granulator and feeder, is part of the QbCon® 1 system. Until now, only a few publications are available that demonstrate the application of the QbCon® 1.

The first aim is to gain deeper insights into the use of this type of dryer by addressing key questions such as:

- What are the influencing parameters in the drying of granules?
- What is the temperature profile within the VFBD?
- Does the mechanical impact of vibration affect the granule quality?

Furthermore, the moisture content of granules is a CQA that needs to be monitored and controlled throughout the process to maintain the quality. For this reason, PATs such as MEB and NIR spectroscopy, shall be implemented to monitor the moisture content.

A second aim of this thesis is to understand the thermodynamics of the VFBD. With this understanding, a MEB will be derived and used to predict the LOD. Additionally, the thesis aims to develop an orthogonal PAT method that combines two independent methods for the measurement of the moisture content, as LOD. The benefits of an orthogonal PAT approach include the mitigation of sensor issues and the prevention of fault messages, especially when the process is monitored and controlled to maintain the product quality without interruption.

Finally, since the QbCon® 1 integrates both the drying and wet granulation processes, there are still unanswered questions despite extensive research on TSG. While previous studies have examined the impact of process parameters and screw configuration on granule and tablets properties, there are remaining knowledge gaps that need to be addressed for a more comprehensive understanding.

This thesis therefore focuses on the impact of variations in the kneading zone, crucial for mixing and densification along the barrel and thus for granule formation. Specifically, it aims to investigate the effects of the number of KEs, their thickness and offset angle. While some publications have explored these factors, none have comprehensively examined all these variables together across different types of formulations. This thesis addresses these gaps by evaluating how variations in the kneading zone affect granule and tablet properties, thereby providing deeper insights into their interactions and influences.

Ultimately, this thesis intends to provide the pharmaceutical industry with the necessary knowledge to consider TSG and the VFBD, as implemented in the QbCon® system, as viable options when selecting the appropriate process type for granulation in continuous manufacturing.

1.5 Outline of the thesis

This thesis utilises the QbCon® 1 to explore the application in continuous wet granulation and drying, as demonstrated through four publications in peer reviewed scientific journals.

The first three chapters provide understanding of the VFBD, while the fourth chapter focuses on the impact of the screw configuration in TSG.

The second chapter describes the drying behaviour using the VFBD. This is accomplished through central composite circumscribed DoE involving two different formulations, both without API. Key influential drying parameters were identified. External temperature and humidity sensors installed within the drying chamber enable the observation of changes in temperature and humidity of the granules during drying.

The third chapter examines the deviation of mass and energy balances for the VFBD, offering insights into the energy requirements for drying. Challenges, such as the entry of ambient air, were addressed, leading to the development of a predictive model for LOD based on sensor data and associated uncertainties. The fourth chapter introduces the use of mass balance and NIR spectroscopy, with an in-house build sensor, as an orthogonal PAT tool to monitor LOD of granules. A model is also developed to predict LOD based on the process parameters with validation across different formulations, including an API.

The final chapter shifts the focus to the kneading zone in twin-screw granulation. It investigates the effects of various KEs using full factorial DoEs for both an API-free formulation and a hydrophobic API formulation. The thesis concludes with a discussion of the performed studies and provides and outlook for future research and improvements.

2 Drying behaviour of a horizontal VFBD for continuous manufacturing

Pretext

There are only a few publications available where VFBDs are used for the drying of granules, particularly for continuous drying after TSG. To understand and identify the influencing factors, central composite circumscribed DoEs were conducted with two different formulations. The first formulation consisted of alpha-lactose monohydrate, MCC and polyvinylpyrrolidone (PVP). MCC was included due to its high-water absorption capacity, making the drying of these granules more challenging. The second formulation comprised mannitol and PVP. Besides the insights gained into the influence of these drying parameters, changes in temperature and humidity were measured along the dryer. Thus, temperature and humidity profiles indicated whether the drying was complete or if the granules did not reach the second drying period. This publication provided insights into the drying behaviour and process and investigated how long the dryer needs for heating and reaching steady-state conditions. This knowledge was required and useful for the deviation of mass and energy balances, which is described in the following chapter.

The following publication was published in the journal "Pharmaceutical Development and Technology" in 2023. The idea to conduct a central composite circumscribed DoE as well as the study design was provided by K. Kiricenko with improvements and further contribution by P. Kleinebudde. The experimental part was conducted solely by K. Kiricenko and the evaluation and interpretation of the data was done together with P. Kleinebudde. The manuscript was drafted by K. Kiricenko and reviewed by P. Kleinebudde.

Contribution of the authorship

author / co-author	idea / %	study design / %	experimental / %	evaluation / %	manuscript / %
Katharina Kiricenko	70	70	100	80	80
Peter Kleinebudde	30	30	0	20	20

Drying behavior of a horizontal vibrated fluidized bed dryer for continuous manufacturing

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Pharmaceutical Development and Technology, 28 (2023) 440-451

https://doi.org/10.1080/10837450.2023.2205932

Abstract

Twin-screw wet granulation offers the possibility to granulate continuously. A drying step after wet granulation is required to realize a full continuous manufacturing line. Aim of this study was to gain insights into the drying behavior of a continuous vibrated fluidized bed dryer intended for pharmaceutical research and development. A Design of Experiment was conducted to examine the influence of process parameters during the drying of granules using drying temperature, air flow, and vibration acceleration as factors. The obtained temperature and humidity profiles during the drying of lactose-MCC and mannitol granules displayed the first and second drying stage which is spatially resolved. With a higher drying temperature or higher air flow, the second drying stage was achieved earlier. An increase in vibration acceleration shortened the residence time and by this, the second drying stage was reached later at a lower granule temperature and thus higher residual moisture of the granules. Formulation-dependent impact of the drying parameters was observed as lactose-MCC led to smaller granules when increasing the temperature or air flow.

3 LOD prediction for a VFBD by means of MEB

Pretext

This publication was created with the assistance of engineers from L.B. Bohle. Since the LOD is a critical quality attribute, adequate monitoring and further control is required to maintain the product quality. In addition to the standard methods NIR spectroscopy and microwave resonance technology, which can monitor the moisture content in real-time, mass and energy balances offered an alternative without the need for additional sensors installation and validation. For the derivation of mass and energy balances the placement of the sensors was crucial. These balances utilised the sensors already installed in the drying system of the QbCon® 1 along with implemented granulation parameters. The application of mass and energy balances assumes that the amount of mass and energy entering a system equals the amount exiting it. Understanding the inlet and exhausting air in the drying system is important to calculate the amount of evaporated water through drying, allowing the prediction of the LOD. First, an empty dryer was investigated. Surprisingly, the mass of water entering the drying chamber was lower compared to the measured amount leaving the dryer. Based on this observation a correction was applied using data from the empty dryer investigation during the heating phase. Deriving the mass and energy balances for the VFBD was possible with this correction and yielded LOD values comparable to those determined offline using a moisture analyser. The application was demonstrated under different drying conditions over time for the two formulations already discussed in Chapter 2. Additionally, since this prediction depends on the precision of the sensors installed in the QbCon® 1, the uncertainty of the LOD prediction was investigated using error propagation. These developed mass and energy balances provide a viable alternative, as demonstrated by the good correlation between offline and inline results. The application of mass balances for predicting LOD will be further explored in the next chapter and provides therefore the basis for the next publication.

The paper was published in the journal “Journal of Pharmaceutical Innovation” in 2023. The concept of the mass and energy balances was primarily developed by K. Kiricenko and P. Kleinebudde with F. Hartmann and A. Altmeyer contributing to the implementation of sensor uncertainty using error propagation. K. Kiricenko and P. Kleinebudde designed the study with the input from F. Hartmann. K. Kiricenko conducted all experiments and evaluated the data with F. Hartmann, A. Altmeyer and P. Kleinebudde. K. Kiricenko derived the mass and energy balances and evaluated the data, while F. Hartmann evaluated sensor uncertainties.

K. Kiricenko drafted the manuscript and incorporated corrections from F. Hartmann, who wrote the section error propagation, A. Altmeyer and P. Kleinebudde.

Contribution of the authorship

author / co-author	idea / %	study design / %	experimental / %	evaluation / %	manuscript / %
Katharina Kiricenko	50	70	100	60	70
Felix Hartmann	10	5	0	20	10
Andreas Altmeyer	10	0	0	10	5
Peter Kleinebudde	30	25	0	10	15

Loss-on-drying prediction for a vibrated fluidised bed dryer by means of mass and energy balances

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Journal of Pharmaceutical Innovation, 18 (2023) 2429-2446

https://doi.org/10.1007/s12247-023-09802-w

Abstract

Purpose Continuous wet granulation and drying requires an adequate process control strategy to ensure the product quality. The most important critical quality attributes of dried granules are the granule size distribution and moisture content. Process analytical technologies (PATs) are available for real-time monitoring of moisture content by e.g. near-infrared spectroscopy (NIRS), which requires additional installation and complex multivariate validation. Thus, a mass and energy balance (MEB) was derived for a vibrated fluidised bed dryer, which is part of the QbCon® 1 intended for continuous wet granulation and drying. **Method** Process parameters that are frequently logged were used for the derivation of a MEB. The predicted MEB was compared with the measured loss-on-drying (LOD) for two different formulations. **Results** The model-derived data were in good agreement with the observed LOD, leading to RMSE values of 0.12 - 0.45. **Conclusion** The implemented MEB can predict the LOD over time and thus might be suitable as a soft sensor without the installation of additional sensors. The obtained energy flux gives insight into the heat transfer, and the derived energy balance might be used to determine the required energy under certain drying conditions.

4 Proof of a LOD prediction model with orthogonal PAT methods

Pretext

The derived and introduced mass balances for predicting LOD formed the foundation of this study. The primary aim of this publication was to demonstrate the application of the previously developed mass balances as a PAT method. MEB was compared with an in-house built NIR spectroscopy system to evaluate whether both approaches are suitable as an orthogonal PAT system. Furthermore, a model for predicting LOD was developed based on the following process parameters: L/S ratio, solid feed rate, drying temperature, air flow and vibrated acceleration. Thus, a model was created that can not only predict the LOD based on process parameters but also predict the setting of one of these five process parameters to achieve a targeted LOD. The obtained LOD was measured offline with a moisture analyser and this data were used to calibrate the NIR spectroscopy model. Additionally, the LOD was predicted using both NIR spectroscopy and the mass balance. This study demonstrated the benefit of orthogonal PAT methods to avoid false sensor readings, which could lead to incorrect process adaptations in an implemented control system. Different formulations and drying settings were used for model verification demonstrating that the mass balance is an easy approach that can be implemented into the QbCon® to provide operators with direct real-time LOD values. This chapter concludes the investigation using the VFBD, as the next chapter focuses on the TSG process.

The publication is published online and will be part of a special issue in the journal "Journal of Pharmaceutical Sciences" in January 2025. The main idea for this study was provided by K. Kiricenko and P. Kleinebudde with support from S. Klinken. K. Kiricenko and P. Kleinebudde developed the study design, selecting the formulations and model settings with S. Klinken consulting on a suitable D-optimal DoE. The granulation and drying experiments were performed by K. Kiricenko. S. Klinken set up of the NIR sensor, created the Python script for the measurement and finally calibrated and evaluated the NIR data. K. Kiricenko evaluated the design of experiments, mass balances and correlation between the different methods with support from P. Kleinebudde. The manuscript was drafted by K. Kiricenko and reviewed by S. Klinken and P. Kleinebudde. S. Klinken wrote the section on the methodology of NIR spectroscopy.

Contribution of the authorship

author / co-author	idea / %	study design / %	experimental / %	evaluation / %	manuscript / %
Katharina Kiricenko	70	65	100	70	80
Stefan Klinken	5	15	0	20	10
Peter Kleinebudde	25	20	0	10	10

Proof of a LOD prediction model with orthogonal PAT methods in continuous wet granulation and drying

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Journal of Pharmaceutical Sciences, 114 (2025) 176-184

https://doi.org/10.1016/j.xphs.2024.07.008

Abstract

Real-time monitoring of critical quality attributes, such as residual water in granules after drying which can be determined through loss-on-drying (LOD), during wet granulation and drying is essential in continuous manufacturing. Near-infrared (NIR) spectroscopy has been widely used as process analytical technology (PAT) for in-line LOD monitoring. This study aims to develop and apply a model for predicting the LOD based on process parameters. Additionally, the efficacy of an orthogonal PAT approach using NIR and mass balance (MB) for a vibrating fluidized bed dryer (VFBD) is demonstrated. An in-house-built, cost-effective NIR sensor was utilized for measurements and exhibited good correlation compared to standard method via infrared drying. The combination of NIR and MB, as independent methods, has demonstrated their applicability. A good correlation, with a Pearson r above 0.99, was observed for LOD up to 16 % (w/w). The use of an orthogonal PAT method mitigated the risk of false process adaption. In some experiments where the NIR sensor might have been covered by powder and therefore did not measure accurately, LOD monitoring via MB remained feasible. The developed model effectively predicted LOD or process parameters, resulting in an R2 of 0.882 and a RMSE of 0.475 between predicted and measured LOD using the standard method.

5 Systematic investigation of the impact of screw elements in continuous wet granulation

Pretext

The QbCon® 1 combines both the TSG and drying processes. While the previous three chapters focused on the VFBD, this study aims to provide insights into the use of kneading zone and other screw configurations during TSG using a systematic approach. L.B. Bohle supplied a wide variety of screw elements, including specially produced kneading elements with different thickness. This allowed for the investigation of three thickness levels in a DoE considering the offset angle and number of KEs. Two different formulations were used for the design of experiments and the systematic variation of screw configurations. One formulation was the standard, API-free formulation used in the previous chapters, providing a hydrophilic formulation with a broad L/S ratio capacity due to the water absorption properties of MCC. The second formulation was a mixture containing ibuprofen as a hydrophobic API with mannitol in equal amounts and PVP as binder. The impact of screw configuration was less significant compared to the influence of the L/S ratios for both examined formulations within the studied factor space. Additionally, when tablets were produced from the granules obtained using the different formulations, the tensile strength showed minimal variation. Thus, this study demonstrates that TSG is a robust method, and the standard screw configuration, using at least one kneading zone, is sufficient to produce granules with low friability and tablets with adequate tensile strength. The results from this study may encourage the use of TSG over high-shear granulation, especially as an intermediate step.

The idea to investigate screw configuration was proposed by K.Kiricenko, R. Meier and P. Kleinebudde. R. Meier provided additional suggestions, including the idea of the production kneading elements with different thickness. K. Kiricenko planned the study design and decided to perform DoEs. P. Kleinebudde suggested incorporating tooth mixing elements in the screw configuration during granulation of the ibuprofen formulation and further recommended selecting the formulation of ibuprofen and mannitol. K. Kiricenko conducted the granulation experiments, tableting and characterisation of granules and tablets. K. Kiricenko evaluated the complete data, with P. Kleinebudde offering suggestions on data interpretation, and R. Meier supporting the results. K. Kiricenko drafted the manuscript, which was reviewed by R. Meier and P. Kleinebudde. Afterwards, P. Kleinebudde revised certain sections.

Contribution of the authorship

author / co-author	idea / %	study design / %	experimental / %	evaluation / %	manuscript / %
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Systematic investigation of the impact of screw elements in continuous wet granulation

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International Journal of Pharmaceutics: X, 8 (2024) 100273

Abstract

Twin-screw wet granulation (TSG) is a continuous manufacturing technique either for granules as final dosage form or as an intermediate before tableting or capsule filling. A comprehensive process understanding is required to implement TSG, considering various parameters influencing granule and tablet quality. This study investigates the impact of screw configuration on granule properties followed by tableting, using a systematic approach for lactose-microcrystalline cellulose (lactose-MCC) and ibuprofen-mannitol (IBU) formulations. The most affecting factor, as observed by other researchers, was the L/S ratio impacting the granule size, strength and tabletability. Introducing tooth-mixing elements at the end of the screw, as for the IBU formulation, resulted in a high proportion of oversized granules, with values between 36 % and 78 %. Increasing the thickness of kneading elements (KEs) produced denser, less friable granules with reduced tablet tensile strength. Granulation with more KEs, larger thickness or stagger angle increased torque values and residence time from 30 to 65 seconds. Generally, IBU granules exhibited high tabletability, requiring low compression pressure for sufficient tensile strength. At a compression pressure of 50 MPa, IBU tablets where at least one kneading zone was included resulted in approximately 2.5 MPa compared to lactose-MCC with 0.5 MPa. In conclusion, the TSG process demonstrated robustness by varying the screw design with minimal impact on subsequent tableting processes.

6 Discussion and outlook

The presented studies focus on the application of continuous granulation and drying using the lab-scale QbCon® 1. Existing literature on the VFBD which is part of the QbCon®-system intended for granule drying has been relatively scarce [99, 103-106], especially when compared to the segmented FBD used in other CM systems. Chapter 2 provides a deeper understanding of granule drying with a VFBD and identified the critical process parameters on LOD and mean residence time. Higher drying capacity was necessary for MCC containing granules, achieved by increasing the drying temperature, air flow or reducing vibration acceleration.

Moreover, this study extended the finding by Meier et al. [104] demonstrating that drying parameters do not affect granule size distribution. Wikström et al. developed a statistical model that considered the varying amount of MCC, granulation parameters (L/S ratio and throughput) and drying parameters (drying temperature, air flow and vibration acceleration). This model was developed for the production scale VFBD in the QbCon® 25 [118] and yielded results consistent with those observed for the QbCon® 1 [119]. Their study indicated that higher drying capacity was needed with higher amounts of MCC in the formulation, that could be achieved by increasing drying temperature, air flow or by reducing vibration acceleration [118]. Similar effect was observed when comparing drying of MCC containing granules to those containing only mannitol.

Furthermore, a mechanistic model using a one-dimensional plug flow approach was developed, that estimated the conveying speed of granules based on the data from the QbCon® 1 study introduced in chapter 2. The predicted LOD and outlet air temperatures generally aligned well with the measured values, although some over- or underprediction occurred. The product temperature was often overpredicted by the mechanistic model. Overall, the model demonstrated good agreement between the predicted and observed temperature and relative humidity changes along the drying bed for the production scale [118].

The observed temperature profile along the drying bed followed a sigmoidal curve. Investigating and predicting how changes in process parameters affect the granule temperature or the shape of the sigmoidal curve would enhance process understanding and enable the selection of optimal drying conditions to achieve a desired temperature profile. This is particularly important when drying of heat-sensitive materials is planned.

Meanwhile, further investigations into continuous drying have been conducted using other type of dryers. Zhang et al. presented a phenomenological modelling approach for drying using a horizontal FBD with a screw conveyor inside. This dryer was shortly introduced previously. Their work investigated a hybrid model for describing the drying kinetics and developed a dispersion model that included RTD measurements and the drying kinetic. They observed a good model fit for the moisture content when comparing the measured values with simulated process values. However, the solid temperature along the dryer was over predicted. The moisture content was primarily affected by the air temperature and air velocity, while the rotation rate of the screw conveyor influenced the RTD, similar to how vibration acceleration affects during drying with VFBD. The observed temperature profiles inside the drying chamber indicated both first and second drying period [120].

Koyanagi et al. introduced a new continuous granulation and drying system, LaVortex®, developed by the company EarthTechnica (EarthTechnica Co., Ltd., Japan). This system consists of a continuous agitating mixer for granulation, a double-layer spiral drying passage and a cyclone separator. A similar type of dryer is mentioned in the introduction section implemented in the GRANUCON®. Granulation with LaVortex® is controlled by the centrifugal force generated by tube rotation and the shear force from the blades. For drying, a rapid high-speed process is employed, using centrifugal force in a spiral path, resulting in drying within seconds [121].

Further studies were published where a segmented FBD was applied. Grelier et al. observed despite evenly distributed air flow, a variation in temperature of the air, which was more pronounced for drying at higher temperatures thus a variability in drying performance between the cells could be obtained [122]. Lu et al. presented the development of a soft sensor for the six-segment FBD implemented in the ConsiGma®-25 line. They conducted experiments to examine the thermal behaviour during heating and drying to develop a drying model based on a combined heat transfer model with drying kinetics. For the drying model, MEB were considered. This model, together with measured values such as inlet airflow and temperature, was able to predict the LOD in real-time. Heat transfer from segment to segment was determined to be 7 % of the provided heated air. The developed soft sensor allowed LOD prediction with an error margin of 0.5 % and a segment temperature deviation of 2 °C [123].

Chapter 3 provided a step-by-step plan to predict the LOD using mass and energy balances for the VFBD in the QbCon® 1. In this study heat loss due to convection was determined to be approximately 30 % in empty state and up to 10 % during drying depending on the set drying conditions. The heat loss is primarily due to the heating of the stainless-steel wall. The available literature using mass and energy balances does not provide the total heat loss during drying [77, 88, 123]. Thus, the drying process via VFBD is demonstrated more transparently, allowing for further investigation. Using the energy balance helps to determine if the system can provide the energy needed to dry the granules to a target LOD. Furthermore, mass balances were derived based on the logged sensors in the QbCon® 1, providing values with 1 Hz for incoming and exiting air flow, temperature, humidity and pressure. The implementation of mass balances in an empty dryer observed a higher mass flow of water leaving the dryer through the air than entering it, which was assumed to be due to the ambient air. The same phenomenon was also reported by Mortier et al. for the segmented FBD [88]. Therefore, the determination of the difference in mass flow of water between inlet and outlet air in an empty dryer needs to be investigated. With this, the prediction of the LOD using mass balances was feasible and resulted in a root mean square error (RMSE) of below 0.5 %, as demonstrated for the drying of mannitol and lactose-MCC granules [124]. Unlike other studies involving mass and energy balances, this study accounted for the uncertainty of each sensor used in the prediction, resulting in a predicted LOD that included a specific degree of uncertainty. This aspect had not been previously investigated by other researchers [77, 87, 88].

Building upon the findings of this study, the next phase, as described in chapter 4, explored the application of mass balances together with a NIR spectroscopy as an orthogonal PAT approach for monitoring LOD. Additionally, a statistical model using a D-optimal DoE was developed to predict the LOD using process parameters during granulation and drying for QbCon® 1. This approach is comparable to the design used by Wikström et al. for the QbCon® 25, without the variation of MCC amount. To build the model, three different LOD measurements were used: moisture analyser, mass balances and NIR spectroscopy. The model utilising the LOD measured with the moisture analyser showed more significant interactions between the factors compared to the model by Wikström et al. Even though the dryer type and its function are similar, the dimensions of the two equipments and the investigated factor spaces differ leading to different interactions and a statistical effect is also present. The study demonstrated the ability of the statistical model to predict one of the five investigated process parameters required to achieve a set LOD during the drying process. For verification, additional experiments were conducted, showing good agreement between predicted LODs and those measured offline using the moisture analyser with a R^2 of 0.85 and RMSE of 0.54 %.

The orthogonal PAT system for LOD monitoring using mass balances and NIR spectroscopy was demonstrated with a total of 84 experiments involving different formulations and two levels of MCC fraction. This approach yielded in a good correlation with a R of 0.97 and RMSE of

0.76 %. Unfortunately, 8 experiments showed a high deviation assumed to be due to the NIR sensor being covered with powder. After excluding these experiments an even higher correlation between NIR and mass balances was observed with a R of 0.998 and RMSE of 0.42 %. Thus, the two methods that predict the LOD independently are suitable for application as orthogonal PAT methods for VFBD. These studies offer alternative approaches to predict LOD as previously introduced by Wikström et al. [118] or Domokos et al. [101]. While mass balances combined with NIR spectroscopy were previously demonstrated by Pauli et al. [77] for a ten segmented FBD, this study [125] extends the application to the lab scale VFBD in QbCon® 1. Aoki et al. offered an alternative method for monitoring moisture content using acoustic emission, a non-invasive technique similar to NIR spectroscopy. They found that while the acoustic emission method is suitable for monitoring moisture content during drying and determining the endpoint, it is not as accurate as NIR spectroscopy [126].

Further investigation into a cleaning system of the NIR sensor and the integration of both methods into the QbCon® system would improve these methods and enable real-time LOD values. As demonstrated by Lu et al., the mass balances could also be adapted as a soft sensor in the future. Since the studies from chapter 3 and 4 focused on the QbCon® 1, similar investigation should be conducted for the production scale dryer in the QbCon® 25. This would require that all sensors necessary to set up a mass balance are included in the VFBD of the QbCon® 25.

Although the TSG process and particularly the screw configuration was investigated by some researchers [46, 48, 50, 57], there is still the need to understand the effect of the different variables in kneading zone as number, thickness of KE and offset angle.

Focusing on the influence of the KE-zone on granule and tablet properties two formulations were studied. One containing 80 % lactose and 17 % MCC and the other 48.5 % ibuprofen and mannitol. The findings revealed distinct effects based on the formulation and screw configuration with the L/S ratio having a more pronounced influence compared to screw configuration within the chosen factor space. For the lactose-MCC formulation, the granulation process was significantly influenced by the screw elements. Increasing the number of KEs, their stagger angle and thickness let to increased resistance to flow of the wet mass, resulting in longer residence times and higher torque. This configuration decreased the fraction of fines and reduced granule friability due to greater consolidation and densification. The granule properties of the ibuprofen formulation were primarily affected by the L/S ratio. Notably, using TME at the during the granulation of the ibuprofen formulation resulted in larger granules and a higher fraction of oversized granules compared to the lactose-MCC formulation.

Variations in screw configuration were explored including setups with only CEs, one KE-zone or two KE zones, using both DME or TME. For the lactose-MCC no difference in tabletability was observed between configuration with only CEs or one KE-zone. Higher tensile strength was achieved by including two KE-ones or DME or TME in the screw configuration. For the poorly soluble ibuprofen formulation at least one KE-zone was necessary regardless of the type to obtain higher tabletability and granules with lower friability. This requirement is likely due to enhanced liquid distribution and densification promoting granule growth as was reported by Yu et al. for hydrophobic formulations [127].

The study provided additional insights into the robustness of the TSG process, indicating that high variation in screw configuration is not always necessary, although it can be beneficial by reducing the required liquid. This was observed recently by Vandevivere et al., who explored two screw configurations with variations in binder and L/S ratio. One screw configuration included two KE-zones with 60° separated by CEs and size control elements at the end, while the second configuration had two 90° KEs at the end of each KE-zone. They found that granules with a friability below 30 % were obtained using a lower L/S ratio with granulation using the second screw configuration, suggesting that the 90° KEs improved liquid distribution due to increased residence time, leading to better granule formation and a lower amount of fines with a higher fraction of oversized granules. [128].

Meanwhile, another study published by Zidan et al. investigated the influence of screw design on extended-release tablets using a fractional factorial design. The variables included the number of KEs (2 or 4) in each KE-zone, offset angle (60° or 90°), number of CEs between KE-zones (2 or 10) and the number of sizing elements at the end (1 or 3). The number of KEs and offset angle significantly influenced granule size distribution, granule cohesion and tablet breaking strength. The number of sizing elements and offset angle were critical for compressibility [129]. Thus, the influence of the screw configuration might be formulation dependent. As demonstrated previously [130] as well as by Yu et al. [127] and Mundozah et al. [131], a KE-zone is particularly important for hydrophobic API or excipients with low solubility to enhance liquid distribution between the granulation liquid and powder mass, thereby improving granule formation. Additionally, a recent publication by Pohl et al. focused on predicting mass hold-up during TSG based on the throughout, screw speed, screw configuration and barrel lengths as well as properties of the starting material. This study demonstrated progress in predicting the barrel fill level, which has a major impact during granulation [130].

To extend the study from the last chapter, investigating additional granule properties such as porosity or flowability would be valuable. Moreover, varying screw configurations with formulations of different solubility profiles would help to elucidate how the kneading zone affects granules and subsequently tablets. Beyond the manufacturability of granules into tablets examining dissolution characteristics would also be of interest.

In conclusion, the three consecutive studies, along with the fourth study on the impact of screw configuration, provided deeper insights into the application of twin-screw wet granulation and continuous drying using the QbCon® 1. Initially, only a few publications were available, with this thesis firstly describing the change in granule temperature along the dryer with VFBD, which could be used to predict required process parameters. The experiments showed that mechanical stress and drying parameters do not affect the granule properties, such as granule size. Furthermore, mass and energy balances were able to show more transparency regarding heat flow. The robustness of TSG was demonstrated, as the screw configuration had little effect and tablets with similar properties were produced. Lastly, Leane et al. extended the manufacturing classification system, that was previously introduced only for batch manufacturing, for continuous manufacturing and highlighted important API properties for the implementation into CM. Additionally, a flowchart was proposed for deciding whether to use batch or continuous manufacturing [29].

Marketing authorisation holders, such as Vertex of the drug product Orkambi®, have published their manufacturing route involving wet granulation using TSG and drying with a segmented FBD, followed by milling, tableting and coating [132]. This underscores the importance and interest in wet granulation and the QbCon® system offers another option with its different type of dryer. The application of this CM system has gained more interest in recent years. Köster et al. examined the impact of binders on granules and tablets through wet granulation and drying using the QbCon® 1 [133, 134]. Furthermore, Franke et al. investigated scale-up strategies from lab to production scale [69, 135]. Wikström et al. explored the drying capacity of the VFBD from QbCon® 25 and identified that vibration acceleration was the most influential parameter, as previously discussed [118]. Forster et al. compared continuous granulation and drying using QbCon® 1 with three different batchwise approaches: TSG followed by drying using a tray dryer, FBG and high-shear granulation followed by FBD. Granules made via TSG and drying, whether continuous or batchwise, showed similar granule performance. Similar tablet qualities were observed for the continuous technique and FBG. However, differences were detected, especially with high-shear wet granulation, due to the difference in granulation mechanisms [136]. This demonstrated the increased interest using the VFBD for drying after TSG.

7 Summary

Continuous manufacturing offers several advantages and has gained increased interest in recent years. Consequently, several products manufactured continuously involving wet granulation have already been approved. Typically, twin-screw wet granulation and segmented fluid bed dryers are integrated into continuous manufacturing lines. The application of this type of CM line is well investigated in the literature, but a few challenges have been identified. Limited drying capacity and variability in air temperature between different segments can lead to inconsistent moisture content. Additionally, the pneumatic transfer from the twin-screw granulator to the dryer can result in granule breakage and attrition.

An alternative granule drying technique adapted from the food industry involves a VFBD after twin-screw wet granulation as demonstrated in the QbCon®-System. This method offers benefits in heat and mass transfer and allows for easier adaptation of residence time due to vibration. Compared to segmented FBDs, VFBDs for pharmaceutical purposes present a gap in the literature. Therefore, the aim of this thesis was to provide deeper insights into the application of twin-screw wet granulation and continuous drying using the QbCon® 1 through three consecutive studies, along with a fourth study on the impact of screw configuration.

First, the drying behaviour of granules was studied using two different formulations. One with mannitol and a second with alpha-lactose and MCC. By keeping the drying conditions constant, a higher LOD was observed for lactose-MCC granules due to the water absorption capacity of MCC indicating that higher drying capacities are needed. Changes in temperature and relative humidity were recorded along the drying chamber. For lactose-MCC with high LODs, the second drying state and critical moisture content were not reached. This was indicated by the lack of increased temperature of granules along the dryer. LOD is reduced with higher drying temperatures or air flow and decreased vibration acceleration. Decrease in vibration acceleration and air flow led to longer residence time. The drying parameters including the vibration showed no effect on granule size. Stepwise deviation of mass and energy balances provided insights into heat loss and mass flow in the empty state and during drying of granules. Considering the ambient air determined in empty state, it was possible to predict the LOD based on logged sensor data in the empty state. The LOD can be predicted with some uncertainty, as the prediction accuracy depends on the used sensors. This approach presents an alternative to NIR spectroscopy and microwave resonance technology for real-time LOD monitoring as a potential PAT tool. Building on these results, the combination of mass balance together with

NIR spectroscopy was demonstrated as an orthogonal PAT system. The in-house built NIR sensor was calibrated against the LOD values obtained offline using a moisture analyser. Both methods, mass balances and NIR spectroscopy, independently predicted the LOD thus providing accurate LOD values. If a sensor problem occurs with the NIR spectroscopy, the mass balance can still provide LOD values. Furthermore, in the case of deviations between the two PAT methods, the cause can be investigated, such as a sensor issue with the NIR spectroscopy. However, moisture and temperature sensors used in the mass balance can also be faulty. The correlation between both measurements was observed up to an LOD of 16 % using different drying conditions and formulations. Additionally, a statistical model was developed to predict the LOD based on the set process parameter such as the L/S ratio and powder feed rate in granulation and drying temperature, air flow and vibration acceleration in drying. The model was developed using a lactose-MCC formulation and verified with additional experiments beside the design of experiment. Applying the model to another formulation with MCC was possible, although higher deviations were observed. A benefit of the developed is its ability to predict one of the five process parameters to target a defined LOD value. This study provided the first step for an application of an orthogonal PAT approach that might be further implemented into the QbCon® system. The developed model is suitable for estimating appropriate process settings or approximating the LOD obtained with different process parameters.

Lastly, the investigation of screw configuration for hydrophilic and hydrophobic formulations showed minimal influence of variations in the kneading zone, such as the number of kneading elements, thickness or offset angle between the kneading elements. The most influential parameter, as extensively examined in the literature, was the L/S ratio regarding granule friability and size. Changes in screw configuration using more kneading elements, different offset angle or thickness led to longer residence time. When tooth-mixing elements were included in the screw configuration at the outlet, a high fraction of oversized granules was observed, particularly with an increased L/S ratio. Since tablets were produced from the granules, the process was robust, as the screw configuration did not affect the resulting tablets. By varying the kneading zone by using zero, one, or two elements and investigating the effect of sizing elements, it was observed that the ibuprofen formulation, considered hydrophobic, required at least one kneading zone to produce granules with sufficient strength and a reduced proportion of fines, which also increased the tensile strength of the tablets. This configuration is necessary to improve liquid distribution, increase residence time inside the barrel, and thus enhance granule formation. This study assumed that the influence of screw configuration might be formulation dependent and thus requires further investigations. Overall, the findings suggest that TSG followed by a VFBD is a promising alternative for continuous manufacturing.

8 Zusammenfassung

Die kontinuierliche Herstellung von Arzneimitteln bietet zahlreiche Vorteile und hat in den letzten Jahren zunehmendes Interesse geweckt. Einige kontinuierlich hergestellte Arzneimittel, bei denen Feuchtgranulierung verwendet wird, sind bereits zugelassen. Typischerweise werden Doppelschnecken-Feuchtgranulierer und segmentierte Wirbelschichttrockner in einer kontinuierlichen Produktionslinie integriert. Die Anwendung dieser kontinuierlichen Herstellungslinie ist in der Literatur ausführlich beschrieben. Dennoch bestehen Herausforderungen, wie die begrenzte Trocknungskapazität und Schwankungen der Lufttemperatur in den Segmenten, die zu einer uneinheitlichen Granulatfeuchte führen können. Zudem kann der pneumatische Transport vom Granulator zum Trockner zur Zerkleinerung der Granulate führen.

Eine alternative Trocknungsmethode, die aus der Lebensmittelindustrie adaptiert wurde, ist der Wirbelschichtvibrationstrockner, der im QbCon®-System integriert wurde. Dieser Trockner verbessert den Wärme- und Stoffaustausch und ermöglicht eine einfachere Anpassung der Verweilzeit. Im Vergleich zu segmentierten Wirbelschichttrocknern gibt es nur wenige Studien zu Vibrationstrocknern im pharmazeutischen Bereich. Ziel der vorliegenden Arbeit war es, die Anwendung der Doppelschnecken-Feuchtgranulierung und des kontinuierlichen Trocknens mit der QbCon® 1 zu untersuchen.

Zunächst wurde das Trocknungsverhalten von Granulaten aus zwei Zubereitungen analysiert, eine mit Mannitol und eine andere mit Alpha-Lactose Monohydrat und mikrokristalliner Cellulose (MCC). Unter gleichen Trocknungsbedingungen wiesen Lactose-MCC-Granulate aufgrund der Wasseraufnahmefähigkeit von MCC eine höhere Produktfeuchte auf, das auf die Notwendigkeit einer höheren Trocknungskapazität hinweist. Änderungen in Temperatur und relativer Luftfeuchtigkeit entlang der Trocknungskammer wurden detektiert. Bei hohen Produktfeuchten erreichten Lactose-MCC-Granulate bei den gewählten Einstellungen der Prozessparameter nicht die zweite Trocknungsstufe. Die Granulattemperatur blieb unverändert entlang der Trocknungskammer. Es zeigte sich, dass die Feuchte durch höhere Trocknungstemperaturen, Luftströme und verringerte Vibrationsbeschleunigung gesenkt werden kann, wobei die Verweilzeit durch geringere Vibration erhöht wird. Die Trocknungsparameter hatten keinen Einfluss auf die Granulatgrößenverteilung.

Die schrittweise Herleitung von Massen- und Energiebilanz lieferte Einblicke in den Wärmeverlust und den Massenstrom, sowohl im Leerzustand als auch während des Trocknens von Granulaten. Anhand der im Leerzustand gemessenen einströmenden Umgebungsluft war es möglich, die Produktfeuchte basierend auf den aufgezeichneten Sensordaten vorherzusagen. Die Produktfeuchte wird mit einer Unsicherheit vorhergesagt, da die Vorhersagegenauigkeit von den verwendeten Sensoren abhängt. Dieser Ansatz stellt eine Alternative zur NIR-Spektroskopie und Mikrowellenresonanztechnologie für die Echtzeitüberwachung der Produktfeuchte als potenzielles Prozessanalytik-Technologie (PAT) dar. Es wurde gezeigt, dass Massenbilanzen zusammen mit NIR-Spektroskopie als orthogonales PAT-System fungieren können. Der entwickelte NIR-Sensor wurde mit offline erhaltenen Feuchtewerten aus Infrarot-Waagen-Messungen kalibriert. Beide Methoden konnten unabhängig die Feuchte vorhersagen, welches vorteilhaft im Falle von Messfehlern durch Sensorproblemen ist. Die Korrelation beider Methoden wurde bis 16 % Produktfeuchte unter verschiedenen Bedingungen belegt. Zusätzlich wurde ein statistisches Modell entwickelt, das die Feuchte basierend auf Prozessparametern wie Flüssig-zu-Feststoff-Verhältnis, Pulverdosierrate, Trocknungstemperatur, Luftstrom und Vibrationsbeschleunigung vorhersagt. Das Modell wurde mit Lactose-MCC-Formulierungen entwickelt und verifiziert, wobei es sogar mit höheren Abweichungen auf andere Formulierungen mit MCC anwendbar war. Der Vorteil des Modells liegt in seiner Fähigkeit einen der fünf Prozessparameter zur Erreichung der gewünschten Feuchte vorherzusagen. Diese Studie ist ein erster Schritt zur Implementierung eines orthogonalen PAT-Ansatzes im QbCon®-System. Das Modell eignet sich zur Schätzung geeigneter Prozesseinstellungen oder zur Vorhersage der Produktfeuchte basierend auf den Prozessparametern.

Zuletzt zeigte die Untersuchung der Schneckenkonfiguration für hydrophile und hydrophobe Formulierungen einen minimalen Einfluss von Variationen in der Knetzone. Dabei wurde die Anzahl der Knetelemente, deren Dicke oder Versatzwinkel variiert. Der einflussreichste Parameter war das Flüssig-zu-Feststoff-Verhältnis hinsichtlich der Friabilität und Größe der Granulate. Änderungen in der Schneckenkonfiguration, wie eine erhöhte Anzahl von Knetelementen, führten zu einer längeren Verweilzeit. Wenn Zahnmischelemente am Auslass vorhanden waren, wurden besonders bei erhöhtem Flüssig-zu-Feststoff-Verhältnis viele übergroße Granulate erhalten. Bei der Variation der Schneckenkonfiguration bestehend aus lediglich Förderelementen, sowie einer oder zwei Knetzonen und der Untersuchung von Zerkleinerungselementen zeigte sich, dass die hydrophobe Ibuprofen-Formulierung mindestens eine Knetzone benötigt, um Granulate mit ausreichender Festigkeit und weniger Feinanteil zu erzeugen. Dies erhöhte auch die Zugfestigkeit der Tabletten. Die Knetzone verbessert die

Flüssigkeitsverteilung und erhöht die Verweilzeit, was die Granulatbildung optimiert. Die Studie legt nahe, dass der Einfluss der Schneckenkonfiguration von der Formulierung abhängen könnte und weitere Untersuchungen erfordert, um diese Hypothese zu bestätigen. Insgesamt zeigen die Ergebnisse, dass die Doppelschnecken-Nassgranulierung gefolgt von einem Wirbelschichtvibrationstrockner eine vielversprechende kontinuierliche Herstellungsmethode ist.

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Danksagung

Mein besonderer Dank gilt meinem Doktorvater Prof. i.R. Dr. Dres. h.c. Peter Kleinebudde für die Aufnahme in seinem Arbeitskreis und die Möglichkeit, unter seiner Betreuung als (wirklich) allerletzte Kleinebudde-Doktorandin ein so spannendes Thema zu erforschen. Ihre Unterstützung und Betreuung während meiner gesamten Promotionszeit, selbst, nachdem Sie in den Ruhestand gegangen sind, war jederzeit verlässlich. In stressigen Situationen sind Sie mir stets mit Ruhe, Professionalität und großem Verständnis begegnet und haben jede aufkommende Panik in Luft aufgelöst. Darüber hinaus haben Sie mich nicht nur wissenschaftlich, sondern auch persönlich gefordert und gefördert, was maßgeblich dazu beigetragen hat, meine fachlichen Fähigkeiten weiterzuentwickeln und den Umgang mit konstruktiver Kritik zu verbessern. Zudem möchte ich mich herzlich für die Arbeitskreis-Events anlässlich Ihrer Geburtstage und die Weinverkostungen bedanken. Auch wenn der Arbeitskreis im Laufe meiner Promotion geschrumpft ist, waren diese Abende stets ein besonderes Erlebnis.

Herrn Prof. Dr. Jörg Breitkreutz danke ich für die Übernahme des Koreferats und die Mentorschaft. Ihre kritischen Rückfragen und Anmerkungen in den Fokusgruppen und Doktorandenvorträgen waren stets sehr hilfreich und haben mir dabei geholfen, meine Ergebnisse aus einer neuen Perspektive zu betrachten.

Jun.-Prof. Dr. Michael Hacker möchte ich für das konstruktive Feedback nach meinen Doktorandenvorträgen danken. Obwohl das Thema außerhalb deines Forschungsbereiches liegt, hast du mir stets hilfreiche Rückmeldungen gegeben und dich bemüht, einen wertvollen Beitrag zu leisten.

Dr. Robin Meier, ich danke dir für deine wertvollen Hinweise, Anregungen und deine Unterstützung bei Fragestellungen sowie bei der Korrektur der Manuskripte. Die Gelegenheit an so einem innovativen und neuen Gerät arbeiten zu dürfen, ist alles andere als selbstverständlich. Zudem bin ich dir sehr dankbar, dass du es Martin und mir ermöglicht hast, zwei Wochen lang Experimente im Produktionsmaßstab bei euch in Ennigerloh durchzuführen.

Zusätzlich möchte ich mich bei Daniel Emanuele für die zuverlässige Erreichbarkeit, die schnelle Hilfestellung bei der Inbetriebnahme der QbCon sowie die zügige Zusendung von Ersatzteilen bedanken. Du hast maßgeblich dazu beigetragen, dass viele der geplanten Experimente reibungslos ablaufen konnten.

Außerdem danke ich Andreas Altmeyer und Felix Hartmann für eure Unterstützung und die intensiven Diskussionen bei der Erstellung der Massen- und Energiebilanz. Durch euch habe ich den Prozess und die Maschine viel besser verstanden. Ohne eure Hilfe wäre das Ergebnis nicht dasselbe gewesen.

Ein besonderer Dank gilt auch den engagierten Mitarbeitern von L.B. Bohle, insbesondere Philipp Harbaum, Daniel Bexte, Charlotte Ribeiro Maier und allen nicht namentlich genannten Kollegen, für die herzliche Aufnahme währen den zwei Wochen in Ennigerloh sowie für ihre große Hilfsbereitschaft.

Dr. Stefan Klinken-Uth, dir danke ich für deine Zeit und deine kontinuierliche Unterstützung bei allen Fragen rund um die Lehrtätigkeit, statistische Versuchsplanungen und deren Interpretationen. Die Zusammenarbeit mit dir war immer lehrreich und ich schätze es sehr, dass du dir auch kurzfristig Zeit für mich genommen hast.

Dr. Jerome Hansen und Dr. Anja Göbel, euch danke ich für die freundliche Aufnahme in eurem Büro. Es hat mir dort so gut gefallen, dass ich bis zum Ende meiner Promotionszeit geblieben bin, selbst, nachdem ihr das Institut verlassen habt. Jerome, dir möchte ich besonders für die gemeinsamen Abende danken, das Korrigieren meiner englischen Aussprache und die unvergessliche PBP World Meeting Konferenz in Rotterdam – die erste Konferenz nach Corona. Ich habe dort gelernt, wie man mit wenig Schlaf und viel Alkohol trotzdem morgens pünktlich erscheint. Unsere gemeinsamen Jelly Shots-Sessions, bei denen wir das perfekte Verhältnis gefunden haben, werden mir immer in Erinnerung bleiben.

Dr. Hanna Grumann, dir danke ich für die herzliche Aufnahme im Arbeitskreis und für die Unterstützung, die du mir bereits während der Anfertigung meiner Masterarbeit entgegengebracht hast. Ebenso möchte ich mich für die schönen Instituts- und Arbeitskreisabende sowie die unvergesslichen gemeinsamen Konferenzen bedanken, die ohne dich nicht so wunderbare Erinnerungen hinterlassen hätten.

Ein besonderer Dank gilt Leonie Uth und Felix Reichel für die unvergesslichen gemeinsamen Momente im und außerhalb des Büros. Die Zeit, die wir sowohl zu viert mit Martin als auch später zu dritt verbracht haben, verbinde ich ausschließlich mit schönen Erinnerungen. Unsere Bürozeiten, Abende mit Wein, Konferenzfahrten und alle Institut Veranstaltungen sowie die ständige Frage, was wir essen könnten – besonders angesichts von Felix' bescheidenem Essensgeschmack – bleiben unvergessen. Ich danke euch von Herzen, dass ihr mich in jedem Hoch und Tief unterstützt habt und immer ein offenes Ohr für mich hattet. Auf euch konnte ich mich stets verlassen, was alles andere als selbstverständlich ist.

Dr. Sebastian Pohl, dir danke ich für die Einblicke und Motivation in Bezug auf die Zweischneckengranulierung. Du warst eine große Unterstützung bei allen Fragen und hast mir insbesondere zu Beginn meiner Promotion hilfreiche Hinweise gegeben.

Claudia Köster danke ich für das Bereitstellen und die wertvollen Erkenntnisse im Umgang mit unserer Lady Q. Dein Engagement für die HHU-Today, die Erstellung von Pub-Quizzen und Rätseln war eine große Bereicherung für meine Promotionszeit.

Finn Siebel danke ich für die gegenseitige Unterstützung, besonders in der Zeit, als wir die letzten Doktoranden im Arbeitskreis Kleinebudde waren. Die gemeinsamen Abende, sei es bei Institut Veranstaltungen, bei denen du oft als DJ-Zwiebel eingesprungen bist, bei Arbeitskreis-Events oder Konferenzen, sowie deine Liebe zu gutem Essen und leckeren Cocktails haben meine Promotionszeit bereichert.

Des Weiteren möchte ich mich bei Andrea Michel für die DSC-Messungen bedanken. Dr. Sebastian Braun danke ich für die wertvollen Einblicke in die pharmazeutische Industrie, insbesondere hinsichtlich des Projektmanagements. Außerdem danke ich Dorothee Eikeler für die lustigen Gespräche und Stefan Stich danke ich für seine Hilfe bei Reparaturen und die Vorbereitung des Transports, wenn die QbCon abgeholt oder geliefert wurde. Mein Dank gilt

auch allen ungenannten, ehemaligen und aktuellen Institutsmitgliedern. Vielen Dank für das wertvolle Feedback bei Doktorandenvorträgen und die schönen Momente bei den Institutsveranstaltungen, besonders bei unseren Weihnachtsfeiern, Karnevalsfeiern, dem Oktoberfest und den gemeinsamen Konferenzbesuchen.

Der größte Dank gilt meinen Herzensmenschen. Martin Lück, dein Einzug ins Büro hat meine Promotionszeit nicht nur bereichert, sondern auch erheblich verbessert. Ich danke dir von Herzen für deine unermüdliche Unterstützung, dein Verständnis, wenn sich der Feierabend aufgrund meiner Messungen verschoben hat, und deine kontinuierliche Hilfe. Du warst und bist eine große Stütze und mein Ruhepol in jeder stressigen Situation. Herzlichen Dank dafür.

Meiner Familie danke ich für ihre stets grenzenlose Unterstützung, ihr Verständnis und ihre beständige Liebe. Ein besonderer Dank geht an meine Eltern, Irina und Aleksej Kiricenko, sowie an meine Geschwister, Stefanie und Kevin, und meine liebe Oma Amalia. Ihr seid immer für mich da und glaubt an mich, wofür ich euch unglaublich dankbar bin!

Eidesstattliche Erklärung

Ich versichere an Eides statt, dass die vorliegende Dissertation von mir selbstständig und ohne unzulässige fremde Hilfe unter Beachtung der „Grundsätze zur Sicherung guter wissenschaftlicher Praxis an der Heinrich-Heine-Universität in Düsseldorf“ verfasst worden ist.

Katharina Kiricenko