Process characterization and development of simplified, high drug loaded formulations for the continuous manufacturing of tablets, based on twin-screw granulation

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List of abbreviations

API	active pharmaceutical ingredient
APV	International Association for Pharmaceutical Technology
BU	blend uniformity
CPP	critical process parameter
CQA	critical quality attribute
CU	content uniformity
EMA	European Medicines Agency
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
GSD	granule size distribution
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
L/S	liquid to solid
MCC	microcrystalline cellulose
MIT	Massachusetts Institute of Technology
OOS	out of specification
PAT	process analytical technology
QbD	Quality by Design
QTPP	quality target product profile
RTD	residence time distribution
RTRT	real-time release testing
SFL	specific feed load
TSG	twin-screw granulation
VRR	variance reduction ratio

1. Introduction

1.1 Continuous manufacturing in the pharmaceutical industry

1.1.1 Driving forces

Traditionally, the manufacturing of medicinal products in the pharmaceutical industry has always been a batchwise process, in which every single unit operation is conducted separately. In contrast to that, different industry branches, such as the food-, chemical-, detergent- or oil refining-industry have already been performing continuous manufacturing for decades [1-4]. However, until recently, the pharmaceutical industry refused to modify its production principles to continuous manufacturing. Reasons for that could be found in the industry's rigid structures, which were caused by the strict supervision of regulatory agencies, such as the Food and Drug Administration (FDA) for the U.S. market or the European Medicines Agency (EMA) for the European market [5, 6]. However, driven by changing frameworks in the healthcare systems of the industrial countries, which are accompanied by budget reductions and economization processes, in recent years the pharmaceutical industry has experienced a shift in its mindset regarding the way of producing medicinal products. This change in the way of thinking was intensified by the FDA guidance on process analytical technologies (PAT) [7] and the guidelines Q 8, Q 9 and Q 10, dealing with pharmaceutical development, quality risk management and quality systems, released by the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) [8-10]. These guidelines encourage the pharmaceutical industry to develop and apply new technologies and processes, based on scientific approaches and complete understanding of the process in use. It should be the aim to control and monitor the process in real-time to produce pharmaceuticals, which conform to a predefined quality target product profile (QTPP). This approach, which is part of the Quality by Design (QbD) concept, should ensure that quality is built into a product instead of a quality control testing of a product after the manufacturing process. The aim is to setup a predefined and validated design space, which is a multi-deminsional room of process parameters and raw material properties, in which each critical quality attribute (CQA) of a product lies within a specified range. A CQA is defined as "a physical, chemical, biological, or microbiological property or characteristic that

should be within an appropriate limit, range, or distribution to ensure the desired product quality" [8]. By an appropriate control system, which ensures a constant conformation to the design space, product variability and the amount of non-conforming products could be reduced.

In the pharmaceutical field, primary and secondary manufacturing have to be distinguished. Primary manufacturing, also called upstream operations, involves the production of an active pharmaceutical ingredient (API) from the starting reagents and can be performed continuously by the principles of flow-chemistry. Secondary manufacturing, also called downstream operations, comprises the manufacturing of the finished dosage forms as, for example, granules or tablets [3]. Especially the Novartis-MIT (Massachusetts Institute of Technology) Center for Continuous Manufacturing [11], which is a 65 million dollar collaboration of Novartis and the MIT for a period of ten years, deals with the applicability and design of end-to-end continuous manufacturing, which is the combination of primary and secondary manufacturing. However, this thesis addresses the secondary continuous manufacturing of pharmaceuticals only.

1.1.2 Advantages of continuous manufacturing

When dealing with the topic of continuous manufacturing, the advantage of this kind of processing becomes obvious, both from the economic and the product quality point of view, which may overlap in some parts [1-3, 12-17]. By applying continuous manufacturing, a distinct reduction in machine footprint is possible. The required machines can be designed smaller, as they can produce the equal volume of materials as large batch processes solely by increasing the production time. Furthermore, some unit operations can be combined in a single step. This leads to smaller designated areas that have to be installed under GMP (good manufacturing practice) conditions, which is a great potential to save expenses. Storage and transport of intermediates from different production sites, likely in different countries, do not occur, as the different unit operations are connected to each other. Thereby, the protection of the employees can be improved, which is an important matter for high-potent APIs. The amount of material produced only depends on the throughput and the production time of the machines and is thereby variable. This means that to scale up from smaller to bigger machines is not an issue and the production of material can easily be adapted to market demands. Additionally, this implicates the possibility of shorter times-to-market, as the market production of a product can be conducted on a pilot scale line.

Regarding quality, the need to completely monitor a process, has the most significant implications. Applying PAT alongside the process, the quality of the product is consistently monitored and deviations from preset ranges of the CQAs

can be detected and eliminated by interventions of the control system. Thereby, the disposal of complete failure batches is omitted and fewer materials, which are out of specification (OOS), have to be rejected and the variability of a product decreases. The so-called real-time analysis of process and product furthermore implies the chance to establish a real-time release of medicinal products with the advantage of a 100 % and non-destructive control of all produced product.

1.1.3 Obstacles to be overcome

Besides the numerous advantages of continuous manufacturing, this way of processing also features some disadvantages, or rather challenges and obstacles which have to be overcome and solved. Even if the advantages and opportunities of continuous manufacturing in the pharmaceutical industry are promising, it is still a long way to go until all these visions can be fulfilled. Raw material variability can occur for APIs as well as for excipients [18]. Two batches of the same material are never exactly equal, and thus a continuously running process can be disturbed when a new batch gets introduced into the process. The manufacturers have to account for this source of variability and, for example, have to build up models to adequately react on these disturbances. Fonteyne et al. [19] did this for the continuous wet granulation of different grades of microcrystalline cellulose (MCC) to the result of constant granule quality throughout different non-homogenous raw material batches.

In addition to the chances of PAT in real-time quality control of continuous processes, the handling of generated data remains challenging [20]. Short residence times of some unit operations require higher sampling rates than batch processes, in order to be able to monitor and to react on disturbances [21]. These high sampling rates of various sensors induce plenty of gigabyte of data, which continuously have to be handled, processed and stored appropriately, especially for regulatory purposes.

Another PAT-related issue can be found in the possibility of sensor fouling during continuously running processes, which by definition do not include interim cleaning cycles. A solution suggested by Page et al. [20] would be the development of in-situ cleaning sensors or the application of materials less susceptible to material adherence.

To conduct a continuous process economically and to release a finished product without delay, real-time release testing (RTRT) of products is necessary. In 2012, EMA released a guideline regarding this topic, which replaced the former guideline for parametric release that especially concerned release after sterilization [22]. Although it is a promising idea, the implementation of RTRT is not trivial. The conventional testing of random samples, which is conducted in batch

manufacturing and in most instances is of destructive nature, is against the idea of continuous manufacturing. The principle of RTRT is based on destruction-free test methods, a deep understanding of the process and the relationship between product quality and process disturbances, as stated in the guideline. Therefore, it might be necessary to develop new methods and to apply models for different quality attributes, which use data of PAT sensors, critical process parameters (CPPs) and raw material attributes. Markl et al. [23, 24] for instance established optical coherence tomography, which was used for biomedical purposes and which can be used as an inline tool in real-time quality control. The challenge, however, lies in the previously mentioned raw material variability. Through changes in starting material or product composition or even unknown changes not necessarily affecting the product quality, model outcomes can be interpreted wrong. Hence, the models for RTRT have to be built up in a way that they can act dynamically on changes of input variables or that they can be updated on a frequent basis. Once a validated RTRT procedure is implemented, it is necessary to include rejections points capable of discarding OOS material. This is not only necessary for the release testing, but also for different points after each individual unit operation, in case the intermediates do not conform to the defined CQAs and cannot be corrected by interventions (s. 1.1.4).

One major obstacle that has to be overcome is the traceability of materials in the continuous stream of introduced and discharged material [25]. From a regulatory point of view, for each produced unit it has to be fully known which batch of excipients and API are incorporated, in order to be able to undertake a product recall, if necessary. To address this problem, a deep knowledge and understanding of flow and residence time distributions (RTD) of material through every unit operation is necessary. Furthermore, the knowledge about RTD will help to track disturbances through a process and to reject OOS material at the predefined rejection points [26]. In terms of traceability, a sharp and short residence time, which is a characteristic of ideal plug flow without axial mixing, would be best to trace substances throughout a process.

1.1.4 Control of continuous processes

The previous section described challenges which have to be mastered, when a continuous process is pursued. Plenty of different systems, as for example PAT sensors, different unit operations and transfer steps have to be executed in accurate manner and have to be able to react to each other. Consequently, a proper process control and tuning is necessary. One major requirement is to detect and determine a suitable design space. A design space is considered as an area of each CPP and raw material attributes, in which the intermediates and especially the finished product conform to the defined CQAs [8]. The main task of

a control system is to modify the variables, which are susceptible to manipulations (i.e. CPPs) and to maintain steady state conditions. Myerson et al. [25] avoided the phrase steady state and called it 'quasi steady state', in which the CPPs can be varied according to the design space. They declare that the aim should rather be to continuously conform to the specifications of the CQAs than to maintain a steady state of all CPPs. However, to maintain a control strategy for a continuous process, two important principles have to be employed and have to work hand-in-hand to adequately react on process disturbances and to changes in the monitored product characteristics. Firstly, the feedback controller, which manipulates CPPs as response to the measurement of changes in variables that have to be controlled (e.g. CQAs). Secondly, the feedforward controller, which manipulates CPPs as response to measured process disturbances. Hence, to adequately set up a feedforward control, RTD models again become important to determine the reaction regime of the control and the time shift between detection of the disturbance and reaction to it. These principles should be part (amongst further models) of control strategies for continuous manufacturing plants, as they have already been shown in model studies of end-to-end continuous manufacturing [27-29].

1.2 Continuous manufacturing of solid dosage forms

1.2.1 The required dosage form

Amongst all available solid dosage forms, the tablet is the one which is most important and perhaps most variable. Plenty of different shapes, sizes and colors, different functionalities through variable release profiles, different ways of administration etc. are possible. Also the production time for vast amounts of tablets can be short. According to estimations of the International Association for Pharmaceutical Technology (APV) approximately 80 % of pharmaceutical preparations are produced in solid form. The majority of these solid products are tablets [30]. Therefore, it is not surprising that most of the efforts towards continuous secondary manufacturing have been invested in the continuous production of tablets as final product. Tablets can be compressed from powders and/or their respective powder mixtures in case their flowability is good enough to ensure a constant fill of the die and thus mass homogeneity and content uniformity (CU). If the flowability is not sufficient, a prior particle size enlargement through granulation processes might be necessary. Apart from the flowability enhancement, a granulation is beneficial to prevent segregation of a powder mixture and the generation of dust, which is especially important for

highly potent APIs, and to improve the compaction properties of a powder. Although granules can be applied as independent dosage form, they are more frequently produced as intermediate in the production of tablets instead.

1.2.2 Manufacturing routes

1.2.2.1 Continuous direct compression

The secondary manufacturing of pharmaceuticals sometimes receives only a small space in flowsheets of end-to-end continuous manufacturing [27-29, 31], but it is highly complex and versatile and demands a fundamental understanding of relationships between formulation and process parameters. Basically, the continuous manufacturing of tablets can be conducted via three different routes, which are continuous direct compression, continuous dry granulation with subsequent compression or continuous wet granulation with subsequent compression. Continuous direct compression has barely been investigated, applying self-constructed machinery, consisting of powder feeders, continuous blenders and a tablet press [32-35]. As mentioned before, the direct compression of powder material requires a sufficient flowability to achieve as little mass variation as possible. Furthermore, a segregation of the different components of the powder mixture has to be excluded and a proper compactibility of the material has to be ensured. Therefore, some functional excipients, as for example dry binding agents, glidants or ready-to-use co-processed excipient mixtures have to be employed in a sufficient ratio. Especially for heat- and moisture-sensitive substances it is the production process of choice [36]. In continuous processes in general, therefore also in continuous direct compression, the applied materials have to be fed to the process as a constant stream to ensure a steady state with means of a constant input and output of material. This can be conducted by direct feeding the materials to the hopper of a tablet press or rather by feeding to a continuous blender, which ensures a homogenous mixing and transports the powder mixture to the hopper of the press. The latter method offers the advantage of filtering potential fluctuations of powder feeders to ensure the best possible mixing of the powder [37], especially during the handling of cohesive powders, which might complicate the process of powder feeding. In some cases a milling step prior feeding is necessary, for example if the material tends to agglomeration during transport and storage. Monetary, it is the most favored production route, as no further processing or expensive drying steps are required. In April 2016, FDA approved the first medicinal product manufactured by continuous direct compression of darunavir tablets of the company Janssen, which now need only one day to produce the same amount as in two weeks of batch

processing [38]. However, this route can solely be conducted, when most of the mentioned requirements are fulfilled.

1.2.2.2 Continuous dry granulation / compression

The most common way and currently the only possibility to conduct dry granulation continuously is roll compaction. During roll compaction, powder is transported constantly to the feed zone of two counter rotating rolls. The powder experiences a densification as it passes the rolls, resulting in the generation of ribbons, which are flat, band-shaped products. Usually, a force feeder is applied to stuff the incoming material to the rolls. To result in strong ribbons, the usage of a dry binder within the powder mixture is essential, which often are derivatives of cellulose, starch or povidone [39]. After the compaction process, the dry granulation process takes place by milling the ribbons to granules. By applying different screen sizes during milling, the granule size distribution (GSD) can be influenced. After granulation the granules can be transported to the hopper of a tablet press, where they get compressed to tablets. Prior to that, an optional step to add further excipients to the tableting mixture can be executed. In the framework of control strategy development, roll compaction / dry granulation with subsequent tableting have already been described within a continuous production line [40]. The possibilities to influence the granulation by different CPPs are manifold, starting with the roll compaction process, in which feed-rate, roll surface, roll speed, specific compaction force, gap width and the roll sealing system can be adjusted [41]. It has to be mentioned that the gap between the rolls and the specific compaction force should be constant to ensure constant ribbon porosity. This is often controlled by inbuilt controllers of the machine through adjustment of roll-speed and speed of the feed-screw. The milling process can be influenced by the type of mill, the rotation mode (oscillating or rotating), the mill speed and the screen type and size of the applied sieve. The major advantage of this process is the absence of moisture and thus of a drying step. Thereby, the processing time from powder to finished granule is quite short. A disadvantage of roll compaction/dry granulation can be seen in the generation of high amounts of fines [42], which can be unfavorable or even unwanted for further processing and may disqualify or complicate this process for highly potent substances. Depending on the formulation, the granules can furthermore lose their compactibility to some extent, compared to the raw powder, which complicates a subsequent tableting process [43].

In a broader sense, the melt granulation technique can by definition also be accounted to dry granulation techniques, because it can be conducted without liquid. An exception is the addition of liquid plasticizer (-solution), but this liquid is not used to promote granulation or to propagate the binding of granules. The difference to dry granulation regarding the formulation is the need of a meltable

binder, which is plastified under increased temperature and provides the binding after reaching ambient temperature again. Melt granulation can be executed with different machines, but it would only be continuously possible by now via the application of fluid bed and extrusion techniques, as reported in different studies [44-49]. Naturally, all employed excipients and APIs need to be stable under higher temperatures and must not show degradation or incompatibilities at increased temperatures.

1.2.2.3 Continuous wet granulation / compression

Continuous wet granulation is the starting point for the third principle of producing tablets continuously. All available methods have in common that powders have to be delivered in some way e.g. by powder feeders and/or continuous mixers, that the powders have to be wetted and agglomerated successively or simultaneously and that the wet granules have to be dried. After drying, granules can be processed further by sieving, milling or mixing with additional components to produce tablets, subsequently.

Vervaet and Remon [2] gave an overview of different possibilities of performing wet granulation continuously. Interestingly, one of the most common batch granulators in the pharmaceutical field, the high shear granulator, has not yet been employed in a reliable way for continuous granulation purposes, although there have been attempts by the companies L.B. Bohle and Glatt.

Spray drying of solutions or suspensions is a reliable way to produce powder continuously and can also be applied to solutions of several components to result in granules. This method has the huge disadvantage of high energy costs because of a constant stream of hot air, which is required to dry the droplets that are introduced by a nozzle in shortest time. Also, the resulting granule sizes will be small, because the size of the droplets determines the size of the granules. The bigger the droplets get, the longer the required drying tower has to be and the higher is the amount of energy that has to be employed.

The most important and most frequently used processes were relying on fluidized bed or extrusion techniques. Fluidized bed granulation features the advantage of agglomeration and drying in a single machine. Additionally, the produced granules are usually of high porosity and thus well compressible. One disadvantage is the comparably long process time for the agglomeration step. In the food- and chemical industry, continuous fluidized bed granulators are already common. They mainly operate linear and high throughputs up to tons per hour are common. In the pharmaceutical sector, conventionally smaller throughputs are used, which might be the reason why practically no truly continuous fluidized bed granulator for pharmaceutical purposes is on the market or extensively described and evaluated in literature [2, 50]. The difficulty to spray the

granulation liquid in a reliable way into small chambers without deterioration of the spraying efficiency might be one reason for that. The challenge of preventing congestion of the exhaust-air filters, which would lead to a frequent changeover of the filters, might be a second reason.

A well-established and extensively described method to perform continuous wet granulation with the possibility of subsequent tableting is twin-screw granulation (TSG), which is based on twin-screw extruders. In the beginning of the 2000s, it was described by Ghebre-Sellassie et al. [51] and Keleb et al. [52] and followed up by several research groups in the following years. By now, there is one prominent system on the market for continuous wet granulation and tableting, which is supplied by GEA, but several other companies or consortia (e.g. L.B. Bohle, Excellence United) are close to marketability with their own systems [5]. In July 2015, the FDA gave approval for the first ever continuously produced medicinal product, which was Orkambi of the company Vertex. The cystic fibrosis drugs lumacaftor and ivacaftor are formulated by continuous wet granulation and result in film coated tablets [53].

Several advantages, as for example great flexibility at multiple aspects are core features of TSG processes and will be illuminated in the following section.

1.3 Twin-screw granulation based continuous manufacturing

1.3.1 Introduction to the process

As briefly mentioned in the prior section, TSG is performed on co-rotating twin-screw extruders. Material is delivered to two screws, which rotate in the same direction and transport and shear the material along the process distance to the point of the extruder outlet. The major difference of TSG to extrusion processes is that the die plate at the end of the machine is removed. The wet material does not experience a densification in front of a die plate and the shape of the product is not predetermined by the dimensions of the die holes as in extrusion processes. The wetted and shaped granules solely fall out of the extruder when the end of the screws is reached. The extruder provides a lot of adjustable parameters and possibilities to vary the setup of it. Furthermore, different machines, mainly feeders, are employed alongside of the process, which increase the degree of freedom of the system even further. This chapter gives an overview of the processes and the manufacturing route, which have partially been employed in this work to produce tablets from the starting powder material.

1.3.2 Impact of the equipment

1.3.2.1 Twin-screw extruder

1.3.2.1.1 Design

A twin-screw extruder is the core of the TSG based continuous manufacturing. Although, in extrusion technique counter rotating screws are also deployed, in TSG studies and production only co-rotating twin-screw extruders have been described by now. Amongst other things, an extruder is defined by the screw diameter and the length to diameter ratio of the screws. In this thesis, screws with a diameter of 16 mm and a length to diameter ratio of 40 and 41 were used. Hence, the screws had a length of 640 mm or 656 mm. The ratio of inner and outer diameter of the screw elements influences the amount of material that can be transported and thus the maximum possible fill-level of an extruder. The fill-level of an extruder depends on the feed-rates of the material, the screw speed of the extruder and the geometry and thus the free volume of the extruder screws. Although, there has been extensive research with each of these parameters [54-58], neither systematic investigations regarding the influence of the fill-level, nor attempts to measure the fill-level of an extruder have been conducted by now.

The utilized extruder is divided into ten zones of equal length, which can be heated and cooled independently from each other. Each zone offers the possibility to insert different ports on top of it. Thereby, feeding and the application of PAT become feasible.

The screw is not a predefined parameter in extrusion and granulation processes. Virtually, an infinite number of different screw configurations is possible by combining different types of elements. Conveying elements are used to transport the material through the extruder barrel with minimal input of shear energy. The pitch of the elements can also be varied. With increasing pitch of the elements, the conveyed mass per revolution decreases. Kneading elements are thin discs, usually of a length of 1/4 D or 1/8 D and can be combined to kneading zones or blocks. The imparted shear energy increases and the conveying capacity decreases with an increasing advanced angle of the subsequently arranged kneading discs. An intermediate between these two extremes is represented by distributive flow elements, which feature conveying capacity as well as shear energy.

Through combination of different elements, granule characteristics can be influenced. A lot of studies dealt with the influence of the screw configuration on granule size and shape characteristics and some of them derived granulation regime maps and rules for the growth of granules from the results [55, 59-65]. The aim of this is to explain the underlying mechanisms of granule growth and comminution within the different elements and to find rationales for the selection

of an appropriate screw configuration. Unfortunately, the variability of used materials has been low. Mainly α-lactose monohydrate, MCC or mixtures containing more than 93 % of them were applied for these studies. Solely Kumar et al. [61] acknowledged the narrowness of these results and that the investigation with differently behaving materials at equal process conditions is necessary to draw reasonable and more general conclusions. The research with materials, providing different deformation mechanisms i.e. brittle, plastic and elastic behavior and with different solubility in the granulation liquid should be applied for this objective.

However, a twin-screw extruder displays an ideal tool to perform continuous granulation, because it combines several processes. Conveying, mixing, wetting and shearing take place in one machine in exceptionally short time [66, 67].

1.3.2.1.2 Critical process parameters

A CPP is defined as "a process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality" [8]. According to this definition, some parameters of a twin-screw extruder need to be monitored and controlled, as they may have huge influence on the product's CQAs. The screw speed is the most remarkable parameter, which can be set for an extruder. Higher screw speeds lead to a faster transport of material and, under constancy of all other parameters, to a lower fill-level and vice versa [54, 68]. Some studies investigated the influence of the screw speed on CQAs of the product. Dhenge et al. [69] for example showed for screw speeds ranging from 250-550 rpm that the influence on median granule size was minor and only occurring at the highest values for screw speed. The shape of the granules changed for a higher screw speed, as the granules elongated. Vercruysse et al. [70] performed experiments with screw speeds ranging from 600-950 rpm and also observed no influence on granule and tablet quality.

The barrel temperature of the different extruder zones is another major factor, which can be manipulated directly at the extruder. There is not much data regarding the influence of the barrel temperature and often it is considered as a parameter resulting from the friction inside the barrel. Nevertheless, in one study Vercruysse et al. [70] could show that an increased barrel temperature resulted in a decrease of fines, an increase of coarse granules and an increase of granule strength. They recommended an intensive control of the barrel temperature, especially during the application of freely soluble compounds.

A process parameter that is influenced by a lot of factors and can only be adjusted qualitatively is the RTD, which describes the probability of material to stay inside the extruder during a steady-state process. It is essential to know the RTD and the influencing factors on RTD to understand a continuous process and

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to control it properly. In a lot of investigations the RTD in TSG has been measured offline or inline [57, 68, 71-74]. In face of the short residence times, which lie below one minute and often in the region of seconds, and the recommendation that 3-5 samples for each time period equal to two times the standard deviation of the RTD should be recorded to result in adequate description of the RTD [21], it is inevitable to use inline methods for RTD measurements.

1.3.2.2 Feeding systems

1.3.2.2.1 Powder feeder

As it is necessary in every continuous process, the raw material needs to be constantly delivered to the process to ensure mass balance. This is usually conducted by the application of powder feeders as first process step [75]. As mentioned before, during the description of direct compression, prior to feeding the powder can be homogenized by sieving. The feeding of powders can be problematic, because powders do not behave as liquids regarding their flow behavior. This can be ascribed to cohesion of the powder, possible electrostatic charging, shear sensitivity and changes in bulk densities during processing. A powder feeder consists of a reservoir for the material that will be fed. Depending on the fill degree of the reservoir, which changes during the process, different normal forces impact the bulk in terms of varying bulk porosities and hence varying bulk densities [76]. The consequence is varying output, caused by an unstable filling of the feeding tool of the feeder. The most common type of powder feeding is the screw feeding, which can be carried out by single or co-rotating twin-screw feeders. Other principles, as for example vibratory feeders or scraper feed discs may play a role in the feeding of very small amounts of powder. Powders can be fed either volumetrically or gravimetrically. Volumetric feeders deliver the material at constant agitation rate of the feeding tool (screw, vibrating chute, etc.), which needs to be calibrated to the corresponding feed-rate beforehand. In these cases the feeder is not capable of displaying the momentary feed-rate of the powder and drifts in the feed-rate cannot be recognized. Furthermore, the feeder cannot react on short-term fluctuations in feed-rate. This principle is mainly applicable to free flowing powders, if the short term accuracy is not important or if the subsequent process features a high degree of axial mixing quality. Consequently, gravimetric feeding of powders is state of the art in the pharmaceutical industry. Gravimetric feeders operate volumetrically and are placed on and electronically coupled to a dynamic balance, also called a loading cell. The loading cell measures the weight loss during a feeding process in high frequency and consistently sets the motor speed by integrated and mostly self-optimizing controllers, to meet the desired feed-rate. Thereby, a momentary feed-

rate can be monitored and recorded and inaccuracies of the feeder can be levelled off. From the view of QbD and process control, the knowledge of the momentary feed-rate is essential, as the feeding displays the introduction of raw material to the process. Disturbances can directly be measured and the process can react to them, if it underlies a proper control.

Usually, the powder is delivered to one of the first zones of an extruder. It can be distinguished between the delivery of a premix and the delivery of APIs and all excipients by separate feeders. This in turn, can be conducted via a single or multiple feeding ports at different positions of the extruder. In a continuous process, the mentioned powder reservoir will be empty at some time point and has to be refilled frequently. During this refill phase, the feeder is shifted to volumetric feeding mode, because the gain in powder weight would be detected by the balance and all controls of the feeder would be confused, which results in huge feeder errors [77]. Consequently, during this refill phase the powder feeder is blind to deviations from the set feed-rate and cannot react on those. Engisch and Muzzio were able to show that an overfill of the screw flights during the refill phase, caused by a fast densification of the powder inside the reservoir, led to a periodic overfeeding during all refill phases. The feed-rate deviations during the refill-phase were measured by feeding on an external scale. They suggested to find an adequate ratio between a gentle refill of the reservoir and the refill time, to keep the refill time and the deviations as small as possible [77]. However, although the blind phase during feeder refill is a huge problem, there is no PAT solution available yet to monitor and perhaps control the feed-rate during refill. A method for this could positively influence process control and steady state conditions.

Numerous studies regarding influences of different process parameters and different setups on CQAs of wet granules and tablets have been published, but despite the challenges in proper feeding and refilling of raw materials, the influence of the accuracy of powder feeders on granule or tablet quality has not yet been investigated. Additionally, a method to describe feed-rate deviations more elaborate than just by the coefficient of variation could help to design and improve proper feeding processes.

The feeding of low-dosed material, especially low-dosed API, still remains a challenge because of the resulting low feed-rates. Miniaturized feeders are available on the market but these are still not the overall solution, especially due to poorly flowing materials. Besenhard et al. [78] introduced a system to deliver powder < 1-2 mg/s to a process by applying an own built vibratory sieve-chute. Another principle, investigated by Llusa et al. [79], is the introduction of low-dosed material as a fine dispersed suspension via a liquid pump. This principle was tested for an extrusion process, and extrudates containing 0.021 and 0.043 %

of API were produced with a coefficient of variation for the measured content of between 2 and 7 % over 30 min. The only requirement for this principle is the stability of the API within the liquid.

1.3.2.2.2 Liquid Feeder

By definition, in wet granulation processes a liquid needs to be introduced at some point of the process. The liquid can be pure water, a binder solution or an organic solvent, depending on the formulation and the desired granulation mechanism. For this purpose liquid pumps are employed, which need to be controlled to deliver a constant amount of liquid. The pumps work volumetrically by rotation of the specific tool, which conveys the liquid. A gravimetric control by placing the liquid reservoir on a balance or the application of flow metering devices, such as Coriolis flow-meters are feasible and described for liquid pumps [80-82]. For wet extrusion the advantages of small nozzle openings and the application of high pressure pumps have been shown [81, 83]. A more homogeneous distribution of liquid and the prevention of nozzle blockage by powder were the consequence. The majority of published studies reported the usage of peristaltic pumps [52, 70, 71, 74, 84, 85] and most of them did not provide data on the control of the pump so that it has to be assumed that the liquid feeders were calibrated offline for their mass flow rate. A disadvantage of peristaltic pumps is the pulsatile flow of liquid through the tubes, which is caused by the movement of the rolls of the pump. Thereby, the short-term accuracy of the liquid feeder is declined. Furthermore, the nozzle of the liquid feeding port of the extruder must not be too small, for as peristaltic pumps are not capable of generating much pressure. Because of the dimensions of the nozzle, the droplet size, which is introduced in the extruder and which is responsible for the nucleation of the granules, is huge. This might be problematic, because the huge droplet size is responsible for poor wetting uniformity in TSG, which has been recognized within several studies [59, 63, 86]. Especially hydrophobic powders seemed to be a problem for uniform wetting or wetting in general, which is demonstrated for TSG and high shear wet granulation [87-89].

Similar to powder feeders, only little effort has been put into investigating influences of different liquid feeding systems and strategies on CQAs of granules and tablets. Vercruysse et al. [68] decreased the nozzle opening of the feeding ports and used a piston pump as comparison, but did not observe any influences on CQAs. One research group developed a method to deliver foam as binder to the process. A reduction of the liquid to solid (L/S) ratio was achieved but other granule properties were not influenced significantly [90-92]. Djuric and Kleinebudde applied a membrane pump in TSG, which is different to any other pump described in TSG related literature, but no comparison to conventional pumps has been made so that its role remains unclear [55].

1.3.2.3 Continuous blending

The CU is one major CQA to achieve within a finalized dosage form. Feeding is a crucial unit operation to achieve CU, but can be problematic, as explained in a prior section. In truly continuous processes every excipient and API usually is delivered by its particular feeder, which also gets refilled following a scheme, depending on the feed-rate of the ingredient. This complicates CU issues even more. Normal feed-rate deviations and deviations caused by refill phases of the feeder will arise constantly. Continuous blenders can be applied to dampen feeder fluctuations before a particular unit operation [93, 94]. In contrast to batch blending, during continuous blending only small amounts of material are blended at the same time, the blending time is short and the footprint of the machine is smaller [95]. Depending on the construction of the blender there are a few grams up to a few kilograms within a process, at once [37]. Contrary to traceability issues, in which sharp residence times are desired, continuous mixing relies on axial mixing and thus broad RTDs, to dampen feeder fluctuations and to reach the desired CU. To assess blending performance the variance reduction ratio (VRR), originally introduced for continuous fluid mixers [96], was applied to continuous powder blenders [97]. The VRR is calculated by dividing the input variance of the CU directly after the powder feeders by the output variance of the CU after the blender. The higher the VRR, the better is the performance of the blender. If continuous blending is performed before TSG, the powder can either be introduced to the extruder directly or through an intercalated powder feeder. Caution must be exercised in the prevention of demixing in the latter case.

Twin-screw extruders are also efficient blenders. The flow within an extruder is similar to that of a continuous mixer. Different kneading and mixing elements can prolong residence times and introduce axial mixing into the process. The possibility of using a split feeding of all ingredients and utilize the twin-screw extruder as continuous blender, combined with the wet granulation step would be of interest because of the possibility to eliminate one unit operation. Interestingly, only one publication in the field of TSG dealt with the measurement of the mixing capacity [98]. The authors applied a split-feeding with 2.5 % hydrochlorothiazide as tracer for CU experiments. Samples were taken every minute during a 15 min timeframe. A mean API concentration of 100.2 % and a coefficient of variation of 1.9 % were found, which are excellent values, especially for a low-dosed component. More research in this field would be necessary to confirm the significant potential of this machine regarding the blending to fulfill CU specifications.

1.3.2.4 Drying

After TSG in the extruder, the granules leave the barrel and have to be dried. A transfer to the drying system, e.g. by applying a vacuum is necessary, but

considerations regarding granule strength have to be arranged to prevent a destruction or desagglomeration of the granules. Comparisons between an early published study on GEA's ConsiGma [80] and the web presentation of GEA [99] demonstrate lessons learned by the machine supplier. In the early study granules were transported via vacuum from the twin-screw extruder to the dryer, whereas on recent pictures the dryer is placed directly below the extruder to prohibit stress on the granules. Different continuous techniques, as for example belt drying on a conveyer, optionally under vacuum, are imaginable. But to prevent secondary agglomeration of the wet granules and to handle huge throughputs, fluid bed techniques for drying are the only reasonable method. GEA for instance provides a six-segmented fluid bed dryer, in which at all times one chamber is being filled, three chambers are in drying mode, one chamber is discharging and one chamber is on waiting position. Although this principle is already well-known on the market, it is semi-continuous, because small sub-batches are generated. To conduct drying truly continuous, linear or circular drying systems are conceivable. The main requisite is the application of a single chamber. Glatt introduced the MODCOS system to the market, in which the granules pass through a circularly arranged chamber and are discharged at the end of the circle. A rotary star valve is turning inside the chamber to force the granules through it [100]. One fundamental requirement to operate this process is a reproducible RTD to ensure a constant drying and residual moisture in the dried granules.

1.3.2.5 Preparation for tableting

A direct compression of the granules after the drying step is feasible but with respect to the GSD a milling step might be necessary to have a more uniform size distribution and to positively influence weight uniformity of the tablets, as described in the section on continuous direct compression. For TSG processes, bimodal and broad GSDs are common and frequently described in literature [59, 101-104]. This is often attributed to poor liquid distribution and short residence times, which result in uneven wetting conditions and huge amount of fine and coarse granules. Only at high L/S-ratios the GSD improved significantly, but under a decrease of the granule porosity. These problems implicate the need of a subsequent conditioning process. By the application of a mill and by the adaption of the milling conditions and the screen size of the sieve, the GSD can be shifted to the desired direction. If it would somehow be possible to design the TSG process or the formulation in a way to achieve very narrow and mono-modal GSD, a further unit operation can be cancelled, which simplifies the process control and demagnifies the footprint of the facility.

If the granules did not contain all the desired excipients, another continuous blending step can be conducted before tableting. Sometimes the disintegrant is left out in the granulation mixture because of a lack of clarity regarding the

influence of wet granulation on disintegrant performance [105-107]. The granulation of the entire tableting mixture could also diminish a second mixing step and simplify the process. Also, the lubricant for the tableting process can be added to the mixture, but in this case a short mixing time of lubricant and granules has to be ensured as long mixing time can adversely affect the tableting properties and the CQAs of the finished tablets [108].

1.3.2.6 Tableting

One objective during compression is the uniformity of tablet mass. The basis to reach the required specifications has to be provided by the prior granulation step. Mainly the size uniformity and the flowability of the dried granules influence the tableting efficiency.

The tableting tools have to be lubricated to prevent damage on the tools through friction and stickiness of the tablets on the tools leading to ejection problems of the tablets. The mode of lubrication can be divided into internal and external lubrication. Internal lubrication means the presence of the lubricant within the tableting mixture and external lubrication means the pure lubrication of the tableting toolings. The latter can be conducted by continuously feeding the lubricant in a low rate to the tablet press or by spraying suspensions or solutions of lubricant to the upper and lower punch. Mosig and Kleinebudde investigated differences of both methods and recommended external lubrication as method of choice, because problems related to compression properties, especially for plastic materials, can be circumvented thereby [109]. An external lubrication would be the most appropriate for a continuous process. As mentioned in the prior section, a blending step before compression can be avoided by application of external lubrication.

For direct compression and compression after dry granulation, several studies described material dependencies, e.g. deformation mechanism, on the compression behavior [110-117]. There is no such data regarding tableting after TSG by now. Various studies did not include tableting, as only granulation performance and granule quality were of importance. Indeed, some studies dealt with tableting after the TSG process, but only Vanhoorne et al. [58] investigated the influence of material properties on tabletability. In this particular study, two polymorphs of mannitol, namely delta- and beta-mannitol were compared, with improved tabletability of the delta polymorph. This field of study requires more investigation.

1.3.2.7 Coating

Improvement of the mechanical stability, appearance, taste, odor or swallowability, protection from environmental influences, brand recognition,

separation of incompatible ingredients or tailoring the drug release can be reasons for tablet coating after the compaction process. Due to these reasons, many tablets on the market are coated and hence the process of tablet coating plays a key role in continuous manufacturing. By nature, the tablet coating process is a semi-batch process, which means that materials are added throughout the process (coating solution / suspension) but are discharged at the end of it. Evidence for the difficulty of developing a truly continuous tablet coater can be seen in the deficiency of such a machine on the market. It is assumable that the RTD in a continuous coating pan would be broad with the result of an inferior coating uniformity. In terms of cosmetic coatings this might not be a critical factor, but especially for modified release coating or active (API containing) coatings, this is not acceptable.

A continuous removal of dust from the tablets is a prerequisite to prevent rough surfaces or even failure of the coating after the process. The aspect of elastic recovery of materials also needs to be taken into account, when designing a continuous or even a quasi-continuous (with sub batches) coating process. Materials with a high ratio of elastic deformation undergo a recovery after the compaction process, which means that the tablet gains in height again [118, 119]. It is essential to investigate the kinetics of this recovery before the design of the continuous process. The kinetic of the recovery determines the resting period, before a coating of the tablets is feasible. If coating starts before finishing the relaxation, damage of the coating after the drying process can be the consequence. Especially for modified release coatings, this can result in a dose dumping with major problems for the patient.

1.3.3 Impact of the formulation

1.3.3.1 General considerations for formulations in continuous twin-screw granulation

A general requirement for excipients used in TSG-based processes is the stability against degradation during contact with the granulation liquid. Moreover, (pseudo)-polymorphic transformations need to be known and controlled within the process and should not affect the CQAs negatively. The possibility to reduce the footprint of a production plant, the need to fulfill the requirements of traceability and the occurrence of raw material variabilities should lead to a rethinking of formulation aspects in continuous TSG processes. A concept to tackle these characteristics of continuous processes is to reduce the number of applied excipients. Thereby, the number of deployed powder feeders can be diminished and the built models to trace materials throughout the process become less complex. With each excipient that is left out, the problems related to raw

material variability will also be reduced. Materials, which are susceptible to and known for inter-batch variabilities should be left out or replaced by less susceptible materials with equal functionalities. Aiming at an end-to-end continuous manufacturing process, in which the quality of the produced API is constant and raw material variabilities are not expected, a high loading of API within the formulation could further reduce the raw material variability problem. In such formulations, the mixture mainly depends on the properties of the API that have to be thoroughly understood by the formulation scientists. The obstacles of poor compression properties [120] and hydrophobicity of several APIs [88] need to be overcome by the application of convenient excipients. However, it is inevitable to develop formulations for granules and tablets which correspond to the predefined CQAs and thus, they have to be defined.

1.3.3.2 Critical quality attributes of granules and tablets

In terms of process control it is of advantage that a CQA can be monitored inline. For production purposes, CQAs are usually predefined in a QTPP and do not need to hit a specified value precisely, but must lie within a specified range of the measured quantity. Otherwise the material is OOS and has to be discharged from the process. Tablets need to satisfy with regard to tensile strength (or breaking force), friability, disintegration time, mass uniformity, CU and dissolution. In this thesis it was aimed to produce tablets, which conform to the requirements of uncoated tablets with an immediate release, as described in the United States Pharmacopeia and the European Pharmacopeia. Thus, disintegration times smaller than 15 min were desired. The tensile strength should be sufficient enough to resist further processing. Strict boundaries are not given and the requirements are discussed within the following chapters.

Dried granules mainly need to adhere to predefined values of residual moisture, GSD, granule shape and solid state of the API or excipients [121]. The blend uniformity (BU), which is a precursor for the CU of finished tablets, can also be a CQA for the intermediate granules. Further characteristics, which are difficult to monitor inline and thus difficult to serve as CQA for intermediates in a continuous process, are: granule porosity, granule strength, compactibility / compressibility of granules. For these characteristics, there is still space to improve existing and develop new PAT tools. The granule porosity is an important CQA that determines compression properties and can impact disintegration and dissolution behavior of the finished tablets. Indeed, Bawuah et al. [122] introduced a method to measure the porosity of biconvex tablets inline by terahertz pulsed spectroscopy, which can be an anchor point to develop a similar method for granules. However, the irregular shape of granules certainly complicates the measurements, whereby a one-to-one transfer to granules is difficult. For this thesis it was aimed to produces granules with narrow GSD,

which are mono-modal and show sufficient compression properties at most, which will be discussed in several other chapters.

1.3.3.3 Required excipients

With the identification of the CQAs and the idea to apply high drug loads within the formulation it has to be considered which type of excipients are actually necessary. In literature, there is only little data about API containing formulations in TSG, sometimes including the manufacturing and analysis of tablets, sometimes not. In some studies ibuprofen alone or alongside with paracetamol, caffeine and griseofulvin were applied as APIs, in 15 % concentration [62, 90, 123] but without further compression to and analytical characterization of tablets. Theophylline anhydrate, which converts to its monohydrate form during wet granulation, was used in some studies in concentrations of 20 % and 30 % [70, 124-126]. Due to reasons related to confidentiality, unknown APIs were also applied in 21 % [101] or in unknown percentages with the statement that the API is "highly dosed" [127, 128]. Metoprolol tartrate was employed in 20 % concentration, but with the different aim to produce controlled release tablets [129]. Apart from the study claiming the API to be highly dosed, all other studies have in common that the API was incorporated in lower amount and therefore was not the determining factor to influence the granulation or the compression properties of the finished granules. Only a single study with a paracetamol application of 90 % was conducted [130]. In this study, the granulation mixture consisted merely of the API and the binder (10 %). A disintegrant was added after drying to result in a finished concentration of 85 % paracetamol. The authors reported the achievement of a high tensile strength (> 2 MPa) with only one of the applied binders, and fast disintegration of the tablets, which is due to the application of the disintegrant outside the granules.

In view of the limited data regarding high drug loads in continuous TSG it remains challenging to formulate granules and tablets that satisfy all requirements. In any case a binder is necessary to provide stability for the granules, both in wet and dried state. Thereby, granule strength, compression properties and tablet tensile strength and friability can be controlled. The binder can either be added in dry state within the powder mixture or dissolved as granulation liquid. Studies have been carried out in which the binder addition mode was varied between complete addition in liquid and in solid mode [71, 74]. The results of both studies were contradictory, because both came to different conclusions regarding the quality of binder distribution within the granules, depending on either a liquid or solid addition of binder. However, in a continuous process it is preferred to have, if at all, as little side processes as possible and thus the addition of binder within the powder mixture and the application of pure

water as granulation liquid is preferable. With the exception of one study, in which isopropyl alcohol/water mixtures were applied [130], only aqueous granulation liquids have been presented in literature by now. The use of organic granulation liquids would have numerous implications for the production plant and the process analytics, such as explosion protection, recovery of the solvent and analytics regarding residual solvent content of the dosage forms.

The viscosity of the liquid, which preferably can be either water or a binder solution, can have an influence on granule strength and flowability, which improves at higher viscosities [84]. In the same study it is reported that the surface tension of the liquid only has minor influence on the granule properties. El Hagrasy et al. reported a decrease of porosity with increasing L/S-ratio. Hence it is assumable that the L/S-ratio can influence the compression properties of the granules and thus is also a formulation aspect that needs to be taken into account. The L/S-ratio also influences the granule size and the GSD with the effect of increasing granule sizes and decreasing width of the GSD at increasing L/S-ratios [71, 86].

Theoretically, the temperature of the granulation liquid could be varied. This would influence the wettability of the powder and its solubility within the liquid for the most systems. Thereby, a decrease of the applied L/S-ratio and the drying time could be achieved. Although, heating of the granulation liquid would also cost energy, a save of expenses through the reduction of drying energy could be anticipated. At present, the variation of the temperature of the granulation liquid has not been investigated.

To promote disintegration and dissolution, a disintegrant may be applied. As mentioned before it can be added within the granulation mixture or before the compression to tablets. Currently no data about different types of disintegrants or the influence of TSG on the efficacy of disintegrants is available. It is also uncertain if different disintegrants perform equally with different APIs. As disintegrants are usually of polymeric nature and crosslinked to some extent, a further effect on the granule and tablet strength by binding effects is assumable. This arises the question if the absence of a binder and the use of a disintegrant as multifunctional excipient can lead to conformance of the desired CQAs.

For the tableting, only a lubricant is necessary, which does not need to be included in the mixture due to the possibility of external lubrication of the tableting tools.

Following these explanations, a binder and a disintegrant (and water) should be the only basically required excipients within powder mixtures for TSG processes. Certainly, there are APIs, which need some kind of stabilizers or glidants to be handled accurately. This is, however, not the focus of this thesis. When applying

high loads of API, the amount of excipients can only be small. Therefore, it has to be ensured that the excipients are powerful enough to overcome potentially poor compression properties of many APIs to result in stable tablets and to promote sufficient disintegration ability.

1.4 Aims of the thesis

The TSG process is a relatively new field in the pharmaceutical industry and the adaption into a continuous manufacturing environment is even more recent. Consequently, there are a lot of uncertainties and open questions regarding influences of formulation, CPPs and the interplay of both on CQAs of granules and tablets. Generally, not much work has been conducted with respect to the formulation. The purpose of most studies was to investigate the process itself, which was also of great importance. Furthermore, merely the granules and not the tablets as dosage form were of interest in several of these studies. For this reason, this thesis aims to discuss both, the formulation development for continuous TSG processes and the comprehension of the process, including feeding systems, with respect to the formulation.

In particular, the aims are as follows:

- Investigation of the influence of different feeder performances on the GSD of granules, to result in optimal GSDs. A new approach to assess the performance of feeding systems should be developed.

- Different formulations should be processed at different screw configurations with different RTDs as a result. For the RTDs, the application of an easy model should be tested.

- Evaluation of an innovative PAT-tool to monitor the feed-rate during the refill phase of a powder feeder. Thereby, a method to decrease the uncertainty while feeding unknown amounts of powder to the system should be established.

- Development of novel formulations focusing on high drug loads for TSG processes. The CQAs for this purpose should mainly be an appropriate GSD and strong tablets with disintegration times < 15 min, according to the definition of uncoated tablets by the United States Pharmacopeia and the European Pharmacopeia. Different disintegrants and two APIs with different mechanical behavior should be applied for this purpose.

- Establishment of a method to determine the fill-level of a twin-screw extruder and its adaption as an innovative CPP to control granule and tablet performance.

- Elucidation of underlying mechanisms and reasons for differing disintegrant performances with different APIs. Therefore, a variety of materials behaving mechanically different should be investigated and processed to granules and tablets.

1.5 Outline of the thesis

In this thesis, different unit operations of TSG based continuous manufacturing are applied. These operations, namely feeding, wet granulation, drying and tableting, are studied individually and should serve as anchor points for the industrial partner of this thesis, who is building up an end-to-end continuous manufacturing line.

In the second chapter of this thesis, the focus lays on the investigation of the influence of feeding systems, in particular the powder feeder, on the resulting GSD of wet granulated powders of different composition. A new methodology to evaluate the performance of feeding systems is introduced and the connection to the resulting GSDs at different screw configurations and RTDs is given. It is demonstrated that the feeder performance influences the GSD by different extent, depending on the screw configuration and the applied raw material.

With the knowledge of the crucial influence of feeding systems on the GSD and the unavoidably occurring blind phases of powder feeders within continuous processes, it becomes important to know about and to control the performance of powder feeders during the periodic refill. Chapter 3 gives an insight into the use of a novel PAT instrument, which was originally used in the energy-/coal- and waste industry to measure the throughput of fine and monodisperse coal-dusts. The microwave based sensor proves to be an adequate tool to monitor and perhaps to control the feed-rate during short refill phases of the feeder, but is currently not able to replace the principle of gravimetric feeding.

The experience of the feeder studies should help to generate mono-modal and narrow GSDs during the TSG trials. Prior to the TSG process, the powder feeder is always filled sufficiently, to avoid a refill during granulation. Formulations with high drug loads using the rather plastically deformable API ibuprofen and different disintegrants are produced in the trials, which are described in chapter 4. Almost all formulations result in mono-modal and narrow GSD. Depending on the disintegrant and the formulation used (with or without binder), different tablet strengths, disintegration times and dissolution profiles are achieved.

To exclude a coincidence in the successful development of simplified and high drug loaded formulations with the API ibuprofen, in chapter 5 a second and

mechanically different behaving API, namely the rather brittle hydrochlorothiazide is investigated for the applicability of simplified, high drug loaded formulations. The GSD and the strengths of the tablets again are sufficient but the results for the disintegration times of tablets show distinctive differences compared to ibuprofen. Again, a broad variety of disintegration times is achieved. Furthermore, for two formulations the disintegration time of tablets is identified to depend on the extruder fill-level during TSG.

The observed fill-level dependency, found during the experiments described in chapter 5, is further investigated in chapter 6 and shows in a detailed manner the interaction of formulation and CPPs. The specific feed load (SFL) is introduced as a surrogate for the fill-level of the twin-screw extruder. For the first time, the fill-level in TSG is measured and correlated with several CQAs of granules and tablets and different process parameters. It can be shown, that optimal values for the influence of the SFL on granule and tablet CQAs, such as median granule size, tensile strength and disintegration time exist.

The distinctively different results of ibuprofen and hydrochlorothiazide containing formulations in combination with crospovidone are the starting point for chapter 7. In this part of the thesis nine differently behaving APIs and three excipients, employed as pseudo APIs, are investigated for their behavior within simplified formulations containing crospovidone. This chapter provides insight into material dependencies of TSG processes with subsequent tableting for the first time. An explanation for the differing behavior is suggested.

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2. Granule size distributions after twin-screw granulation - do not forget the feeding systems

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2.1 Pretext

In literature, several studies dealt with the impact of different influences on resulting granule size distributions (GSD) after twin-screw granulation. The following study provides an insight into the influence of the performance of powder feeders on resulting GSD. A method for the offline assessment of the performance of feeding systems is introduced and different formulations, processesd with different screw configurations, are investigated for their susceptibility to variations in GSD, caused by powder feeder errors.

The following research paper has been published in the year 2016 by the European Journal of Pharmaceutics and Biopharmaceutics in Vol. 106 on pages 59-69.

Evaluation of the authorship:

author / co-author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Robin Meier	20	50	80	50	70
Markus Thommes	20	10	20	10	10
Norbert Rasenack	20	10	0	0	0
Klaus-Peter Moll	0	10	0	10	5
Markus Krumme	20	10	0	10	5
Peter Kleinebudde	20	10	0	20	10

Abstract

The aim of this study was to investigate the influence of qualitatively different powder feeder performances on resulting granule size distributions (GSD) after twin-screw granulation of a highly drug loaded, hydrophobic mixture and a mannitol powder. It was shown that powder feeder related problems usually cannot be identified by trusting in the values given by the feeder. Therefore, a newly developed model for the evaluation of the performance of powder feeders was introduced and it was tried to connect this model to residence time distributions in twin-screw granulation processes. The influence of feeder performances on resulting GSD varied, depending on the applied screw configuration and the used powder. Regarding the hydrophobic and highly drug loaded formulation, which was granulated at an L/S-ratio of 0.5, a pure conveying screw and a medium kneading configuration, consisting of 60° kneading blocks were negatively influenced by poor feeder settings. For optimal settings more narrow distributions could be obtained. For an extensive kneading configuration good and poor settings resulted in mono-modal GSDs but were differing in the overall size. Mannitol, a model substance for a liquid sensitive formulation was granulated at an L/S-ratio of 0.075. It was even more important to maintain optimal feeding as mannitol was highly affected by poor feeder performances. Even an extensive kneading configuration could not level the errors in powder feeder performance, resulting in qualitatively different GSDs. The results of this study demonstrate the importance of detailed knowledge about applied feeding systems to gain optimal performance in twin-screw granulation.

3. Implementation of microwave sensors in continuous powder feeding – a novel tool to bridge refill phases

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3.1 Pretext

The prior chapter provided the insight that powder feeder fluctuations can deteriorate CQAs of granules. One unsolved problem in continuous powder-feeding is the blind phase of gravimetric feeders during their refill. Especially during these phases, the susceptibility to errors in powder feeding is high, caused by a fast densification of powder in the feeder reservoir. This study provides a first approach to overcome this problem, by the implementation of microwave sensors, which are capable of measuring the mass flow of powder particles. Repeatability and stability of sensor signals are investigated and refill phases with powders of different size are conducted and monitored by the microwave sensors.

The following research paper has been submitted to Die Pharmazeutische Industrie: pharmind and is currently under review.

Evaluation of the authorship:

author / co-author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Robin Meier	0	60	50	70	70
Julia Harting	0	10	40	30	5
Jens Happel	80	10	10	0	5
Peter Kleinebudde	20	20	0	0	20

Abstract

In continuous processes gravimetric powder feeders need to be refilled, frequently and are temporarily not able to monitor and to control the feed-rate. Especially during these phases, the powder feeder is susceptible to deviations from its setpoint. To prevent negative influences on subsequent processes, there is a need for alternative methods to monitor the refill phases. Therefore, in the present work microwave sensors for the measurement of powder flow during continuous powder feeding of three excipients with different particle sizes were implemented as process analytical technology tool. Feeding of coarse dicalcium phosphate was measured in repetition, accurately. Sensor stability could be shown for coarse and fine dicalcium phosphate. Thereby, a bypass of the refill phase during feeding of fine dicalcium phosphate was easily possible. However, the applied microwave sensors were not able to replace the gravimetric feeding principle at present, as the inter-day precision during the feeding of coarse mannitol was not given. During refill of this material, the microwave signals deviated up to 6 % from the values, obtained by an external balance. Concluding, after these first trials, the microwave sensors showed promising results to bridge the gap of refill phases in continuous powder feeding in future, completely, and should be further investigated to result in the required performance.

4. Simplified formulations with high drug loads for continuous twin-screw granulation

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4.1 Pretext

This chapter is the starting point of the formulation development studies within this thesis and deals with the development of formulations, containing as little excipients and as high loads of API as possible. The API ibuprofen, alongside with different disintegrants at different L/S-ratios, is processed to granules and tablets. Results from the first two studies, dealing with feeding systems, provided the knowledge to achieve monomodal and narrow GSD. Furthermore, various analytics of other CQAs of granules and tablets prove the general applicability of simplified formulation for TSG and subsequent tableting using the API ibuprofen.

The following research paper has been published in the year 2015 by the International Journal of Pharmaceutics in Vol. 496 on pages 12-23. Divergent from the original document, the word "particle" was replaced by "granule" and the abbreviation "PSD" was replaced by "GSD" when applicable, to preserve uniformity within this thesis.

Evaluation of the authorship:

author / co-author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Robin Meier	0	50	90	70	70
Markus Thommes	20	10	10	10	2.5
Norbert Rasenack	30	10	0	0	0
Markus Krumme	30	10	0	0	2.5
Klaus-Peter Moll	0	10	0	0	5
Peter Kleinebudde	20	10	0	20	20

Abstract

As different batches of the same excipients will be intermixed during continuous processes, the traceability of batches is complicated. Simplified formulations may help to reduce problems related to batch intermixing and traceability.

Twin-screw granulation with subsequent tableting was used to produce granules and tablets, containing drug, disintegrant and binder (binary and ternary mixtures), only. Drug loads up to 90 % were achieved and five different disintegrants were screened for keeping their disintegration suitability after wetting.

Granule size distributions were consistently mono-modal and narrow. Granule strength reached higher values, using ternary mixtures. Tablets containing croscarmellose sodium as disintegrant displayed tensile strengths up to 3.1 MPa and disintegration times from 400 - 466 s, resulting in the most robust disintegrant. Dissolution was overall complete and above 96 % within 30 minutes. Sodium starch glycolate offers tensile strengths up to 2.8 MPa at disintegration times from 25 s – 1031 s, providing the broadest application window, as it corresponds in some parts to different definitions of orodispersible tablets. Tablets containing micronized crospovidone are not suitable for immediate release, but showed possibilities to produce highly drug loaded, prolonged release tablets.

Tablets and granules from simplified formulations offer great opportunities to improve continuous processes, present performances comparable to more complicated formulations and are able to correspond to requirements of the authorities.

5. Simplified, high drug loaded formulations containing hydrochlorothiazide for twin-screw granulation

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5.1 Pretext

After successful development and characterization of high drug-loaded, simplified formulations with the API ibuprofen, it has to be examined if these formulations are also functional with other APIs. Therefore, the API hydrochlorothiazide is chosen, which is also poorly soluble and features a predominantely brittle deformation behaviour, compared to the rather plastically deforming ibuprofen. Again, different disintegrants and L/S-ratios are applied during the manufacturing of granules and tablets, which subsequently are analyzed for GSD and tensile strength and disintegration time of tablets.

The following research paper has been submitted to Chemie Ingenieur Technik and is currently under review.

Evaluation of the authorship:

author / co-author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Robin Meier	20	60	100	60	70
Klaus-Peter Moll	30	10	0	10	5
Markus Krumme	30	10	0	10	5
Peter Kleinebudde	20	20	0	20	20

Abstract

Recently, simplified, high drug loaded formulations for use in twin-screw granulation and tableting have been introduced, using the plastically deforming drug ibuprofen. This concept was enlarged by application of the brittle drug hydrochlorothiazide, because opposed deformation behaviour was expected to result in different product performances. Indeed, in most instances results for hydrochlorothiazide differed to ibuprofen. Critical quality attributes like granule size distribution, disintegration time and tensile strength of tablets could be met. Different disintegrants varied the product performance. The study confirms the suitability of simplified formulation with differently behaving drugs for pharmaceutical product design in continuous manufacturing.

6. Impact of fill-level in twin-screw granulation on critical quality attributes of granules and tablets

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6.1 Pretext

The experiments, described in the previous chapter, indicated a dependency of CQAs of granules and tablets on the fill-level of the extruder during production of granules. To investigate this behavior in detail, a method to measure the fill-level of an extruder in TSG is introduced. A central composite DOE with the screw speed and the specific feed-load, which is a surrogate for the fill-level, is conducted. Various process and product attributes are described in dependency of the specific feed load, which gives insights into quantitative relations of extruder fill-level and CQAs of the products.

The following research paper has been submitted to the European Journal of Pharmaceutics and Biopharmaceutics and is currently under review.

Evaluation of the authorship:

author / co-author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Robin Meier	25	60	100	60	70
Klaus-Peter Moll	25	10	0	10	5
Markus Krumme	25	10	0	10	5
Peter Kleinebudde	25	20	0	20	20

Abstract

In a previous study a change of the fill-level in the barrel exerted a huge influence on the twin-screw granulation (TSG) process of a high drug loaded, simplified formulation. The present work investigated this influence systematically. The specific feed load (SFL) indicating the mass per revolution as surrogate parameter for the fill-level was applied and the correlation to the real volumetric fill level of an extruder could be demonstrated by a newly developed method. A design of experiments was conducted to examine the combined influence of SFL and screw speed on the process and on critical quality attributes of granules and tablets. The same formulation was granulated at constant liquid level with the same screw configuration and led to distinctively different results by only changing the fill-level and the screw speed. The power consumption of the extruder increased at higher SFLs with hardly any influence of screw speed. At low SFL the median residence time was mainly fill-level dependent and at higher SFL mainly screw speed dependent. Optimal values for the product characteristics were found at medium values for the SFL. Granule size distributions shifted from mono-modal and narrow shape to broader and even bimodal distributions of larger median granule sizes, when exceeding or falling below a certain fill-level. Deviating from the optimum fill-level, tensile strength of tablets decreased by about 25 % and disintegration times of tablets increased for more than one third. At low fill-levels, material accumulation in front of the kneading zone was detected by pressure measurements and was assumed to be responsible for the unfavored product performance. At high fill-levels, granule consolidation due to higher propensity of contact with the result of higher material temperature was accounted for inferior product performance. The fill-level was found to be an important factor in assessment and development of twin-screw granulation processes as it impacted process and product attributes enormously.

7. How deformation behaviour controls product performance after twin-screw granulation with high drug loads and crospovidone as disintegrant

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7.1 Pretext

The usage of crospovidone in simplified formulation with ibuprofen and hydrochlorothiazide resulted in contrary disintegration performances of tablets. For a rationale formulation development, it is important to understand the mechanisms behind these distinctively pronounced differences. Therefore, twelve different materials have been investigated for their behavior in combination with crospovidone in simplified formulations. Analytics of various raw material, granule and tablet properties lead to a classification of the materials, based on the deformation behaviour, and reveal, why excellent or poor disintegration performances arise for different types of material.

The following research paper has been published online on November 3rd, 2016 by the Journal of Pharmaceutical Sciences (DOI: 10.1016/j.xphs.2016.09.026). It is not yet published as a printed version.

Evaluation of the authorship:

author / co-author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Robin Meier	25	60	100	60	70
Klaus-Peter Moll	25	10	0	10	5
Markus Krumme	25	10	0	10	5
Peter Kleinebudde	25	20	0	20	20

Abstract

The present works deals with the quantitative influence of 12 different materials (active pharmaceutical ingredients and excipients as pseudo-active pharmaceutical ingredients) on critical quality attributes of twin-screw granulated products and subsequently produced tablets. Prestudies showed huge influence of the chosen model materials in combination with crospovidone on the disintegration behaviour of the resulting tablets, despite comparable porosities. This study elucidated possible reasons for the varying disintegration behaviour by intensively investigating raw material as well as granule and tablet properties. An answer could be found in the mechanical properties of the raw materials and the produced granules. Especially, through compressibility studies, the materials could be classified into materials with high compressibility, which deform rather plastically under compression stress and low compressible materials, which rather show breakage under compression stress. In general and under exclusion from (pseudo)-polymorphic transformations, brittle materials featured excellent disintegration performance, even at low resulting tablet porosities $< 8\%$, whereas mainly plastically deformable materials mostly did not show any disintegration at all. These findings have to be kept in mind in the development of simplified formulations with high drug loads, in which the active pharmaceutical ingredient predominantly defines the deformation behaviour of the granule.

8. Summary and outlook

This thesis is about continuous manufacturing based on TSG and deals with the production of granules, their further processing to tablets, and analytics of the process, the formulation and CQAs of the products. In order to achieve an understanding of these topics, the respective parts of this thesis illuminate process and formulation issues from different directions.

As a first step, the obtained GSD after a TSG process, which is an important CQA of granules, was investigated with respect to different powder feeder performances and screw configurations. Therefore, optimal and intentionally poor powder feeder performances were applied to two different formulations, which were either hydrophobic or hydrophilic and thus differently sensitive to the addition of water. The hydrophobic formulation consisted of 90 % (w/w) ibuprofen and 10 % croscarmellose sodium and the hydrophilic formulation consisted of pure mannitol. Three screw configurations with different types of elements were applied to vary the imparted shear energy and to vary the RTD of the process. To evaluate the powder feeder performances, a new methodology, which goes beyond the traditional information of the coefficient of variation, was developed. For the monitoring of the RTD, a new camera based inline tool was established and the applicability of a recent model to describe the RTD in a TSG process was proven to be superior to a long time established model. It is proposed that the new powder feeder evaluation and the RTD model can be connected in future to calculate and to forecast required powder feeder performances for a specific RTD. Results of this study showed that the powder feeder performance had a significant influence on the resulting GSD after TSG. For the hydrophobic, water insensitive formulation, which was granulated with an L/S of 0.5, the influence of the feeder setting decreased with imparted shear energy. At the medium stage of shear energy, which was provided by the application of one kneading zone, the poor feeder performance resulted in a bimodal and broad GSD, whereas the optimal performance achieved an almost mono-modal GSD. By the application of distributive flow elements, the feeder errors of the poor feeder performance could be levelled, with the result of a mono-modal and narrow GSD for poor and optimal feeder performances. For the hydrophilic and water sensitive formulation, which was granulated at an L/S of 0.075 at a higher throughput, compared to the hydrophobic formulation, higher screw speed and thus a lower median residence time, even distributive flow elements were not sufficient to level the differences in powder feeder performance. Mono-modal (optimal performance) and bimodal (poor performance) GSDs were the results of these trials.

The results from the first part of the thesis provided the insight that feeder fluctuations can alter CQAs of produced granules. Powder feeder fluctuations are especially anticipated in the refill-phase of feeders during a continuous process. In this phase, the operator or the control software are not aware about the delivered amount of powder, because the load cell of the feeder is deactivated. Therefore, a new inline PAT-tool, based on microwave signals was evaluated and tested for its applicability to bypass the periodically arising refill phases or even to replace the gravimetric control of powder feeders. In order to measure the feed-rate, the tool had to be calibrated against the actual feed-rate for each of the utilized powders. It became obvious that a replacement of the gravimetric technology by the PAT sensor is impossible at the current stage. Too many factors influence the resulting signal and make it susceptible to changes. For coarse dicalcium phosphate, the inter day reproducibility for the calibration was given but not for a coarse mannitol powder with a median particle size of 291 µm. However, for bypassing the refill phase, the sensor seemed applicable. For this purpose a calibration was conducted with data obtained during the usual feed phase, which then was used to monitor the feed-rate during the refill-phase. An external balance provided the reference values to confirm the accuracy of the obtained sensor results. A high accuracy for the monitoring of the refill phase of fine dicalcium phosphate and a slightly lower accuracy for the monitoring of the refill phase of coarse mannitol was detected. Thereby, interesting new applications in the framework of a closely meshed process monitoring strategy and a possible solution to overcome blind phases of powder feeders were given.

The knowledge of the feeder performances was implemented in the TSG of highly drug loaded and simplified formulations with ibuprofen and hydrochlorothiazide, which were granulated with different disintegrants at various L/S-ratios. In the majority of the cases, mono-modal and narrow GSDs could be obtained with yields for the tableting experiments, of up to 93 %. Formulations containing solely drug and disintegrant (binary) or an additional binder (ternary) were successfully granulated and yielded in most of the cases in strong tablets. Croscarmellose sodium was the most robust disintegrant for ibuprofen tablets with disintegration times ranging from 400-466 s, independent from the type of formulation (binary or ternary). Tensile strengths of these tablets were > 1.5 MPa (binary formulations) and > 2.5 MPa (ternary formulations). For hydrochlorothiazide tablets the disintegration performance was depending on the presence (700-793 s) or the absence (382-428 s) of a binder. The tensile strengths of all batches containing croscarmellose sodium lay in between 2-2.5 MPa. Using crospovidone as disintegrant, ibuprofen tablets showed no disintegration after 20 min (end of the test), in contrast to hydrochlorothiazide tablets, which showed disintegration times < 180 s, independent from binder addition and applied L/S-ratio. In case of ibuprofen tablets containing crospovidone, the tensile strengths were all around

1.5 MPa, whereas the tensile strengths of hydrochlorothiazide tablets varied from the binary (around 1 MPa) to the ternary (1.5-2.5 MPa) formulations. The usage of sodium starch glycolate as disintegrant resulted in very fast disintegrating tablets of ibuprofen in all binary mixtures (< 90s) and in L/S-ratio dependent disintegration times, when a binder was used (461-1031 s). Tensile strengths between 1.2 MPa and 1.5 MPa were achieved for the binary formulations and between 2.5 MPa and 3 MPa for the ternary formulations. For hydrochlorothiazide tablets in combination with sodium starch glycolate, the disintegration time was detected to depend on the fill-level of the extruder during TSG. At low fill-levels, which were used by default, a fluctuating product output rate of granules could be observed. The increase of the fill-level led to an improvement of the process, to a homogenization of the output rate and to a simultaneous improvement of the disintegration time from 620 s to 306 s for a binary formulation and from 937 s to 299 s for a ternary formulation. Tensile strengths were all between 2 MPa and 2.6 MPa, independent from the type of formulation and the fill-level of the extruder during TSG.

The findings of these two studies motivated a further investigation. The fill-level of an extruder was hypothesized to strongly impact the CQAs of granules and tablets. The simplified binary formulation containing sodium starch glycolate and hydrochlorothiazide was applied to investigate this. By introducing the SFL (a quotient of the feed-rate and the screw speed), a surrogate for the fill-level was used, which was anticipated to correlate linearly to the fill-level. To prove this, a novel method to measure the fill-level of an extruder during TSG was established. In the framework of a central composite DOE, the SFL and the screw speed were used as factors and were proven to affect granule and tablet CQAs, in spite of using the same formulation, which was granulated with the same L/S-ratio and the same screw configuration. Medium values for the SFL resulted in optimal values for the product CQAs within the limits of this DOE. GSDs shifted from mono-modal and narrow shape to broader and even bimodal distributions of larger median granule sizes, when exceeding or falling below a certain SFL. The tensile strength of tablets decreased by about 25 % and the disintegration times increased for more than one third, when deviating from the optimum SFL. The utilization of a pressure transducer as a PAT-tool provided the insight of material accumulation in front of a kneading zone, which was made responsible for an unfavored product performance at low SFL. A higher propensity of granule consolidation at higher SFL was accounted for according inferior product performance.

In a last step, the contrary performance of simplified formulations containing crospovidone was investigated further. To find a rationale for this contradictory behavior, nine different APIs and three excipients (as pseudo APIs) were processed to granules and tablets in simplified high drug loaded formulations. Tablets were compressed at six different compaction pressures and investigated for compactibility

and compressibility. The nine APIs could be classified into predominantly brittle and plastically deforming materials. Tablets containing brittle materials showed fast disintegration, despite tablet porosities of $< 8\%$. Tablets with plastically deforming materials in most instances did not show any disintegration at all. Exceptions were some materials which dissolved without force development of the disintegrant and some individual tablet batches that had high porosities and low tensile strengths. One material (caffeine), which originally behaved brittle, showed a pseudopolymorphic transformation to its hydrate form after TSG. The caffeine-hydrate was proven to behave plastically and the corresponding tablets did not show any disintegration at all. The hypothesis that material deformation behavior influences the disintegration performance within the used formulations was confirmed by the application of three excipients as pseudo APIs, which were known for their brittle or plastic deformation behavior. The reason for the distinctively differing performances was seen in the propensity of the granules to break under deformation stress, by which the crospovidone was deliberated out of the granules and could unfold its effect, after contact with water. In case the granules mainly deformed plastically, only minor parts of the crospovidone were available and it could not promote disintegration. The findings of this study can provide insight for a rationale development of TSG formulations with the aim to promote sufficient disintegration for every API, even if it behaves very plastic.

Continuous processes based on TSG are a relatively new field within the pharmaceutical technology. A lot of connections between material properties and the process are still rarely understood. As mentioned in different parts of this thesis, it is always difficult to draw general conclusions from conducted experiments with solely few formulations. Most of the findings from literature claimed to be generally applicable, but require the testing with a minimum of a second formulation, because throughout this thesis a strong material dependency of the granule and tablet performance could be shown. One example for it and an interesting topic, derived from this thesis could be the investigation of different performances with the disintegrant sodium starch glycolate. Similar to the disintegrant crospovidone, albeit not equally intensive, tablets with different APIs, showed different performances in combination with this disintegrant.

To create a larger picture of the connection of material properties (especially deformation behavior) and the process characteristics, it would be of great interest to set up research collaborations. The aim could be to establish and to provide generic basis formulations for each specific type of material and each desired CQA. Furthermore, differently sized machines with different geometries could be investigated with different basis formulations to increase and improve the understanding of TSG based continuous processes.

9. Zusammenfassung und Ausblick

Die vorliegende Arbeit handelt von der kontinuierlichen Herstellung von Granulaten und Tabletten auf Basis von Doppelschneckengranulation (TSG) und der Analyse von Prozess-, Zubereitungs- und kritischen Produktattributen. Zur Erlangung eines tiefgehenden Verständnisses der verschiedenen Bereiche beleuchten die einzelnen Kapitel dieser Arbeit Prozess- und Zubereitungsaspekte von verschiedenen Richtungen.

Zuerst wurden die Einflüsse der Dosiergenauigkeit von Pulverdosierern und der eingesetzten Schneckenkonfiguration im TSG-Prozess auf die resultierende Granulatgrößenverteilung (GSD), die ein wichtiges kritisches Qualitätsattribut (CQA) von Granulaten ist, untersucht. Dazu wurden zwei verschiedene Zubereitungen ausgewählt, die unterschiedlich sensitiv auf die Zugabe von Wasser reagieren. Die hydrophobe Zubereitung bestand zu 90 % (m/m) aus Ibuprofen und zu 10 % aus Croscarmellose-Natrium. Die hydrophile und somit sensitiv auf die Zugabe von Wasser reagierende Zubereitung bestand aus reinem Mannitol. Beide Zubereitungen wurden mit bewusst schlechten und mit optimalen Pulverdosiererleistungen granuliert. Es wurden drei verschiedene Schneckenkonfigurationen eingesetzt, die verschiedene Typen von Elementen beinhalteten, wodurch die eingebrachte Scherenergie und die resultierende Verweilzeitverteilung des Materials im Extruder variiert wurden. Um verschiedene Leistungen von Pulverdosierern besser bewerten zu können, wurde eine neue Methode entwickelt, die über die traditionelle Verwendung der relativen Standardabweichung hinausgeht. Für die inline Überwachung der Verweilzeitverteilung wurde ein neues kamerabasiertes Instrument erfolgreich implementiert. Darüber hinaus zeigte ein neueres Modell zur Beschreibung der Verweilzeitverteilung im TSG-Prozess seine Überlegenheit gegenüber einem lange etablierten Modell. Es wurde vorgeschlagen, dass die neue Methode zur Evaluation von Pulverdosierern mit dem Verweilzeitmodell verknüpft werden kann, um in Zukunft benötigte Pulverdosiererleistungen für spezifische Verweilzeitverteilungen voraus zu sagen. Die Ergebnisse der Studie haben gezeigt, dass die Leistung von Pulverdosierern einen signifikanten Einfluss auf die GSD nach einem TSG Prozess hat. Die hydrophobe Zubereitung, die nicht-sensitiv auf die Zugabe von Wasser reagiert, wurde mit einer Feuchte von 0,5 granuliert. Dabei sank der Einfluss der Dosiererleistung mit steigender eingebrachter Scherenergie. Bei einer mittleren eingebrachten Scherenergie durch die Benutzung von einer Knetzone resultierte die schlechte Dosiererleistung in einer bimodalen und breiten GSD. Die optimale Dosiererleistung führte hingegen zu einer fast monomodalen GSD. Durch die

Anwendung von distributiven Mischelementen konnten die Abweichungen des Pulverdosierers vom Sollwert, die bei der schlechten Dosiererleistung auftraten, ausgeglichen werden, woraus auch hier eine enge monomodale GSD resultierte. Die hydrophile Zubereitung, die sensitiv auf die Menge an zugegebenem Wasser reagiert, wurde mit einer Feuchte von 0,075, einem mit der hydrophoben Zubereitung verglichenen höheren Durchsatz, einer höheren Schneckendrehzahl und einer daraus resultierenden kürzeren mittleren Verweilzeit granuliert. Bei diesen Einstellungen reichte selbst eine Konfiguration mit distributiven Mischelementen nicht aus, um die Abweichungen des Pulverdosierers bei einer schlechten Dosiererleistung auszugleichen. Für die optimale Dosiererleistung resultierte eine monomodale und für die schlechte Dosiererleistung eine bimodale GSD.

Die Ergebnisse des ersten Kapitels dieser Arbeit haben gezeigt, dass Schwankungen der Leistung von Pulverdosierern die CQAs von hergestellten Granulaten beeinflussen können. Vor allem während der Nachfüllphase von Dosierern während eines kontinuierlichen Prozesses sind Schwankungen in der Dosierrate von Pulverdosierern zu erwarten. Während dieser Phase wissen der Bediener oder das Kontrollprogramm nichts über die aktuellen Dosierraten und über etwaige Fehler in diesen. Daher wurde ein neuartiges prozessanalytisches Messgerät, das auf Mikrowellensignalen basiert, auf die Möglichkeit getestet, diese periodisch wiederkehrenden Nachfüllphasen zu überbrücken oder sogar die gravimetrisch kontrollierte Pulverdosierung zu ersetzen. Um Pulverdosierraten messen zu können, musste das Gerät für jedes benutzte Pulver gegen die jeweiligen Dosierraten kalibriert werden. Es wurde deutlich, dass ein Ersatz der gravimetrischen Dosiertechnik für die Mikrowellensensoren momentan unmöglich ist. Für den Einsatz von grobem Dicalciumphosphat wurde eine Reproduzierbarkeit der Kalibrierung an verschiedenen Tagen erreicht, jedoch nicht für grobes Mannitol einer medianen Partikelgröße von 291 μm. Allerdings zeigte sich, dass der Sensor geeignet war, um die Nachfüllphase von Pulverdosierern zu überwachen. Dazu wurde die Kalibrierung der Sensoren mit den Daten durchgeführt, die während der normalen Dosierphase erhalten wurden. Sobald die Nachfüllphase eingeleitet wurde, wurde die vorangegangene Kalibrierung benutzt, um die Dosierung mittels Mikrowellensensoren zu überwachen. Eine zusätzliche Waage, auf die das Pulver dosiert wurde, lieferte einen externen Bezugswert und zeigte die Richtigkeit der Sensorsignale. Dabei wurde eine hohe Richtigkeit für die Überwachung der Nachfüllphase von feinem Dicalciumphosphat und eine etwas geringere Richtigkeit für Überwachung der Nachfüllphase von grobem Mannitol erhalten. Dadurch konnten interessante neue Anwendungen im Rahmen eines engmaschig kontrollierten Prozesses und eine Möglichkeit zur Überbrückung der Blindphase von Pulverdosierern gezeigt werden.

Die gesammelten Erfahrungen bezüglich der Dosiererleistung wurden auf die TSG von vereinfachten Zubereitungen angewendet, die hohe Arzneistoffbeladungen aufwiesen. Die Arzneistoffe Ibuprofen und Hydrochlorothiazid wurden dabei mit verschiedenen Zerfallhilfsmitteln unter Anwendung von verschiedenen Feuchten granuliert. In den meisten Fällen wurden dabei monomodale und enge GSD mit Ausbeuten für die Tablettierung von bis zu 93 % erreicht. Zubereitungen, die lediglich aus Arzneistoff und Zerfallhilfsmittel (binär) oder zusätzlich aus einem Bindemittel (ternär) bestanden, konnten erfolgreich granuliert werden und resultierten in den meisten Fällen in festen Tabletten. Croscarmellose-Natrium war das robusteste Zerfallhilfsmittel für Tabletten mit Ibuprofen und zeigte Zerfallszeiten von 400-466 s, unabhängig davon, ob mit oder ohne Bindemittel granuliert wurde. Die Druckfestigkeiten dieser Tabletten waren größer als 1,5 MPa (binäre Zubereitungen) beziehungsweise größer als 2,5 MPa (ternäre Zubereitungen). Für Tabletten mit dem Arzneistoff Hydrochlorothiazid hing die Zerfallszeit davon ab, ob ein Bindemittel benutzt wurde (700-793 s) oder nicht (382-428 s). Die Druckfestigkeiten der Tabletten waren dabei unabhängig von einem zugesetzten Bindemittel und lagen zwischen 2 und 2,5 MPa. Bei der Anwendung von Crospovidon als Zerfallhilfsmittel zeigten Tabletten, die Ibuprofen enthielten, keinen Zerfall innerhalb von 20 min (Ende des Tests). Im Gegensatz dazu zerfielen entsprechende Tabletten mit Hydrochlorothiazid in weniger als 180 s, unabhängig von der Nutzung eines Bindemittels und von der eingestellten Feuchte. Im Falle der Ibuprofen-Tabletten lagen alle Druckfestigkeiten im Bereich von 1,5 MPa, wohingegen sich die Druckfestigkeiten der Hydrochlorothiazid-Tabletten der binären (um 1,5 MPa) und ternären (1,5-2,5 MPa) Zubereitungen unterschieden. Die Verwendung von Carboxymethylstärke-Natrium als Zerfallhilfsmittel führte zu schnell zerfallenden Ibuprofen-Tabletten aus den binären Zubereitungen (< 90 s) und zu Zerfallszeiten, die von der angewendeten Feuchte und resultierenden Bindemittelmenge abhingen, im Falle der ternären Zubereitungen (461-1031 s). Druckfestigkeiten von 1,2-1,5 MPa wurden für die binären Zubereitungen und von 2,5-3 MPa für die ternären Zubereitungen erreicht. Für Tabletten mit dem Wirkstoff Hydrochlorothiazid wurde gefunden, dass die Zerfallszeiten von dem Füllgrad des Extruders während der Granulierung abhingen. Bei den standardmäßig angewandten niedrigen Füllgraden resultierte ein fluktuierender Auswurf der Granulate aus dem Extruder. Die Erhöhung des Füllgrades führte zu einer Verbesserung des Prozesses, zu einer Vergleichmäßigung des Granulatauswurfs und einer gleichzeitigen Verringerung der Zerfallszeiten von 620 s auf 306 s für binäre Zubereitungen und von 937 s auf 299 s für ternäre Zubereitungen. Die Druckfestigkeiten aller Tablettenchargen lagen zwischen 2 MPa und 2,6 MPa, unabhängig von der Zubereitung und dem Füllgrad des Extruders.

Die Erkenntnisse dieser zwei Studien regten weitere Untersuchungen an. Es wurde die Arbeitshypothese getroffen, dass der Füllgrad eines Extruders die CQAs von

Granulaten und Tabletten stark beeinflussen kann. Um diese Annahme zu untersuchen, wurde die binäre Zubereitung aus Hydrochlorothiazid und Carboxymethylstärke-Natrium verwendet. Um den Füllgrad zu untersuchen und einzustellen, wurde die Beladungskennzahl (SFL), welche ein Quotient aus Dosierrate und Schneckendrehzahl des Extruders ist und sich nach theoretischen Überlegungen linear zum Füllgrad verhalten sollte, als Surrogatparameter herangezogen. Um diese Linearität zu überprüfen, wurde erstmals eine Methode zur Messung des Füllgrads bei der TSG entwickelt. Im Rahmen eines statistischen Versuchsplans, in dem SFL und Schneckendrehzahl als Faktoren benutzt wurden, konnte deren Einfluss auf CQAs von Granulaten und Tabletten gezeigt werden, obwohl bei allen Versuchen dieselbe Zubereitung mit derselben Schneckenkonfiguration bei derselben Feuchte granuliert wurde. Mittlere Werte für die SFL führten zu optimalen Produkteigenschaften im Rahmen dieses Versuchsplans. GSDs verschoben sich von engen und monomodalen Verteilungen zu breiteren und bimodalen Verteilungen, wenn eine bestimmte SFL über- oder unterschritten wurde. Die Druckfestigkeit von Tabletten sank um 25 % und die Zerfallszeit verlängerte sich um mehr als ein Drittel, wenn von der optimalen SFL abgewichen wurde. Die Anwendung eines Druckmessumformers als prozessanalytisches Instrument lieferte die Erkenntnis, dass ein Materialstau vor einer Knetzone stattfand, der verantwortlich für das unerwünschte Produktverhalten bei niedriger SFL gemacht wurde. Die unterlegenen Produkteigenschaften bei hohen SFL wurden mit der erhöhten Möglichkeit der Verdichtung der Granulate bei hohen SFL begründet.

Zuletzt wurde das gegensätzliche Verhalten von vereinfachten Zubereitungen, die Crospovidon enthalten, untersucht. Um Gründe für dieses Verhalten zu finden, wurden neun verschiedene Arzneistoffe und drei Hilfsstoffe (als Pseudo-Arzneistoffe) innerhalb vereinfachter hochbeladener Zubereitungen zu Granulaten und Tabletten verarbeitet. Die Tabletten wurden bei sechs verschiedenen Pressdrücken hergestellt und bezüglich Kompaktibilität und Kompressibilität untersucht. Die neun Arzneistoffe konnten in vornehmlich sprödbrüchiges und vornehmlich plastisches Deformationsverhalten klassifiziert werden. Tabletten, die vornehmlich sprödbrüchige Arzneistoffe enthielten, zeigten kurze Zerfallszeiten trotz Porositäten, die teilweise kleiner als 8 % waren. Tabletten, die vornehmlich plastisch verformbare Arzneistoffe enthielten, zeigten größtenteils überhaupt keinen Zerfall. Ausnahmen bildeten Arzneistoffe, die sich ohne Kraftentwicklung auflösten, und einzelne Tablettenchargen, die eine geringe Festigkeit bei hoher Porosität aufwiesen. Der sprödbrüchige Arzneistoff Coffein verhielt sich nach der TSG und dadurch ausgelöster pseudopolymorpher Transformation zum Hydrat plastisch, woraufhin die Tabletten mit diesem Arzneistoff keinen Zerfall zeigten. Die Hypothese, dass Tabletten aus sprödbrüchige Materialien innerhalb dieser Basiszubereitung Zerfall zeigen und plastisch verformbare Materialien keine Zerfall zeigen, wurde durch den

Einsatz von drei Hilfsstoffen mit bekanntem Deformationsverhalten bestätigt. Der Grund für dieses unterschiedliche Verhalten wurde in der verschieden ausgeprägten Neigung der produzierten Granulate gesehen, unter Druck zu brechen. Durch den Bruch der Granulate bei der Tablettierung konnte das Zerfallhilfsmittel Crospovidon aus den Granulaten gelangen, frei zur Verfügung stehen und die zerfallsfördernde Wirkung bei Kontakt mit Wasser entfalten. Im Falle einer vornehmlich plastischen Verformung der Granulate wurden lediglich geringe Mengen des Zerfallhilfsmittels aus den Granulaten freigesetzt, wodurch kaum eine oder keine zerfallsfördernde Wirkung erzielt werden konnte. Die Ergebnisse dieser Studie können dabei helfen, Zubereitungen für die TSG zu entwickeln, die Tabletten mit jedem Arzneistoff zum Zerfall bringen, unabhängig vom Materialverhalten.

Die kontinuierliche Herstellung auf Basis von TSG ist ein vergleichsweise neuer Bereich in der Pharmazeutischen Technologie. Viele Zusammenhänge zwischen Material- und Prozesseigenschaften sind noch nicht richtig untersucht und verstanden. Wie bereits in verschiedenen Teilen dieser Arbeit beschrieben, ist es schwierig, generalisierte Schlussfolgerungen aus durchgeführten Experimenten mit nur wenigen benutzten Zubereitungen zu ziehen. Die meisten Erkenntnisse, die in der Literatur beschrieben und zum Teil generalisiert wurden, benötigen mindestens die Bestätigung durch die Verarbeitung einer weiteren Zubereitung. Denn wie in dieser Arbeit gezeigt wurde, besteht eine starke Abhängigkeit der erzielten CQAs von Granulaten und Tabletten von den Eigenschaften der verwendeten Materialien. Ein Beispiel dafür und gleichzeitig ein weiteres interessantes von dieser Arbeit abgeleitetes Thema könnte die Untersuchung von verschieden starken Wirkungen des Zerfallhilfsmittels Carboxymethylstärke-Natrium sein. Ähnlich wie das Zerfallhilfsmittel Crospovidon, wenn auch nicht gleich stark ausgeprägt, zeigte dieses Zerfallhilfsmittel ein unterschiedliches Verhalten mit verschiedenen Arzneistoffen.

Um ein vollständiges Bild vom Zusammenhang der Materialeigenschaften (im Besonderen der Deformationseigenschaften) und der Herstellungsprozesse zeichnen zu können, wäre es hochinteressant, Forschungskollaborationen zu starten. Ein Ziel könnte die Einführung und Bereitstellung von Basiszubereitungen sein, die für jeden spezifischen Materialtypen die gewünschten CQAs liefern. Weiterhin könnten unterschiedlich skalierte Maschinen mit verschiedenen Geometrien und Basiszubereitungen untersucht werden, um das Verständnis von TSG basierten kontinuierlichen Herstellungsprozessen zu verbessern.

10.   List of original publications

1. Robin Meier, Markus Thommes, Norbert Rasenack, Markus Krumme, Klaus-Peter Moll, Peter Kleinebudde
Simplified formulations with high drug loads for continuous twin-screw granulation
International Journal of Pharmaceutics, Volume 496, Issue 1, December 2015, Pages 12-23.

2. Robin Meier, Markus Thommes, Norbert Rasenack, Klaus-Peter Moll, Markus Krumme, Peter Kleinebudde
Granule size distributions after twin-screw granulation – do not forget the feeding systems
European Journal of Pharmaceutics and Biopharmaceutics, Volume 106, September 2016, Pages 59-69.

3. Robin Meier, Klaus-Peter Moll, Markus Krumme, Peter Kleinebudde
How deformation behaviour controls product performance after twin-screw granulation with high drug loads and crospovidone as disintegrant
Journal of Pharmaceutical Sciences, published online: November 3rd, 2016 (DOI: 10.1016/j.xphs.2016.09.026).

4. Robin Meier, Klaus-Peter Moll, Markus Krumme, Peter Kleinebudde
Simplified, high drug loaded formulations containing hydrochlorothiazide for twin-screw granulation
submitted to: Chemie Ingenieur Techik, September 2016.

5. Robin Meier, Klaus-Peter Moll, Markus Krumme, Peter Kleinebudde
Impact of fill-level in twin-screw granulation on critical quality attributes of granules and tablets granulation
submitted to: European Journal of Pharmaceutics and Biopharmaceutics, September 2016.

6. Robin Meier, Julia Harting, Jens Happel, Peter Kleinebudde
Implementation of microwave sensors in continuous powder feeding – a novel tool to bridge refill phases
submitted to: Die Pharmazeutische Industrie: pharmind, September 2016.

11.   Contributions to meetings

11.1   Oral presentations

1. Robin Meier, Markus Thommes, Norbert Rasenack, Markus Krumme, Peter Kleinebudde
   Simplified, high drug-load formulations in twin-screw wet granulation processes - impact of disintegrant type
   8th Annual PSSRC Symposium, Ljubljana, Slovenia, 2014

2. Robin Meier, Markus Thommes, Norbert Rasenack, Markus Krumme, Klaus-Peter Moll, Peter Kleinebudde
   Monomodal particle size distributions in twin-screw granulation - do not forget the feeding systems
   7th International Granulation Workshop, Sheffield, United Kingdom, 2015

3. Robin Meier, Klaus-Peter Moll, Markus Krumme, Peter Kleinebudde
   Influence of fill-degree of a twin-screw granulator on granule and tablet performance
   9th Annual PSSRC Symposium, Ghent, Belgium, 2015

4. Robin Meier, Klaus-Peter Moll, Markus Krumme, Peter Kleinebudde
   Feuchtgranulierung im Doppelschneckengranulierer - Einfluss von Füllgrad und Verweilzeit auf die Produktqualität
   Jahrestreffen der ProcessNet-Fachgruppen Agglomerations- und Schüttguttechnik, Mehrphasenströmungen und Computational Fluid Dynamics, Bingen, Germany, 2016

11.2   Poster presentations

1. Robin Meier, Christian Muehlenfeld, Markus Thommes
   Evaluation of continuous powder feeding
   9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lisbon, Portugal, 2014

2. Robin Meier, Markus Thommes, Norbert Rasenack, Markus Krumme, Peter Kleinebudde
   Impact of liquid feeders on particle size distributions in a twin-screw granulation process
   9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lisbon, Portugal, 2014

3. Robin Meier, Peter Kleinebudde
   Performance evaluation of powder feeders - small scale feeding as a challenge
   DPhG Jahrestagung, Duesseldorf, Germany, 2015

4. Robin Meier, Markus Krumme, Klaus-Peter Moll, Peter Kleinebudde
   High drug loads in twin-screw granulation - crospovidone as suitable disintegrant for every drug?
   AAPS Annual Meeting and Exposition, Orlando, FL, USA, 2015

5. Robin Meier, Markus Krumme, Klaus-Peter Moll, Peter Kleinebudde
   API depending performance of crospovidone at high drug loads in continuous wet-granulation
   10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Glasgow, United Kingdom, 2016

6. Robin Meier, Julia Harting, Juri Salomatin, Jens Happel, Guenter Koerblein, Morten Schlothauer, Peter Kleinebudde
   Monitoring of continuous powder feeding by a microwave sensor - tackling problems of gravimetric feeders
   10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Glasgow, United Kingdom, 2016

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