GHENT UNIVERSITY

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FORMULATION DESIGN FOR CONTINUOUS TWIN SCREW WET GRANULATION

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“In den Wissenschaften ist viel Gewisses,
sobald man sich von den Ausnahmen nicht irremachen lässt
und die Probleme zu schätzen weiß.“

Johann Wolgang von Goethe

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Nina

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OBJECTIVES

For decades, the pharmaceutical industry has relied on batch-wise manufacturing for the production of solid dosage forms. In the recent years, however, continuous manufacturing became of interest due to its potential for rapid and efficient development, advanced process control and time-scaling. In view of solid dosage form production, some well-established unit operations are continuous by nature following the first-in first-out principle, e.g. tablet compression or roller compaction. In contrast, for wet granulation the batch-wise working principle using fluid bed or high shear wet granulation (HSWG) techniques is still widely applied in pharma. Continuous wet granulation technologies are now emerging as an alternative wet granulation technology to realize the concept of a fully integrated continuous manufacturing line.

In view of a Quality by Design (QbD) -based product and process design, an understanding of the influence of formulation characteristics on the critical drug product quality attributes as well as on the process performance is needed. Formulation attributes and process parameters are interrelated and can impact the products' quality attributes and thus also safety and efficacy of the medicines. Being an established granulation technology for decades, profound knowledge for formulation development on a HSWG process is available within the pharmaceutical industry. Comparing continuous twin screw wet granulation with HSWG, the shorter granulation time of <10 seconds (continuous) in contrast to 15-30 minutes (batch high shear) can be considered as one of the most crucial differences. Taking the shorter granulation time into account, the question arises if the knowledge about formulation processability and excipient influence on drug product quality attributes are comparable for HSWG and continuous wet granulation technology.

In recent years numerous studies in industry and academia investigated the influence of process parameters on process and product performance for continuous twin screw wet granulation (further details are provided in chapter 1). However, at the start of this PhD project there were few studies published regarding the impact of excipients and formulations to provide sound knowledge for formulation design in a continuous twin screw wet granulation process (Figure 1).

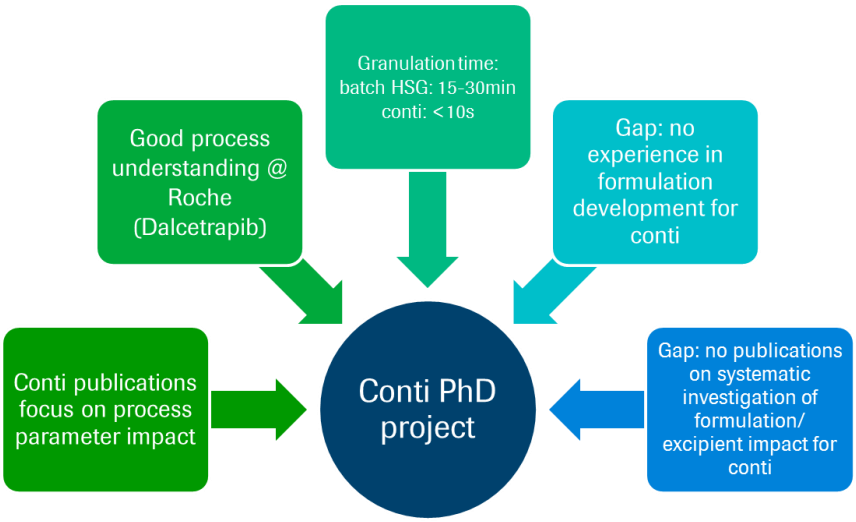

Figure 1. Main drivers for PhD project objectives

The overall objective of this research project was to understand the influence of excipient characteristics on drug product attributes and process performance of a continuous twin screw wet granulation process in order to support a QbD-based formulation design. The study was focused on commonly known pharmaceutical fillers and binders. A combination of principal component analysis (PCA) and design of experiments (DoE) was applied as systematic experimental approach in order to cope with the multitude of variables (i.e. attributes of these pharmaceutical excipients): PCA as a tool for multivariate data analysis helps to analyse large amounts of data (e.g. excipient characteristics), to extract the most relevant information out of a data set as well as to identify similarities and differences among the excipients. This understanding was used to enable systematic variation of formulation characteristics in a DoE using the continuous wet granulation technology. The resulting statistical models allowed to link the excipient characteristics with the process and product performance to support an advanced formulation design. The knowledge gained through this project is moreover intended for formulation optimization and trouble shooting by applying the predictive power of statistical models. In scope of this work were pharmaceutical fillers and binders which are typically used for wet granulation purposes, since these functional groups of excipients have a major impact on formulation characteristics as they are often the major fraction in the formulation. Finally, the focus of this work was to understand which excipients are suited best for continuous wet granulation. Out of scope were functional excipients like disintegrants, lubricants or glidants.

CHAPTER 1

INTRODUCTION: CONTINUOUS MANUFACTURING OF SOLID DOSAGE FORMS

1. Continuous manufacturing in the pharmaceutical industry

Pharmaceutical manufacturing activities must be compliant with good manufacturing practice (GMP) regulations. Compared to other industries, the pharmaceutical sector can thus be considered highly regulated, since health authorities request a consistent supply of high quality drug products such that medicines are at all times available to the patients [1],[2]. The traditional and conservative batch-wise manufacturing principle which is widely implemented in pharmaceutical industry has therefore not been questioned for drug product manufacturing. In contrast, other industries like mining, paper production or production of chemicals already started to apply continuous manufacturing principles in the times of the Industrial Revolution [3]. However, due to competition from generic manufacturers and increasing development costs, pharmaceutical companies are currently pushed towards the implementation of more efficient manufacturing principles [4]. Furthermore, leading health authorities are also encouraging Pharmaceutical Manufacturers to implement continuous manufacturing [5].

In a batch manufacturing process the raw materials are charged in the beginning of the process. During processing, no ingredients will leave or be added to the system. At the end of the process, all processed material is discharged at once. The material passes several sequential unit operations until the final drug product is obtained. Between the unit operation steps, the intermediates are stored and undergo in-process control checks to ensure that the desired quality is obtained. In contrast, during a continuous manufacturing process raw materials are continuously charged and the product is continuously discharged from the manufacturing line based on the first-in first-out principle. Process parameters as well as raw material, intermediate and product quality are consistently monitored during processing, which offers the opportunity for rapid detection of adverse events and real-time adjustments in the process via feedback loops [1],[4].

Reacting to the overall change in the pharmaceutical industry from high volume blockbuster products to low volume and often high potent products for niche markets, the manufacturing infrastructure has to be revised towards smaller and more agile facilities. Therefore, significant investments in developing continuous manufacturing have been made in pharma as well as in academia during the last decade, aiming to benefit from the advantages and opportunities of continuous manufacturing processes [6].

2. Advantages and opportunities of continuous manufacturing

2.1. Rapid & efficient development

Continuous manufacturing offers the opportunity for savings in active pharmaceutical ingredient (API), which reduces costs during the product development phase [3]. The API savings result from the facts that the processing unit in a continuous manufacturing process

typically requires only small amounts of materials in process at a time and quick changes of process parameter settings are possible. Hence, experiments can be performed with a limited amount of API. Batch processes usually undergo several scale-up steps from small scale to the commercial scale equipment. As normally the impact of scale is considerable, additional development experiments after a scale up step are required resulting in an iterative development approach which consumes considerable amounts of API, time and resources. Continuous manufacturing limits the scale-up issues since instead of moving to a larger equipment size to increase the batch size, simply the process run-time can be increased to manufacture larger amounts of drug product with the same equipment [7]. Consequently, the overall development time can be reduced which is in particular beneficial for products with accelerated development timelines, supporting a faster access to market.

2.2. Increased flexibility and cost effectiveness

Compared to batch processes, continuous manufacturing enables a reduction in equipment footprint since the design of the equipment is usually more compact. Thus, a smaller equipment has a higher production capacity compared to a batch line. In addition, space for storage of intermediates is reduced due to a direct conversion of raw materials into drug product in continuous manufacturing lines. Also lab space needed to conduct off-line in-process controls becomes redundant when switching to continuous manufacturing processes by implementing on-line quality controls. Overall, continuous manufacturing results in smaller and more effective manufacturing facilities. Due to the smaller foot print of continuous manufacturing facilities, they can be installed in portable containers and shipped to different locations around the world. This highly flexible set-up allows a quick change of manufacturing locations and to get the line ready for production in very short times compared to standard batch processes. The so-called PCMM® (portable, continuous, miniature, and modular) system was developed by Pfizer (in collaboration with GEA Pharma Systems and G-CON Manufacturing). This system is an autonomous “pod-based” GMP cleanroom facility for continuous oral solid dosage form manufacturing to be installed in any standard warehouse space [8],[9],[10].

Making use of on-line process control, the intermediate and product quality is consistently monitored, offering the possibility to adjust process parameter in order to prevent out-of-specification events or to reject parts of the material. This provides the opportunity to run the process in unattended operation mode when it is in a state of control such that personnel costs can be reduced. Savings in staff can in addition be achieved by real-time-release-testing (RTRT) as it can partly or fully replace end product testing. On the other hand, the development, validation and maintenance of on-line PAT (process analytical technology) methods can be labour intensive. Quality checks for batch processes are usually performed after completion of a unit operation which puts the entire batch at risk for failure and thus rejection [4],[11]. A continuous manufacturing process with online monitoring of

CQAs and tracking of product attributes throughout the manufacturing line allows in a failure mode to only reject the amount of material, which was affected by the failure mode.

The commercial drug product demand naturally changes along a product lifecycle and also the success of clinical indications can change substantially the commercial volumes of a product. A fixed commercial batch size defined at registration of the product may therefore not be optimal to ensure an efficient market supply and hence a scale-up and tech transfer to larger equipment might be necessary, which means a major technical effort under regulatory oversight. A continuous manufacturing line, however, is flexible in batch size (provided that a flexible batch size is successfully approved by regulatory agencies) and supports an optimal supply throughout the whole product lifecycle which mitigates supply risks. In conclusion, continuous processing provides agility to support a cost efficient and flexible market supply.

2.3. Improved drug product quality

The ICH Q8 guideline about pharmaceutical development states that quality should be designed into the product by generating and applying process and formulation understanding [12]. This process and formulation understanding is typically generated in a risk-based approach by performing experimental studies, preferably in a multivariate manner (design of experiments, DoEs). One of the strengths of continuous manufacturing (as described above) is that it allows to perform experiments on the commercial equipment with less API and in shorter time. Thus, with an existing stock of API and limited resources more experiments can be performed and, as a consequence, a better process understanding can be generated. In addition, continuous manufacturing processes are typically accompanied by real time process monitoring of critical quality attributes with PAT. The additional information provided by PAT provides an advanced level of process control and understanding during the product development phase and finally supports also a higher level of quality assurance in the frame of an attribute-based control strategy. First, with in-line, on-line or at-line PAT tools a higher proportion of intermediates and final product undergoes quality monitoring compared to the small proportion of samples that is taken from a batch process for offline IPC and quality control testing. Second, a better process understanding is also available at the time of filing and validation since due to the absence of scale-up effects for continuous processes the process understanding which was gained during development phase is fully representative for the commercial process. On the contrary, in batch manufacturing the majority of the experimental data that is collected during process development is typically generated at a scale which is significantly below the commercial scale and therefore associated with questionable relevance for the commercial process. The nature of a continuous manufacturing process allows to implement feed-forward or feedback loops to account for raw material variability, resulting in a more consistent quality of the final drug product and a mitigation of out-of-specification (OOS) events. Also - except for the start-up and shut down phase - continuous processes naturally

run in a steady-state, where the process condition experienced by the material is very constant and thus leads to a very constant product quality [1],[4].

3. Challenges for the pharmaceutical industry regarding the implementation of continuous manufacturing

Besides all advantages offered by continuous manufacturing, there are still significant hurdles to be overcome, slowing down the implementation of continuous processes in the pharmaceutical industry. Some aspects are discussed in the following section [1],[4],[13],[14],[15].

The implementation of continuous manufacturing is oftentimes considered as a ’disruptive’ change, since first, new equipment has to be purchased to replace existing operative batch equipment, and second, since the implementation of continuous manufacturing completely changes the way a product is developed, manufactured and controlled. Factories might need to be (re-) designed to match the requirements of continuous manufacturing lines. In addition, process knowledge has to be build up for the new continuous technology to support an efficient formulation design and the development of robust processes. Operators have to be trained in machine handling according to new or revised operation procedures. A control strategy is needed to ensure the process is in a state of control and is consistently capable of manufacturing high quality product. Hence, suitable analytical techniques and appropriate places for implementing checks of critical quality attributes within the process stream must be identified. For consistent process monitoring, the in-line application of PAT is useful as a probe can be directly inserted into the product stream to monitor critical quality attributes of intermediates in a non-destructive way as the product is manufactured. To define the most appropriate spots in the process stream for quality control tests, aspects like penetration depth of the measurement signal, the potential for probe fouling (i.e. product adhering to the measurement interface) and the impact on the product or process have to be considered. Moreover, the sample size and frequency must be defined to statistically represent the production volume as well as to ensure sufficient resolution to be able to detect deviations in quality which for example result from process disturbances or failure modes. Therefore, it is helpful to take process knowledge like the residence time distribution into account. In the event of PAT failure, the control strategy should include back-up tests to maintain consistent quality control. Different spectroscopic and non-spectroscopic techniques have already proven their usefulness for in process analysis. Near infrared (NIR) spectroscopy is applied to measure blend uniformity of powder blends and content uniformity of tablets as well as moisture content of granules and powders. Raman spectroscopy is suitable to monitor the solid state properties of APIs (e.g. phase transformation during wet granulation). High speed cameras and focused beam reflection (FBR) measurement techniques were successfully applied to measure particle size distribution of granules. The quality of film-coated tablets can for example be tested via digital imaging methods. Overall, the strong focus on on-line process monitoring and control

via PAT requires a different skill set in pharmaceutical development and manufacturing in order to develop, validate and maintain the models which are needed to apply PAT in continuous processes.

Due to the lack of experience, there are some regulatory uncertainties in view of the implementation of continuous manufacturing in the pharmaceutical industries. FDA and EMA encourage pharmaceutical manufacturers towards continuous manufacturing. However, for rest of the world (ROW) countries there is the risk for a delay in filing due to the uncertainty about regulatory acceptance or even a potential non-acceptance. In any case, early and frequent discussions with authorities during development activities will facilitate the acceptance.

Overall, the above-described activities initially require substantial investments in resources and equipment. Hence, a convincing business case analysis is needed to support the decision to switch from batch processes to fully integrated continuous processes.

Despite these remaining challenges, the advantages of continuous manufacturing clearly prevail and examples of continuously produced products which already received approval from health authorities and which are available on the market (e.g. from Janssen or Vertex [16]) show that the above mentioned hurdles can be overcome. In July 2015, the FDA approved Vertex© ”Orkambi”, a pharmaceutical product against cystic fibrosis. Manufactured in a facility in Boston, it was the first product which was manufactured via continuous wet granulation technology to receive approval [17]. The manufacturing line is based on the GEA technology [18]. Moreover, it was announced in March 2016 that Vertex and Hovione (a company offering contract manufacturing services) decided to partner: Hovione is going to install a commercial-scale continuous manufacturing facility in its plant in New Jersey in order to support Vertex in continuously manufacturing their approved products in the future [19]. In April 2016, Janssen received the FDA approval (and EMA approval in 2017) to switch production of their HIV drug product “Prezista™” from batch to a full-scale continuous direct compression process in its manufacturing facility in Puerto Rico. The switch from batch to continuous manufacturing reduced the 2 weeks production time to one day [20],[21]. Other pharmaceutical companies like Pfizer and GSK implement continuous manufacturing in research and development. GSK has built a 50 Mio $ continuous manufacturing plant for API production in Singapore. The PCMM® system for continuous oral solid dosage form manufacturing is operative at Pfizer`s manufacturing unit in Groton (Connecticut, USA) and a next-generation design of this system will be developed in collaboration with GSK who can provide beneficial experience and expertise in continuous processing [8],[9],[10],[18],[22].

Regarding all the advantages continuous manufacturing offers, the ICH is currently in the process to develop a new guideline (ICH Q12) to facilitate the implementation of continuous manufacturing processes across the pharmaceutical industry [23].

4. Continuous drug product manufacturing of solid dosage forms

Among the solid dosage forms tablets are widely applied due to their advantages, such as convenient administration for patients, dosing accuracy, stability and relatively low costs. A number of different technologies can be used for the manufacturing of solid dosage forms. For the production of tablets, different single unit operations are conducted consecutively. Some of them are designed to operate in continuous mode while other unit operations are only suitable for batch mode. Continuous unit operations by design are for example roller compaction as a dry granulation method, hot melt extrusion, milling, tablet compression and spray drying. In contrast, unit operations like blending, wet granulation, drying and coating were traditionally designed for batch production [11]. However, with the implementation of continuous manufacturing processes, batch unit operations have been revised to follow the first-in first-out principle of continuous manufacturing, e.g. continuous ribbon powder blenders were designed to replace the traditional tumble blenders. Considering a manufacturing process as a series of single unit operations, continuous manufacturing can be achieved by connecting inherently continuous unit operations like blending and tablet compression. GEA Pharma Systems for example offers an integrated continuous manufacturing line for direct compression of tablets (ConsiGma™ CDC). Direct compression with the advantages of a low number of unit operations (typically feeding, blending and compression) and its applicability for moisture or heat sensitive ingredients is the preferred technology for tablet manufacturing. However, the final blend intended for tableting has to comply with certain requirements regarding compressibility and flowability to ensure smooth processability. Therefore, granulation unit operations like dry or wet granulation technologies are frequently used to optimize intermediate properties (e.g. flowability, tabletability and homogeneity) before tablet compression [24]. Roller compaction, a by nature continuous granulation technology, can for example be easily implemented into a continuous manufacturing process in contrast to traditional wet granulation processes which are designed for batch mode production.

A few examples of continuous granulation unit operations are given in the following sections.

4.1. Continuous dry granulation

Roller compaction is a typical inherently continuous dry granulation technique. A schematic overview of the working principle is given in Figure 2 [7].

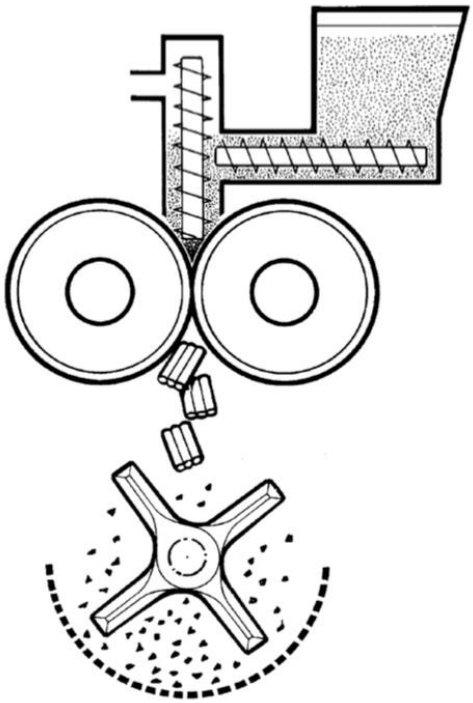

Figure 2. Working principle of a roller compactor (source [7])

Besides its suitability for integration in continuous manufacturing processes, roller compaction does - due to the absence of water or granulation liquids - not require a drying step after granulation which makes it suitable for heat and water sensitive APIs. Since the agglomeration mainly depends on the compressibility properties of the applied materials, the suitability of this granulation method might be limited, especially for products with high drug load and APIs with unfavourable compression characteristics. A disadvantage of roller compaction is moreover that often large amounts of fines are generated in the subsequent milling step after granulation [7]. Furthermore, the roller compaction process consumes already part of the compressibility of the blend, which then is partially lost for the tablet compression process.

4.2. Continuous wet granulation

As the traditionally available batch wet granulation technologies were as such not suitable for continuous operation, several technologies were modified or new equipment was designed to perform wet granulation in a continuous way.

4.2.1.Continuous fluid bed wet granulation

Horizontal moving bed agglomerators which enable continuous fluid bed granulation (e.g. Glatt GF series, Niro Vibro-Fluidizer, Heinen Drying Technologies) have been used in the chemical and food industries. The different process steps are included in one chamber which is functionally (not mechanically) divided by introducing nozzles and differences in air velocities and temperature (Figure 2).

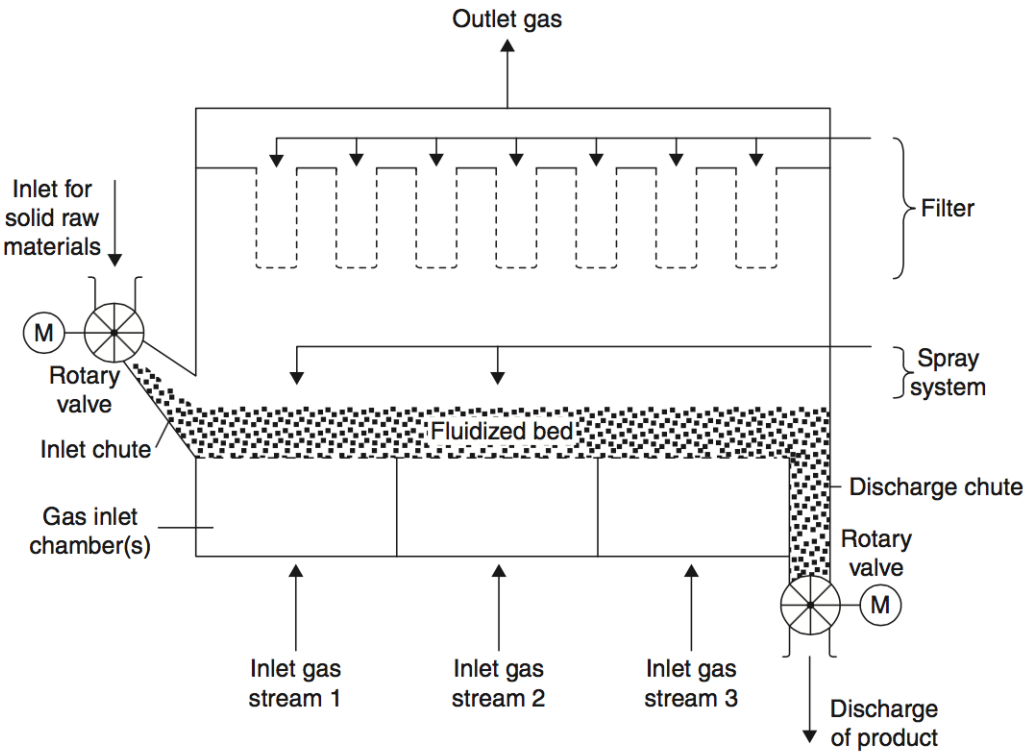

Figure 2. Example for a horizontal fluid bed granulation process (from [4])

After the material is loaded, it is transported horizontally through the equipment, while it undergoes the process steps of initial heating/mixing, spraying, drying and cooling before the material is discharged. This concept, however, is of limited suitability for pharmaceutical applications since the typical throughput starting at 20kg/h is mostly too large for pharmaceutical processes, especially in development phases. Also the risk for uncontrolled back-mixing and the long tail-off in residence time of materials in combination with a lack of plug-flow in the process chamber pose a risk for product degradation and limited process control [7],[25],[26].

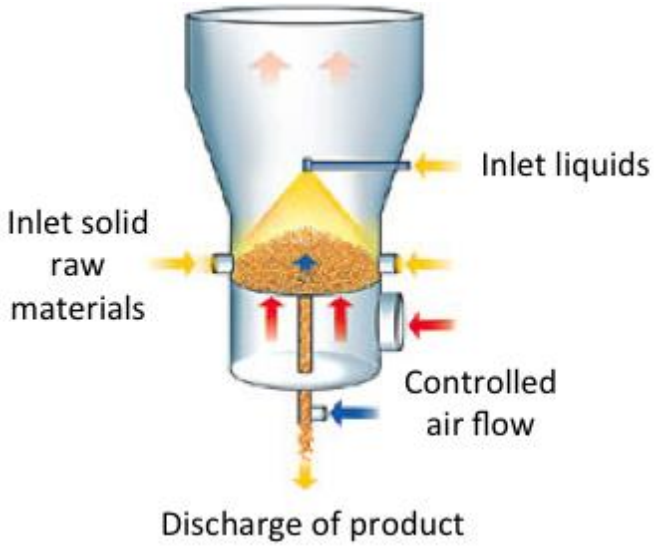

Figure 3. AGT system for continuous fluid bed granulation (source: modified from Glatt)

The company Glatt offers a different design for continuous fluid bed granulation (AGT series, Figure 3). While the round-shaped design is similar to conventional batch fluid bed equipment, the material is continuously discharged via a pipe in the bottom: as soon as the granules exceed a defined size they can overcome the air velocity at the bottom. Liquid raw materials can be dried to form agglomerates as well as a combination of continuously fed powders with a liquid that is sprayed into the chamber. A disadvantage is the missing control over the residence time of material in the process chamber. The advantages of this equipment are a mostly dust-free product (small particles cannot overcome the air current to exit the chamber) and its capability for varying amounts of product since e.g. a small-scale equipment is available [7].

4.2.2. Continuous spouted bed wet granulation

In contrast to the previously described fluid bed granulators where process air enters the chamber from the bottom, in spouted-bed granulators (e.g. Glatt ProCell™) the air is introduced at high velocities from the side through longitudinal slots (Figure 4). An angled airflow enables continuous production by transporting the product through the chamber. Liquid for granulation is added to the process via spray nozzles (top or bottom spray possible). The advantages of spouted-bed granulation are that also difficult-to-fluidize products (like fine and irregularly shaped particles) can be fluidized and processed, the short processing time due to high spray rates as well as a stable process [27],[28].

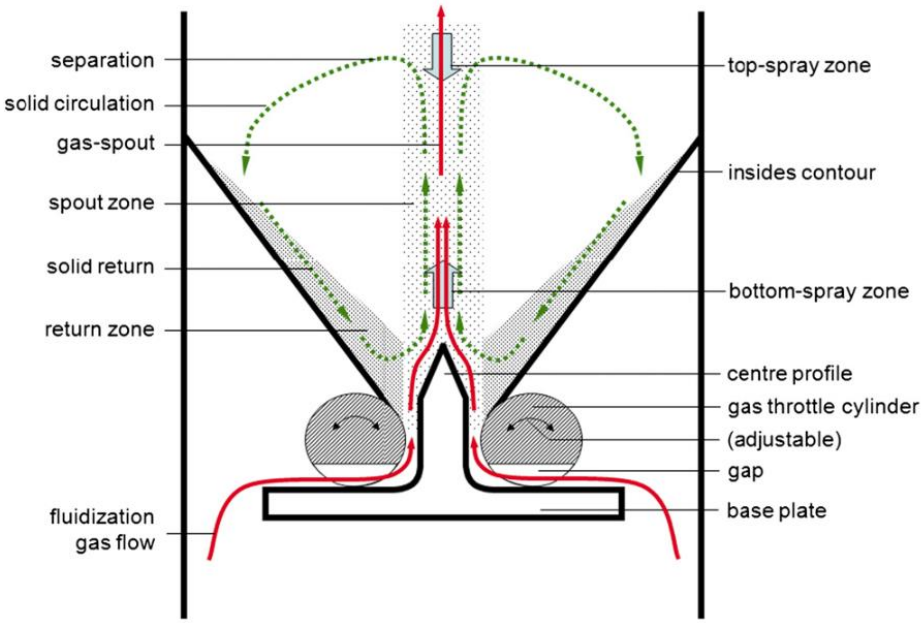

Figure 4. Working principle of spouted bed granulation (source [20])

4.2.3.Continuous high shear wet granulation

High shear granulation is one of the commonly used wet granulation techniques for batch manufacturing processes in the pharmaceutical industries. Bohle modified a high shear granulator for continuous manufacturing (Figure 5) [29]. While the material (powder and liquid) is continuously added to the bowl, an integrated chopper and impeller continuously discharge the granules through a screen. The equipment is used in combination with a cylindrical infrared drying system where vacuum ensures a gentle and fast drying process. The granulator allows flexible material throughput, however, the throughput impacts the residence time of material since the material transport to the dryer is controlled via overflow principle. In contrast to a plug flow system (e.g. extrusion-based equipment) the residence time within the system is less controllable [30].

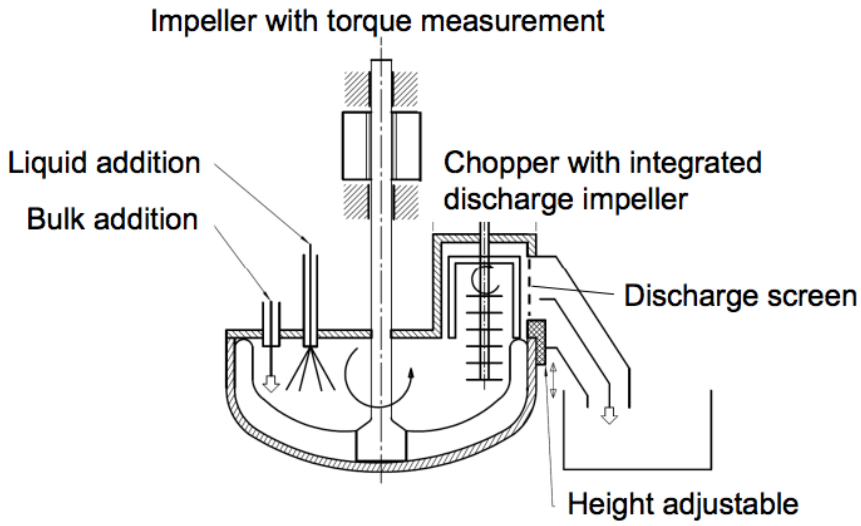

Figure 5. Continuous high shear granulator (Easy flow™ system from Bohle, source [24])

Moreover another continuous high shear granulator (CoriMix™) was developed by Lödige which follows the principle of ring layer granulation (Figure 6). Next to wet granulation purposes, the device can also be used for mixing, wetting and other operations depending on the applied speed of the blades. When high speed is applied, a forward-moving ring layer of powder is formed in the drum. Granulation liquid can be sprayed directly on the layer through a defined number of nozzles so that particles form agglomerates.

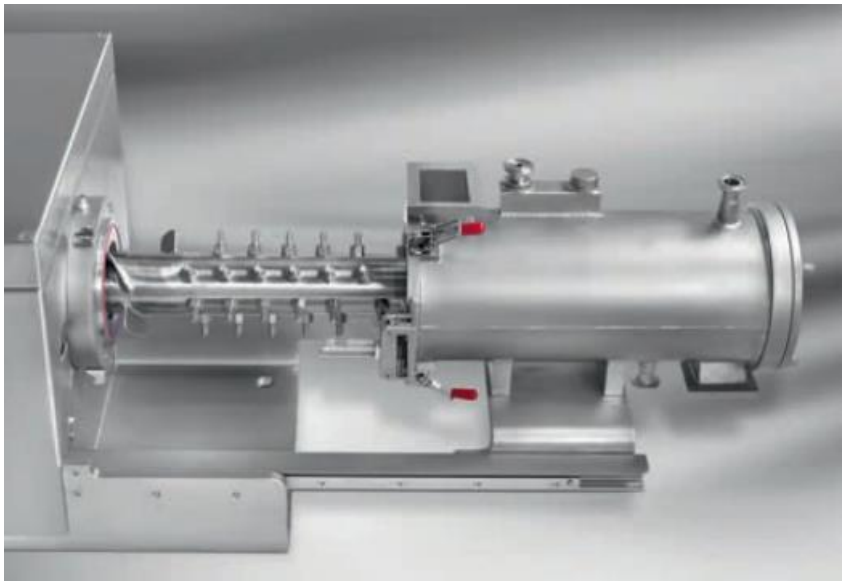

Figure 6. Continuous high shear (ring shear) granulator (CoriMix™ from Lödige)

4.2.4.Continuous twin screw wet granulation

Being an extrusion-based granulation technique, twin screw wet granulation is the most studied continuous granulation method. One or two screws in a barrel are used for mixing,

granulation (by introducing shear forces to the wetted powder) and transportation purposes. In contrast to common extrusion processes (e.g. hot melt extrusion), the equipment is run without a die at the end so that the granules are not strongly densified and are ready for further processing (e.g. drying steps). This technology offers high flexibility regarding the throughput capacity so that the equipment can be used from development to commercial scale. Due to the highly effective granulation process, the process barrel is short and the process will reach steady-state quickly after start-up resulting in limited loss of material [4],[7]. For more details and an example for twin screw wet granulation equipment, the reader is referred to section 4.3.3.

4.3. Integrated manufacturing lines with continuous wet granulation

Continuous wet granulation techniques were integrated in manufacturing lines which are designed for solid dosage form manufacturing in order to fully profit from the benefits of continuous manufacturing. Selected examples from different manufacturers are summarized in the following sections.

4.3.1.MODCOS™ - integrated modular continuous system (from Glatt)

The modular continuous system was developed by Glatt in cooperation with Thermo Fischer Scientific and Fette. It supports continuous manufacturing from powder to tablets (Figure 7). The manufacturing line contains different units for powder dosing via loss-in-weight principle, dry mixing, granulation, milling and tablet compression. Three options for continuous wet granulation can be selected: i. twin screw extrusion (from Thermo Fischer), ii. Glatt's GCG continuous mixer with granulation function (i.e. single shaft wet granulation with a configurable bladed agitator) or iii. fluid bed granulation in the GPCG fluid bed system from Glatt. The fluid bed system can be integrated into the continuous set-up but also be used in batch mode. The fluid bed dryer is equipped with a rotating chamber insert to split the process chamber into sections which enables continuous manufacturing. The manufacturing line is available in 3 different sizes so that wide ranges of material throughputs are possible (from 1-15kg/h for the s-line up to 50kg/h for the l-line) [31],[32].

Figure 7. MODCOS™ integrated modular continuous system from Glatt (source: Glatt.com)

4.3.2. Granucon™ - continuous granulation and fluid bed drying line (from Lödige)

A continuous manufacturing line for granulation and fluid bed drying was designed by Lödige. The line contains a high shear granulator (CoriMix™, as described earlier, Figure 6) which operates via ring layer granulation and a fluid bed dryer. Aiming to limit the span of the retention times in conventional fluid bed dryers, the Lödige dryer was equipped with a screw to convey the granules through the equipment in a controlled way.

4.3.3. ConsiGma™ - continuous from-powder-to-tablet line (from GEA): A fully integrated continuous manufacturing line applying twin screw wet granulation

GEA Pharma Systems was the first pharma equipment manufacturer who developed a continuous manufacturing line integrating unit operations from powder blending to tablet compression in a single manufacturing line. The ConsiGma™-25 continuous tableting line was used for the granulation experiments which were conducted in the context of this research project (**Figure 8**). The line includes the following process steps: preblend powder feeding, twin screw wet granulation, fluid bed drying, dry milling of granules, final blending and tablet compression.

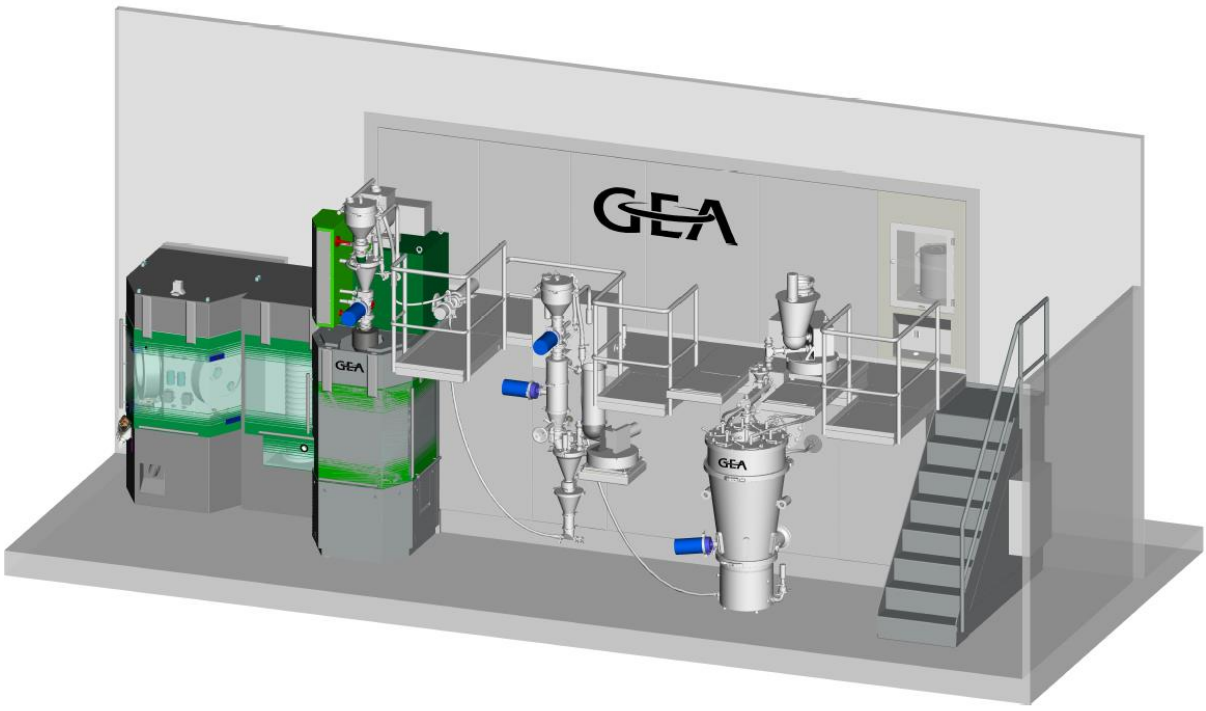

Figure 8. ConiGma™-25 line (source: GEA Pharma Systems)

The working principle of the ConsiGma line is detailed below. The powder blend is fed via loss-in-weight feeder to the granulation unit. Alternatively, the individual raw materials (API and excipients) can be fed separately to a continuous in-line blender before being added to the granulation unit. The granulation liquid is transported via peristaltic pumps and tubing systems to the granulation barrel, while the liquid flow is controlled either via loss-in-weight principle (ConsiGma equipment at Ghent University) or mass flow meters (ConsiGma equipment at Roche). The granulation unit consists of a jacketed granulation barrel which can be set to a defined temperature. Cooling can for example be required to compensate for the temperature increase during granulation due to friction. Two co-rotating screws are mounted inside the barrel containing conveying and kneading elements (**Figure 9**). The screw-configuration is flexible, such that the number, the angle and the dimensions of the kneading elements (usually assembled block-wise) can be varied to modify the shear stress introduced to the product. Granulation mainly takes place in the kneading zone, where the majority of the mechanical energy is generated. A torque gauge records the resulting torque during processing. The typical residence time of material in the granulation barrel is below 10 seconds.

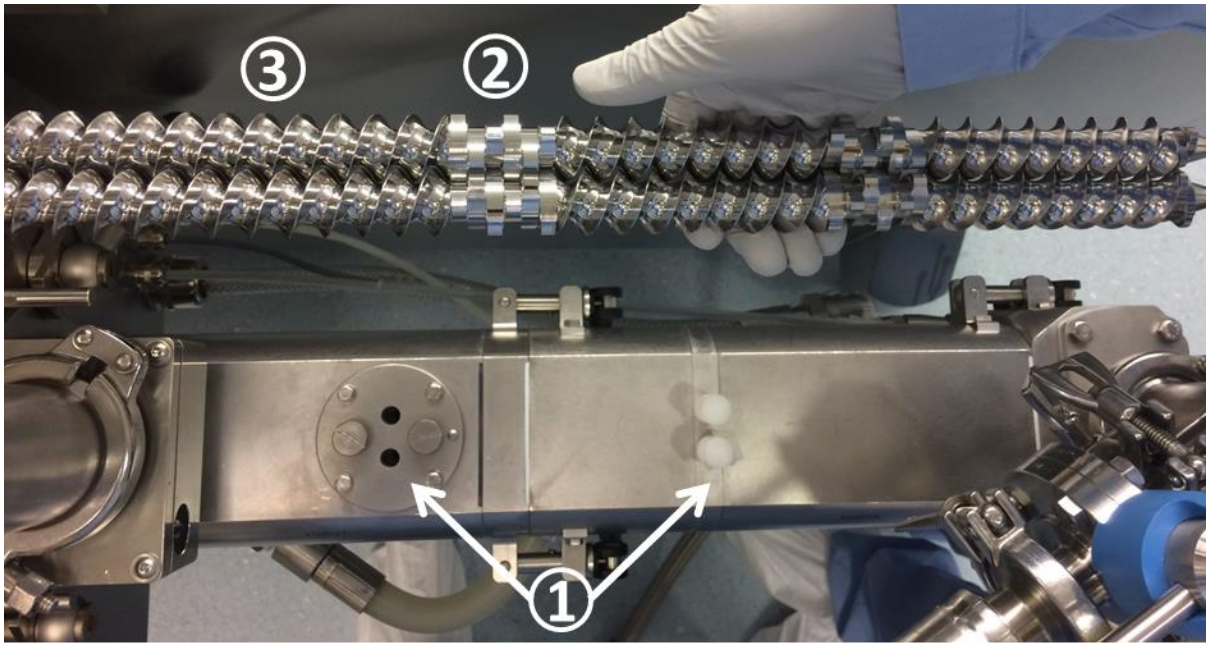

Figure 9. Top-view of granulation unit and twin screws (1=liquid entry ports, 2= kneading zone of screws, 3=conveying zone of screws)

The wet granules are discharged at the end of the granulation barrel and continuously transported into the fluid bed dryer (either gravimetrically or pneumatically through a transport line). The fluid bed dryer is divided into 6 equally-sized segments. The cells are charged through a rotating top valve with the wet granules, one cell after the other to comply with the first-in-first-out principle. Granules are dried as sub-batches by conventional fluid bed technology. After a pre-defined drying time, the granule sub-batches are discharged from the dryer. Thus, in a continuous mode, one dryer cell is being filled, four cells are drying and one cell is discharged (Figure 10).

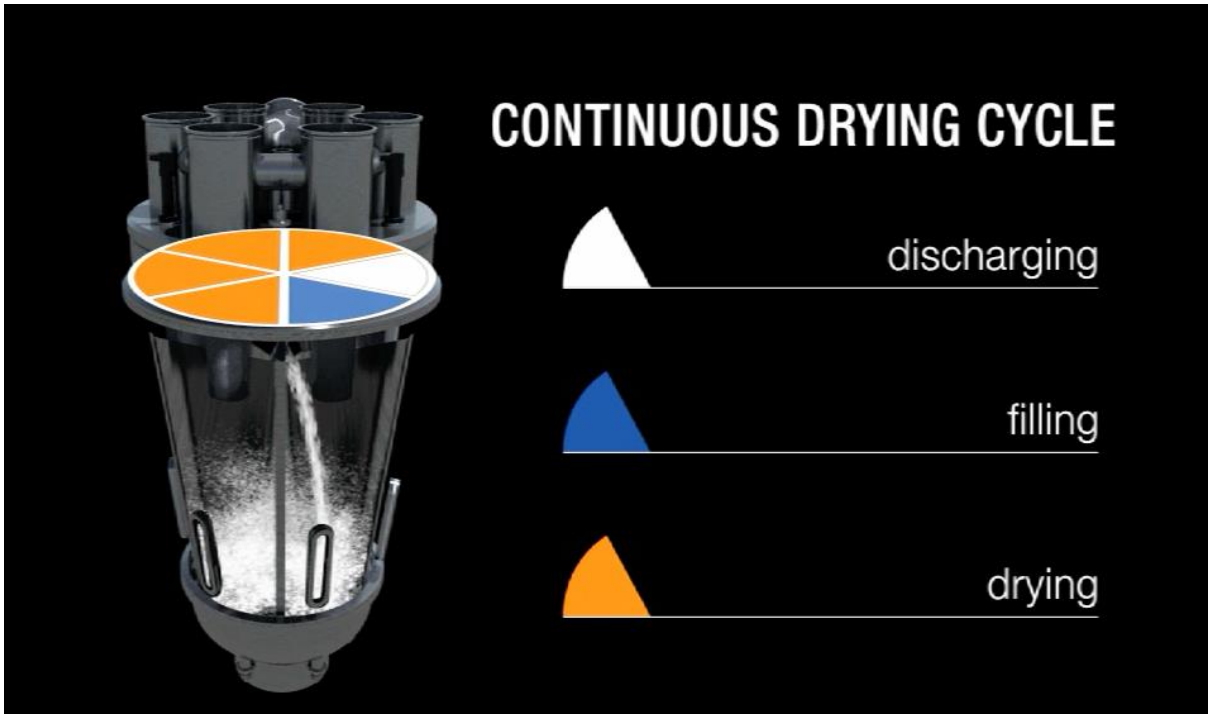

Figure 10. Six-segmented fluid bed dryer (adopted from GEA pharma systems)

The sub-batches are pneumatically transported to the so-called granule conditioning unit (GCU) for further processing (granule milling and final blending). The GCU can be equipped in various ways and can for example contain a cone mill for milling or delumping, interfaces for PAT tools, a balance and a ribbon blender. Excipients like lubricants and glidants can be mixed with the granules in the blender before compression, while the dosing of the external phase is calculated based on the weight of the respective granule sub-batch. A diverter valve at the bottom of the GCU enables to segregate sub-batches from the continuous process in case of failure modes or if any on-line monitored quality attribute is out-of-specification. The final blend is then gravimetrically transported to the hopper of the rotary tablet press.

5. Overview of the process parameters` impact on product properties in a continuous twin screw wet granulation process

A number of studies have been published which investigated the influence of process parameters on the properties of intermediate and final drug product (e.g. wet/dry granules, tablets) for a continuous twin screw granulation process. An overview of some relevant process parameters in a twin screw wet granulation process and their impact is given below.

The *screw configuration* is a process parameter which can highly influence the product properties. By applying the different types of screw elements (conveying elements and non-conveying elements; non-conveying elements can be kneading or comb mixing elements) the intensity of compaction and shear forces will vary. Moreover the number of kneading elements (typically applied block-wise separated by conveying elements) and also their

angle (typically 30°, 45°, 60° or 90°) impact the granulation process and thus potentially the granule properties [33]. Studies were published which proved that a larger angle of kneading elements resulted in larger and denser granules [34],[35],[36],[37],[38]. Moreover, stronger and less friable granules were obtained with a larger number of kneading elements. More kneading elements also increased the particle size of granules [38]. Wei-Da Tu et al. found that there was no difference in granule size distribution when a fixed number of kneading elements was either split in two sections or assembled in one section [33],[39].

The *screw speed* is another process parameter in a twin screw wet granulation process as it influences the filling level of the granulation barrel and thus impacts the shear rate. Several studies showed that its influence on granule properties can be considered of minor relevance, however at higher filling levels the impact might become considerable [33].

A higher *powder flow rate* was shown to increase the compressive forces and thus lager and denser granules were obtained (when applying kneading or comb mixing elements) [14],[33],[37],[40],[41],[42],[43]. With conveying elements only, higher flow rates resulted in smaller but also stronger granules [44]. Overall the impact of screw speed, powder flow rate and thus barrel filling level are interrelated regarding their impact on granule properties.

Fonteyne et al. investigated the influence of *barrel temperature* (from 25°C to 40°C) on granule properties and found that higher temperatures increased the medium granule particle size [14].

In conclusion, the selection of appropriate process parameters is crucial in order to obtain the desired product quality attributes in a continuous wet granulation process.

6. Impact of raw material properties on process performance and product properties

Next to the process parameters, also the selection of an appropriate formulation strongly influences the product quality attributes. In view of the difference in granulation process and in particular the tremendously shorter granulation time of a continuous wet granulation process compared to batch high shear wet granulation (<10s versus 10-30 min granulation time), the effect of excipients on process performance and product properties may not necessarily be transferable. This understanding, however, is of fundamental importance to support a Quality by Design (QbD)-based formulation development. The QbD concept emphasizes the importance of characterizing the critical material attributes like physico-chemical and solid state properties, aiming to understand the role of excipients in the formulation and to support a rationale-based excipient selection.

Some studies were published that investigated the applicability of QbD approaches and multivariate data analysis for formulation and process development purposes, aiming to link starting material properties with product and/or process performance. Kushner et al. combined API properties (API type and particle size), API drug load, excipient variability

(defined via the filler/lubricant particle size ratio) with two different manufacturing methods (dry granulation and direct compression) and investigated their influence on the attributes of immediate-release tablets [45]. The variation in filler/lubricant size ratio had a major impact on the particle size distribution of the blend and the granules as well as on granule flowability, while the API properties had a major influence on blend flowability and ribbon solid fraction. This study indicated that - in spite of the observed statistically significant influences - the immediate release tablet product was robust over the tested formulation and process ranges. Haware et al. studied the relation between material properties of selected lactose grades (milled, sieved, agglomerated and spray-dried), process parameters in a compaction simulator and tablet tensile strength using multivariate data analysis tools. It was observed that certain descriptors of the material compression behaviour as well as the tablet tensile strength could be directly linked to the different lactose grades. Lactose grades with better flowability and compressibility resulted in a higher tablet tensile strength, whereas the lactose particle size did for example not influence the compression properties or tablet tensile strength [46]. In an additional study, Haware et al. developed predictive models for the compression behaviour of pure excipients and binary blends using starch, microcrystalline cellulose and lactose as excipients [47]. Fonteyne et al. evaluated the effect of variation in critical API properties on the critical quality attributes of granules and tablets, produced via continuous twin screw wet granulation technology. The granulation process parameters were kept constant to only examine the differences in the end product quality caused by the variability of the raw materials properties. Seven different theophylline grades were used as API in the formulations. The results showed that differences in the API raw material properties can affect processability and critical quality attributes of the resulting granules and tablets. The granule size distribution was directly correlated with the theophylline particle size since smaller starting material resulted in more fines. Moreover it was reported that the tablets made of granules produced with micronized theophylline had the lowest porosity [48]. Soh et al. studied the effects of raw material properties and process parameters on roller compacted ribbons. Different lactose and microcrystalline cellulose (MCC) grades as well as blends thereof were characterized and roller compacted in a 2^3 full factorial process parameter DoE. The predictive model power was poor when only the process parameters were included, whereas the addition of raw material properties resulted in good predictive model power, indicating the relevance of raw material impact. The study showed that formulation properties like e.g. tapped density, MCC content in the formulation and tabletability had a dominant effect on the roller compaction responses [49]. With the purpose to predict the feeder performance based on material flow properties, Wang et al. presented an approach to correlate material properties with the performance of gravimetric feeders. Using principle component analysis (PCA) and partial least square (PLS) regression as statistical tools, it was shown that the selection of the optimal feeder screw strongly depended on the material flow properties. A correlation was also observed between material flow properties and the feed factor. The models revealed a good predictive power [50].

In summary the above-mentioned studies show that raw material properties of excipients and API can influence both process performance and critical quality attributes of the product. A systematic study of the influence of various excipient properties on the product quality attributes after continuous twin screw wet granulation has not been published so far. Such a study could provide a valuable database to support a rationale-based excipient selection and QbD-based formulation design. The objective of this project is to generate this understanding for selected pharmaceutical fillers and binders processed via continuous twin screw wet granulation.

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CHAPTER 2

IDENTIFYING OVERARCHING EXCIPIENT PROPERTIES TOWARDS AN IN-DEPTH UNDERSTANDING OF PROCESS AND PRODUCT PERFORMANCE FOR CONTINUOUS TWIN SCREW WET GRANULATION

1. Introduction

Continuous twin screw wet granulation is a promising technology for the manufacturing of solid dosage forms, offering better process control, lean scale up and potential savings in drug substance and development time [1]. Given the different manufacturing principle and much shorter granulation times of continuous twin screw wet granulation compared to batch high shear wet granulation, fundamental knowledge about the suitability and processability of excipients for continuous twin screw wet granulation is needed in order to support a QbD-based formulation development. A thorough understanding of the influence of the formulation composition and excipient characteristics on both process performance and the drug product's critical quality attributes is a fundamental part in the product design [2]. A number of studies have been published which studied the excipient and formulation impact on drug product quality and performance for a continuous twin screw wet granulation process. The studied formulations mainly contained excipients such as lactose, microcrystalline cellulose, dicalcium phosphate, or mixtures of them. Different lactose grades were processed [3] [4] as well as lactose isomers [3]. As described by El Hagrasi et al. three lactose grades with different particle sizes showed comparable granule growth behaviour at varied liquid-to-solid (L/S) ratios [4]. Keleb et al. showed that the lactose particle size and particle morphology did not significantly affect the tensile strength of tablets, whereas the isomer type of lactose had an influence on the disintegration time of tablets [3]. Moreover, some papers addressed the raw material variability of formulations [5], [6]. The variation in the degree of crystallinity of different MCC batches were shown to influence the water uptake capacity during granulation and consequently the size distribution of granules [5]. Fonteyne et al. also showed that the variation in particle size of the active pharmaceutical ingredient (API) was correlated with the particle size of the produced granules and that micronized API decreased tablet porosity [6]. With the aim to investigate the behaviour of hydrophobic materials, APIs with different hydrophobicity were studied in a continuous twin screw wet granulation process by Li et al. The hydrophobicity of the API had very limited impact on its distribution in the granulate when a foamed binding agent was used [7]. Also formulations with high drug loads up to 90% were processable in a continuous twin screw wet granulation process [8]. Vanhoorne et al. and Thomson and O`Donnel performed continuous wet granulation experiments on controlled release formulations: using hydroxypropyl methylcellulose as hydrophilic matrix former resulted in tablets with sustained release over 16-20 hours independent of the investigated process and formulation parameters [9]. However, contradictory results in granule shape were obtained when applying controlled release excipients [9], [10].

Next to the impact of process parameters and the manufacturing technique, the selection of appropriate excipients and the composition of the formulation are the most important variables to design the drug product properties towards the defined quality target product profile (QTPP). A comparison of excipients with very different characteristics in the same

study design remains challenging due to different requirements in e.g. L/S ratio processable range for each of the excipients [11]. Thus, most of the above referred studies included a limited variation in the formulation composition and the majority of the obtained scientific conclusions must therefore be considered formulation specific. One of the main drivers for this research was to study the impact of excipients with very different material properties in the same experimental design.

Overall the objective of this research work is to systematically investigate and understand the influence of excipient characteristics and formulation composition on granule and tablet attributes after continuous twin screw wet granulation. Figure 1 provides a stepwise overview of the systematic approach used in this study [12]. Steps 1-4 are summarized in this publication. The research work on subsequent steps (5-8) is on-going and data is not yet published.

First, potentially suitable pharmaceutical fillers and binders for the continuous twin screw wet granulation technology were selected (step 1). Next, an extensive characterization of physico-chemical properties and solid state characteristics was performed for the excipients in order to generate numerical values which describe their properties (step 2). A PCA was then accomplished on the data set aiming to identify the overarching properties of the excipients and to reduce the large number of excipient characteristics down to a few overarching properties (step 3 & 4). As a next step, excipients will be identified which represent best the overarching properties (step 5). These excipients will then be studied as factors in a DoE in order to understand their impact on granule and tablet properties. Ultimately, the resulting statistical model is expected to provide an understanding and prediction of the excipient impact on the performance of the continuous twin screw wet granulation process as well as on the granule and tablet properties (step 6-8).

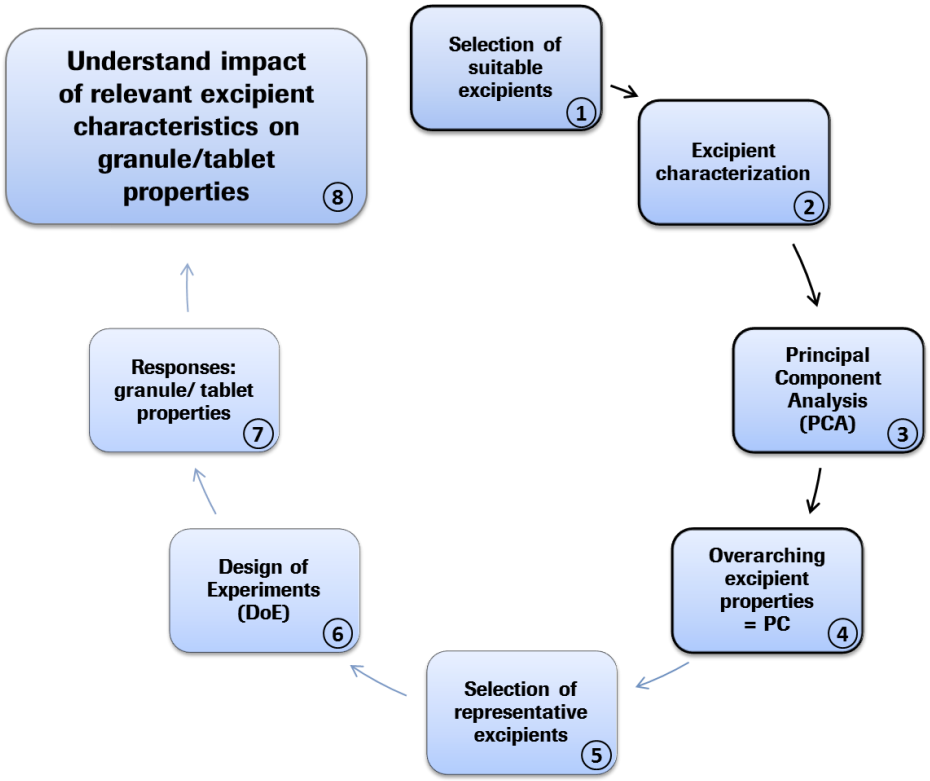

Figure 1. Stepwise overview of the systematic approach to generate formulation understanding

2. Materials and Methods

2.1. Materials

Microcrystalline cellulose (Avicel PH101, Avicel PH105, Avicel PH301, FMC Biopolymer, Philadelphia, USA), α-lactose monohydrate (Pharmatose 200M, Pharmatose 350M, DFE Pharma, Goch, Germany; GranuLac 200, Meggle Group, Wasserburg, Germany), mannitol (Parteck M200, Parteck Delta M, Merck, Darmstadt, Germany) and dicalcium phosphate anhydrous (FCC grade, Innophos, New Jersey, USA) were chosen as fillers. The investigated binders were hydroxypropyl methylcellulose (Pharmacoat 603, Pharmacoat 606, Pharmacoat 615, Shin Etsu, Tokyo, Japan), polyvinylpyrrolidone (Kollidon K30, Kollidon K90F, BASF, Ludwigshafen, Germany), hydroxypropyl cellulose (Klucel LF, Ashland, Kentucky, USA), vinylpyrrolidone-vinyl acetate copolymer (Kollidon VA64, BASF, Ludwigshafen, Germany), fully pregelatinized potato starch (Prejel PA5 PH, DFE Pharma, Goch, Germany) and maltodextrin (Maltrin 150M, Grain Processing Corporation, Iowa, USA).

2.2. Methods for filler characterization

Particle Size Distribution

Particle size distribution was characterized via laser diffraction (Malvern Mastersizer 2000, Malvern Instruments, Malvern, UK). Prior to the measurements, dicalcium phosphate was dispersed in demineralized water, while the other samples were dispersed in heptan and 0.2% Span 80, and stirred at 2000rpm for 2 minutes (5 minutes for Parteck M200). Three parallel measurements were performed. The median particle size (D_{50} in µm) and the span of the particle size distribution were used as variables for the principle component analysis. The span of the particle size distribution was calculated as $(D_{90}-D_{10})/D_{50}$.

Bulk and tapped density

Bulk and tapped density were measured in triplicate using the tapping machine (Stampfvolumeter, J. Engelsmann, Ludwigshafen am Rhein, Germany). 30g of powder was weighed and its volume after 0 (=V_{bulk}), 10, 500 and 1250 taps was documented. If the difference in volume between 500 and 1250 taps was larger than 2ml, another 1250 taps were conducted. The density was calculated as the volume *V* over the mass *m* in g/ml. The compressibility index *C* (in %) was calculated as $(V_{bulk}-V_{tapped})/V_{bulk}*100$ where V_{tapped} is the final volume after 1250 or 2500 taps.

Moisture content

An infrared dryer (Mettler LP16, Mettler-Toledo, Greifensee, Switzerland) in combination with a balance (Mettler PM480 Delta Range, Mettler-Toledo, Greifensee, Switzerland) was used to measure loss on drying (in %). Three measurements were performed for each powder at a drying temperature of 90°C until the weight variation was below 2mg within 30 sec.

Degree of crystallinity

X-ray diffraction measurements were performed with a Philips X'Pert Pro powder diffractometer (model PW 3050/60). Diffractograms were recorded in the reflection mode in a 2-theta angular range of 8.5–40° by steps of ca. 0.02° at room temperature. The Cu Kα radiation (λ = 1.5406 Å) was generated at 45 kV and 35 mA. Diffractograms were recorded from rotating specimens using a position sensitive detector. Profile deconvolution was performed with a multiple peak fit tool using Origin's Peak Analyzer (OriginPro 9, Origin Lab). The fifth-degree polynomial function was used to fit the amorphous background (baseline), and the pseudo-Voigt function was used to express each crystalline reflection [13]. Cellulose crystallinity (in %) was determined by calculating the ratio of the separated crystalline peak area to the total reflection area of all signals, including background.

Particle Shape

The analysis of particle shape was performed via high order image analysis (QICPIC, Sympatec, Clausthal-Zellerfeld, Germany). Prior to the measurements, dicalcium phosphate was dispersed in demineralized water, while the other samples were dispersed in heptan and 0.2% Span 80 and stirred at 2000rpm for 2 minutes (5 minutes for Parteck M200). Particle shape analysis was performed in triplicate. The software Windox 5 was used to calculate the particle aspect ratio based on volume, which is defined as the ratio of the minimal to the maximal Feret diameter.

True Density

True density (in g/cm^3) was measured using a helium pycnometer (AccuPyc, Micrometrics, Norcross, USA). Ten purges at 19.5 psig and ten runs at 19.5 psig were conducted in one measurement. Two parallel measurements were performed.

Specific Surface Area

The specific surface area (in m^2/g) was determined via nitrogen adsorption (Tristar II 3020, Micrometrics, Norcross, USA) in the validity range of the BET-isotherm. Samples were degassed at room temperature overnight before measurements were conducted (n=2).

Water sorption

The water sorption behaviour of the fillers was measured using the Dynamic Vapor Sorption Equipment (Surface Measurements Systems, Middlesex, UK). Vapor sorption cycles were recorded from 0 to 80% humidity and back to 0% (desorption cycle) at a temperature of 20°C. During the measurements, the moisture level was increased when the ratio of mass change over time was max. 0.002 %/min. The maximum moisture uptake (in %) at 80% humidity was used as a descriptor in PCA. Moreover the ratio (in min/%) of time to reach equilibrium at 80% humidity and the overall water uptake at 80% humidity was calculated as another descriptive variable for PCA according to the following equation (Eq.1)

$$water\ uptake\ ratio\ = \frac{t80}{\frac{m80-m0}{m0}*100} \qquad [1]$$

where *t80* is the time needed (in min) to reach the equilibrium state at 80% humidity, *m80* is the equilibrium mass (in g) at 80% humidity and *m0* the equilibrium mass (in g) at 0% humidity.

Flowability

Powders were measured in triplicate with a Ring Shear Tester RST-XS (Dr. Dietmar Schulze, Wolfenbüttel, Germany). A cell of 30 cm^3 volume was used. A pre-shear of 1000 Pa and normal loads of 400 Pa, 600 Pa, 800 Pa and again 400 Pa were applied. The flow function coefficient (*ffc*), which is the ratio of consolidation stress to unconfined yield strength, was used to characterize flowability [14].

Dissolution kinetics

Fillers were characterized regarding their dissolution rate in water. 4.00g of water-soluble fillers, i.e. lactose and mannitol, was added to 50g of water in a beaker stirring at room temperature. The endpoint of the dissolution test was set as the time when no particles were visually observed within 3 seconds. In order to increase the contrast, a black background was used. The measurements were repeated 5 times for each powder. The dissolution rate *D* was calculated as $D = m_{powder}/t$, where m_{powder} is the amount of powder to be dissolved (in mg) and *t* is the time (in sec) within which the powder was fully dissolved. For water insoluble fillers, i.e. dicalcium phosphate and MCC, a dissolution rate of 0.008mg/s was applied in order to quantitatively reflect the 10000-fold difference in solubility between water soluble and insoluble materials that is listed in the European Pharmacopoeia [15].

Dynamic Hardness

Rectangular tablets (2g tablet weight, 19 mm diameter) with a target solid fraction (SF) of 0.85 were compressed using a hydraulic press (Carver Press, GOT 1000, Mitsubishi, Carver, IN, USA). A maximum solid fraction (SF) of approximately 0.75 could be achieved for the tablets consisting of dicalcium phosphate anhydrate. Tablet SF was calculated from tablet mass (*m*) in g, volume (*V*) in cm^3 and true density (ρ_{true}) in g/cm^3 according to Equation 2. [16]

$$SF = \frac{m/V}{\rho_{true}} \qquad [2]$$

Tablet dimensions were measured immediately after compression so that potential relaxation was not considered. True density was determined via helium pycnometry.

The deformation characteristics of the rectangular tablets were determined using the Pendulum Impact Device (PID II, PharmSci LLC, Kalamazoo, MI, USA). The dynamic hardness (in MPa), which is a measure of the ease with which a material irreversibly deforms when rapidly impacted, was calculated as follows (Eq. 3):

$$Dynamic\ Hardness\ = \frac{4\,mgr}{\pi a^4} * \left(h_i - \left(\frac{3}{8}\right) h_r\right) * 10^{-6} \qquad [3]$$

where *m*=mass of indenter in g, *g*=gravitational acceleration in m/s^2 , *r*=radius of indenter in m, h_i=initial height of indenter in m, h_r=rebound height of indenter in m and *a*=radius of dent in m. The measurements were made in triplicate, except for Avicel PH101 and PH105, for which two parallel measurements were performed.

Wettability

Wettability of the samples was determined via contact angle measurements using a Drop Shape Analyzer (DSA 100, Mettler-Toledo, Greifensee, Switzerland) applying the sessile drop method. The powders were compressed with a hydraulic press (Perkin-Elmer, Massachusetts, USA) at a pressure of 50kN for 30 seconds in a punch of 12mm diameter. A 5µl drop of demineralized water was placed on each tablet. Contact angles (in °) were measured when the drop touched the surface of the tablet. Five parallel measurements were carried out.

Dynamic flow of powders in motion

The GranuDrum instrument (APTIS, Liège, Belgium) was used to measure the dynamic properties of the powders (such as flow angle and cohesive index) as a function of the rotating speed. The experimental set-up was a cylindrical drum (10mm diameter and 84mm length) rotating around its horizontal axis [17]. Prior to analysis the drum was filled with approximately 30ml of the powder sample. The rotating drum was monitored with a charge-coupled device camera during the measurements. For each angular velocity, 50 images of the powder pile were recorded at 0.5 s intervals. The average position of the air-powder interface and its fluctuations were computed using a dedicated image processing algorithm. The fluctuations, which were calculated as the standard deviation of the 50 measurements at a certain rotation speed, are related to the cohesion of the powder. The dynamic angle (in °) was measured in the centre of the flow based on the average interface position. The controlled rotating speed mode was used with a linear increase of the rotating speed from 0 to 20 rpm (up curve) and a decrease to zero (down curve) (no stop in between). The flow angle and the cohesive index at 10rpm drum rotation speed were used for the PCA. To evaluate the influence of drum speed on the powder flow behaviour, the drum speed was plotted against the flow angle and the cohesive index. The slope of the resulting trendlines was also used as a variable in the PCA representing the change of powder flow behaviour upon motion.

Electrostatic charge of powders

The triboelectric charge, which is built up in the powder samples while flowing on a stainless steel surface, was quantified with the GranuCharge instrument (APTIS, Liège, Belgium) equipped with an INOX 316 L tube. The initial charge density of the powder sample was measured after sampling. After a controlled flow inside a vibrating conduit the final charge density of the samples were determined. The difference between the initial charge density and the charge density after flow (in µC/kg) was calculated and used as variable for PCA.

Powder cohesiveness

The FT4 Powder Rheometer (Freeman Technology, Gloucestershire, UK) was used to measure cohesiveness of the excipients. The aeration test sequence records the consumed total energy (in mJ) at 0, 0.5, 1, 2, 3, 4, 5 and 6 mm/s air velocity at a constant blade tip speed of 100mm/s. The Aeration Ratio (AR) was calculated as a descriptive value from these measurements (n=2) as $\text{Energy}_{(\text{at air velocity 0})}/\text{Energy}_{(\text{at air velocity 6})}$.

Molecular weight and solubility

The values for molecular weight (in Da) and solubility in water (in %) were taken from the literature [18]. The values that were used for the principal component analysis are summarized inTable 4 in the appendix.

2.3. Methods for binder characterization

Viscosity

The dynamic viscosity of the aqueous binder solutions was measured using a rotational viscosimeter (Modular Compact Rheometer Series 102, PP50, Anton Paar, Graz, Austria) with the plate-plate technique applying a gap size of 1mm and a temperature of 20°C. Three dispersions with different concentrations were investigated for each binder. Varying ranges of shear rate were applied, ranging from 0.1 1/s to 2000 1/s, depending on the viscosity of the liquid. As it was not possible to completely disperse Prejel in water without lumps, no viscosity results could be generated for Prejel. The concentrations for viscosity measurements were selected according to the liquid concentrations established in the literature which cover the range of typical binder concentrations applied in wet granulation processes (Table 1). The viscosity of Kollidon K30, Kollidon K90 and Kollidon VA64 was in addition to the concentrations indicated in Table 1 measured at 8% concentration in order to have comparable values available for PCA at equal concentrations for all binders. 8% w/w was selected for comparability reasons as a medium concentration at which it was possible to produce a binder liquid for all binder types and grades included in this study. The viscosity values (in mPas) measured at 8% w/w concentration were used as descriptive values in the PCA.

Table 1. Concentrations of binder dispersions for viscosity measurements

Binder	Concentration (% m/m)		
Pharmacoat 603	4	8	14
Pharmacoat 606	4	8	14
Pharmacoat 615	2	4	8
Klucel LF	4	8	12
Kollidon K30	5	12.5	20
Kollidon K90F	5	10	15
Kollidon VA 64	5	12.5	20
Maltrin M150	8	29	50

The viscosity slope was calculated as an additional descriptive value in order to reflect changes in viscosity as a function of the binder concentration. Accordingly, the concentration of the binder solution was plotted against the logarithmic viscosity and the slope of the resulting linear graph was used for PCA.

Glass transition temperature

Glass transition temperature (T_G in °C) of the binders was determined via modulated differential scanning calorimetry (Modulated Differential Scanning Calorimeter Q2000, TA Instruments, Zellik, Belgium). Non-hermetic T_{Zero} aluminium pans and lids were used. Equilibration was done at -20°C and a heat rate of 2°C/min was applied. Maltrin M150 was dried for 24 hours at 37°C prior to the measurement. Heat-cool-heat cycles were applied where needed in order to detect the T_G thoroughly (Table 2). Since the T_G of Prejel cannot be determined by DSC [19], a value was taken based on supplier information [20].

Table 2. Settings for MDSC measurements

Binder	Heated up to (in °C)	Cycle
Klucel LF	240	heat - cool - heat
Pharmacoat 606	220	heat - cool - heat
Pharmacoat 615	220	heat - cool - heat
Pharmacoat 603	220	heat
Kollidon K30	200	heat
Kollidon K90F	210	heat
Kollidon VA 64	170	heat
Maltrin M150	220	heat

Surface Tension

8% (w/w) aqueous solutions of the binders were prepared. Kollidon VA64 was pre-treated in an ultrasonic bath for 90 minutes to ensure complete dispersion of the polymer. The density of the solutions (in g/ml) was determined using a 10ml glass pycnometer (Duran) as m/V where m is the mass of the binder liquid in g and V is the binder liquid volume in ml. The surface tension of the solutions (in mN/m) was determined with the pendant drop method in air using a drop shape analyzer (Drop Shape Analyzer 30, Krüss, Hamburg, Germany). Each measurement was conducted at room temperature in triplicate.

Molecular weight

The values for molecular weight (in Da) were taken from the literature. The values that were used for the principal component analysis are listed in Table 5 in the appendix.

2.4. Principal Component Analysis

A PCA was performed using the fillers` and binders` data set of quantified excipient characteristics separately with the SIMCA© software (Umetrics, version 14). Data were centred and scaled to unit variance. A logarithmical (log) transformation of variables is suitable for conversion of a non-normal distributed into a normally distributed data set in order to improve the data analysis efficiency [12]. Log-transformation was performed if needed. For interpretation of the principal components the loading plots were used.

For cross-validation, the data set was split up into 7 subsets. The subsets were step-wise systematically removed from the data set and the missing data points were then predicted based on the model terms and compared with the actual values. The closer the predicted value was to the actual value, the better was the model predictability and the larger the resulting Q^2-bars.

3. Results and Discussion

3.1. Selection of suitable excipients

9 fillers and 9 binders were selected for this study. The selection of fillers included commonly used types for wet granulation processes with differences in chemical nature (e.g. lactose, MCC, mannitol and dicalcium phosphate) and properties like water solubility or compression behaviour (brittle/plastic). In order to achieve a wide variability in excipient characteristics, different filler grades were selected to account for differences in particle size (e.g. Pharmatose 200M vs. Pharmatose 350M) and density (e.g. Avicel PH101 vs. Avicel PH301). Likewise the selection of binders was based on the purpose to cover the different chemical nature of the most commonly used binders for wet granulation processes such as hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (PVP) and hydroxypropyl cellulose (HPC). Maltodextrin is of interest as binder for paediatric formulations since it can improve the mouthfeel and help to counteract bitter flavours [21]. Overall, the selected excipients covered broad material property attribute ranges with the idea that also attributes of excipients that were not included in this study are within these ranges. Thus, the expectation is that a future model would also allow predictions of the impact of non-selected excipients on drug product performance.

3.2. Excipient characterization

The intention was to perform a holistic excipient characterization of the selected 9 fillers and 9 binders such that all properties which might possibly influence the process or product performance during wet granulation as well as the resulting potential critical quality attributes (pCQAs) of the drug product were expressed in numerical values. The excipients were characterized by applying the methods described in section 2.2 and 2.3. The results of the excipient characterization are summarized in Table 4 and Table 5 in the appendix. An overview of all characteristics is provided in Table 3.

Table 3. Overview of determined filler and binder properties and characterization test methods

	Descriptor	Applied method for characterization
FILLERS	Median particle size (D50)	Laser diffraction
	Span of particle size distribution	Laser diffraction
	Bulk density	Tapping machine
	Compressibility index	Tapping machine
	Moisture content	Loss on drying via infrared dryer
	Degree of crystallinity	X-ray diffraction
	Shape of particles	High order image analysis (QICPIC)
	True density	Helium pycnometry
	Specific surface area	Nitrogen adsorption (BET)
	Amount of water uptake	Dynamic vapor sorption (DVS)
	Water uptake ratio	Dynamic vapor sorption (DVS)
	Flowability	Ring shear tester
	Molecular weight	Literature
	Solubility in water	Literature
	Dissolution kinetics	Powder dissolved in water
	Dynamic Hardness	Pendulum impact device
	Wettability - Contact angle	Drop shape analyzer (sessile drop method)
	Dynamic flow - flow angle	Rotating drum with camera (GranuDrum)
	Dynamic flow - cohesive index	Rotating drum with camera (GranuDrum)
	Dynamic flow - change of flow angle	Rotating drum with camera (GranuDrum)
	Dynamic flow - change of cohesive index	Rotating drum with camera (GranuDrum)
	Electrostatic charge	Triboelectric charge after motion (GranuCharge)
	Cohesiveness	Powder rheometer
BINDERS	Dynamic Viscosity	Rotational viscosimeter
	Change in Viscosity	Rotational viscosimeter
	Molecular weight	Literature
	Glass transition temperature	Differential scanning calorimetry
	Surface tension	Glass pycnometer

3.3. Principal Component Analysis (PCA) and identification of overarching excipient properties

3.3.1. PCA of fillers

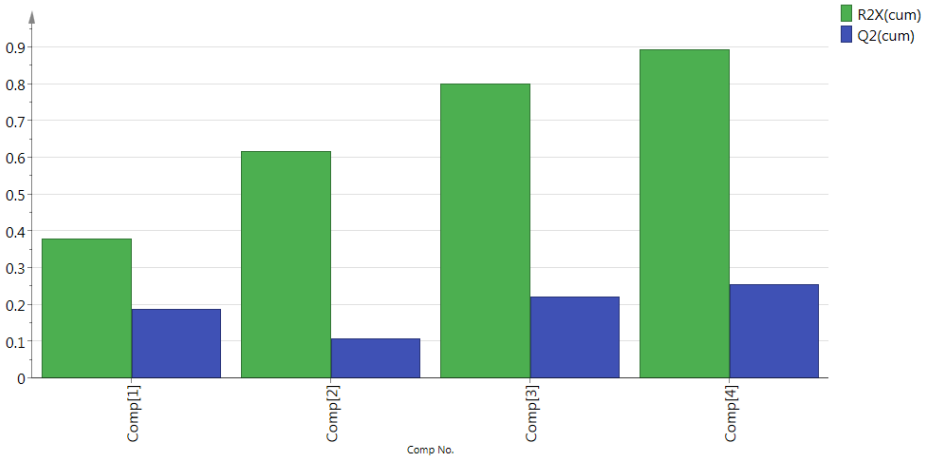

Figure 2. Summary of fit (fillers)

A four PC model was fitted for the fillers` data set. The green R^2-bars in Figure 2 represent the cumulative percentage of variation that was explained by the model for each component separately. The closer the bar is to 1.0 the more perfect the fit of the model is. Here, the first PC explained 38.0%, the second PC 23.8%, the third PC 18.3% and the fourth PC 9.4% of the overall variability in the data set. A total of 89.4% variability was thus explained by the 4 PCs. Typically a number of 2-5 PC is adequate to explain the variation in a data set well. All PCs are orthogonal to each other and their importance descends from the first to the last PC [12]. The blue Q^2-bars in Figure 2 indicate how well the model predicts new data. It is determined by cross-validation. The larger the Q^2-bar is the better is the predictive power of the model. The addition of another 5th PC did not strongly contribute to higher R^2-values and Q^2-values (data not shown). Therefore a number of 4 PC was considered appropriate in order to explain the majority of the variation for the data set.

All data points of the multidimensional model space in a PCA are projected on a plane which is spanned by two principal components. Each data point thus has a vector for the two principal components that explains its location on the plane: the scores. Hence, the scores plot displays the relationship of the excipients on the projection plane. The relation among the excipient properties (which are the variables) is explained by the loading plot. It depicts if variables are related (positively or negatively correlated) or if they are not related to each other. Moreover, loadings show the importance of the excipient properties for the principal components and provide information about the direction of the projection plane in the model space. Each PC can be interpreted as an overarching property which represents specific underlying excipient characteristics (i.e. the variables). The loading plots were used to assign an overarching property to each PC. Variables with large positive or negative loadings strongly influence the PCs, whereas variables located close to the origin of the

loading plot are not well explained by the model and are therefore not relevant for the respective PCs in the plot (Figure 3 and Figure 4).

By applying PCA, the originally 23 variables could be condensed and reduced to 4 overarching properties (PC) which were in orthogonal relation to each other.

PC1: moisture-related properties

The filler characteristics, such as bulk density, dissolution rate, degree of crystallinity, solubility, aspect ratio and water uptake ratio had strongly negative PC1 loading values and were located on the left side of the loading scatter plot. Moisture uptake, LOD, molecular weight, flow angle and slope_FA, however, had strongly positive PC1 loading values and were located on the plots` right side (Figure 3). All of the above-mentioned variables were hence well explained by the model and thus strongly contributing to PC1. The majority of the properties with strongly positive or negative PC1 loading values were identified to be moisture-related properties.

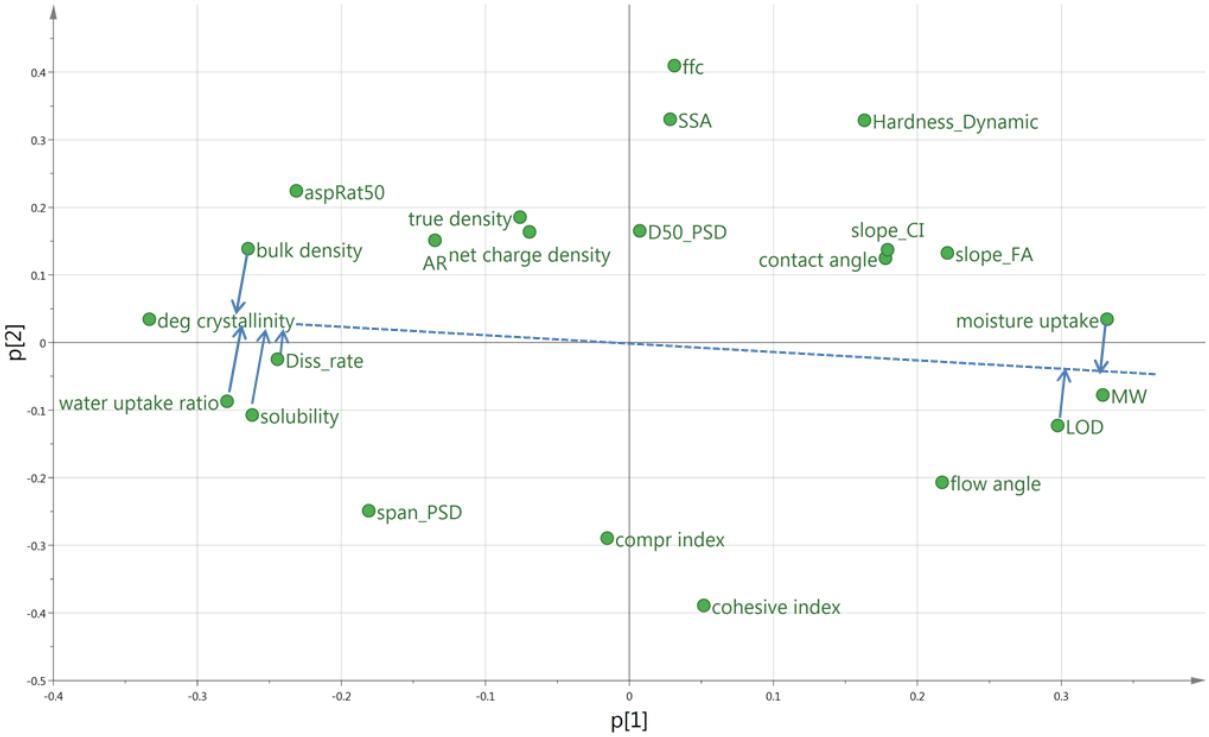

Figure 3. Loading scatter plot of fillers` 1st and 2nd PC

PC2: flow-related properties

The characteristics that significantly contributed to PC2 were ffc, specific surface area and dynamic hardness which had strongly positive PC2 loading values (upper part of plot) in contrast to cohesive index and compressibility index with negative loading values for PC2 (lower part of plot, Figure 3). Consequently, the second PC was identified to represent the flow-related properties of the filler data set.

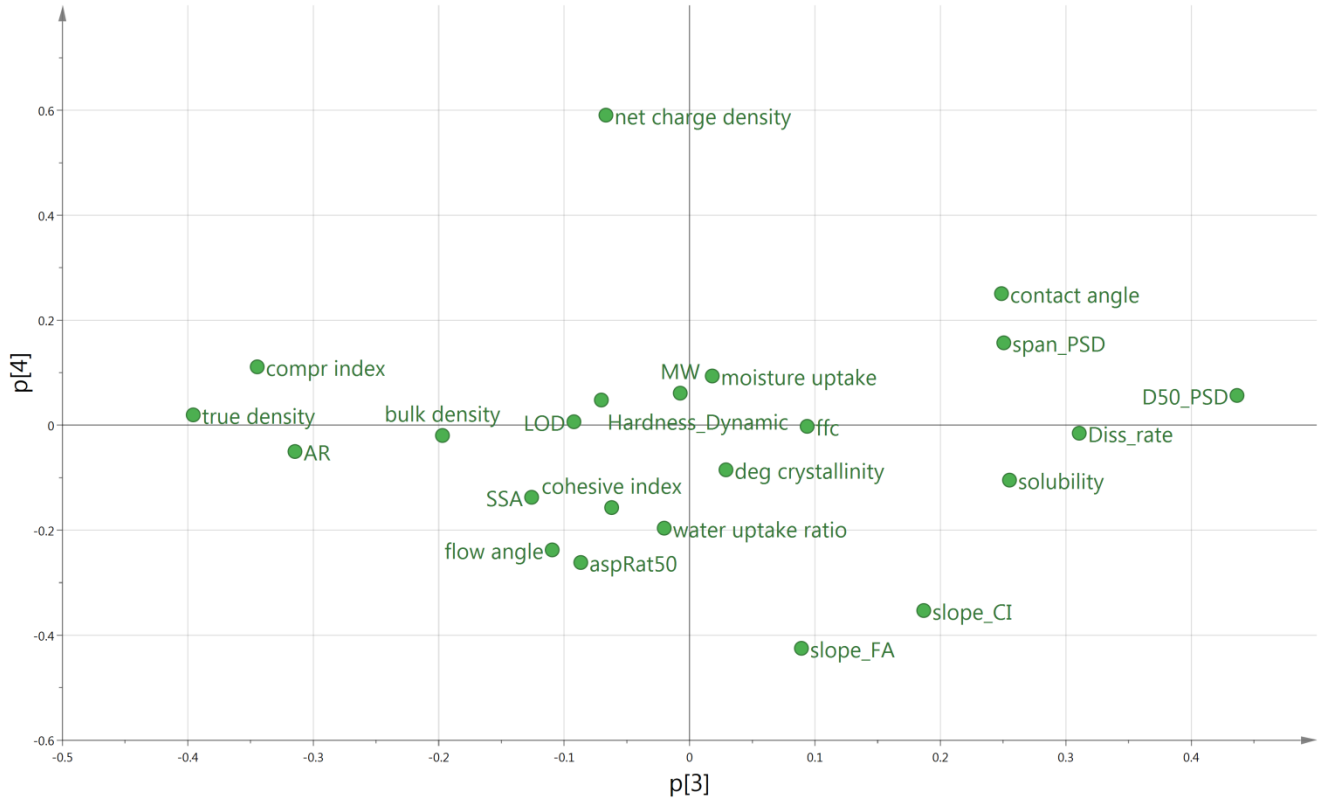

Figure 4. Loading scatter plot of fillers` 3rd and 4th PC

PC3: density/particle size-related properties

PC3 mainly explained the variability in particle size (D50) and dissolution rate as well as true density, compressibility index and aeration ratio (Figure 4). Accordingly, it was concluded that PC 3 represented density/particle size-related properties.

PC4: charge/adhesion-related properties

PC4 mainly explained the variability of the following characteristics in the filler data set: net charge density as well as slope_FA and slope_CI (Figure 4). PC4 was therefore identified to represent the charge/adhesion-related properties in the fillers data set.

Ultimately, PCA is a useful tool to understand the relation between variables in complex data sets. The loading scatter plots describes if characteristics are correlated or anti-correlated with regards to the respective PCs. To visualize this clearly per variable, an

imaginary line is drawn starting from a selected variable (in the example degree of crystallinity was selected) through the plots` origin (Figure 3). Other variables can then be projected on this line. Variables located close to degree of crystallinity on the imaginary line are positively correlated with degree of crystallinity while they are anti-correlated when being projected on the line at the other side of the plot. The closer the projection gets to the plots` origin, the weaker the correlation is. In the given example a high degree of crystallinity was associated with a fast dissolution rate, high solubility and a high water uptake ratio (i.e. a positive correlation between the variables). In contrast, a low moisture uptake and LOD were linked to a high degree of crystallinity, in other words these variables were anti-correlated with degree of crystallinity. The relations among the mentioned variables were reasonable in view of common pharmaceutical knowledge, e.g. a lower degree of crystallinity was linked to a higher water binding capacity [5] which also corresponded to a higher moisture uptake. As a further example, the correlation between bulk density and degree of crystallinity could be explained as a result of the molecular order: crystalline materials have a higher degree of structural order and thus also a higher density compared to amorphous materials which leads to higher bulk density for fully crystalline materials.

This procedure of identifying variables that are correlated or anti-correlated in the data set can be followed for any variable in a similar way.

In conclusion, all filler characteristics were considered relevant for the PCA model. Variables which are not relevant for the model should be located in or close to the origin in both loading scores plot of PC1 vs. PC2 as well as PC3 vs. PC4. In the PC3 vs. PC4 loading plot some variables such as molecular weight and degree of crystallinity were located close to the origin, however both were important for PC1.

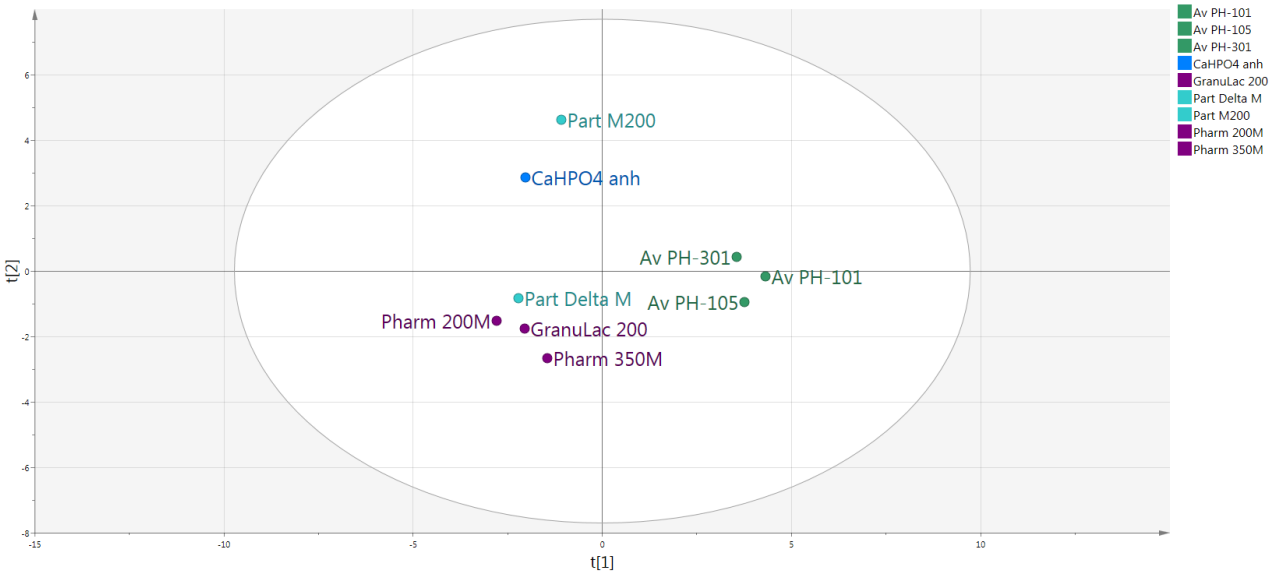

Figure 5. Scoresplot PC1 vs PC2 (fillers) - Colours indicate chemical nature of fillers

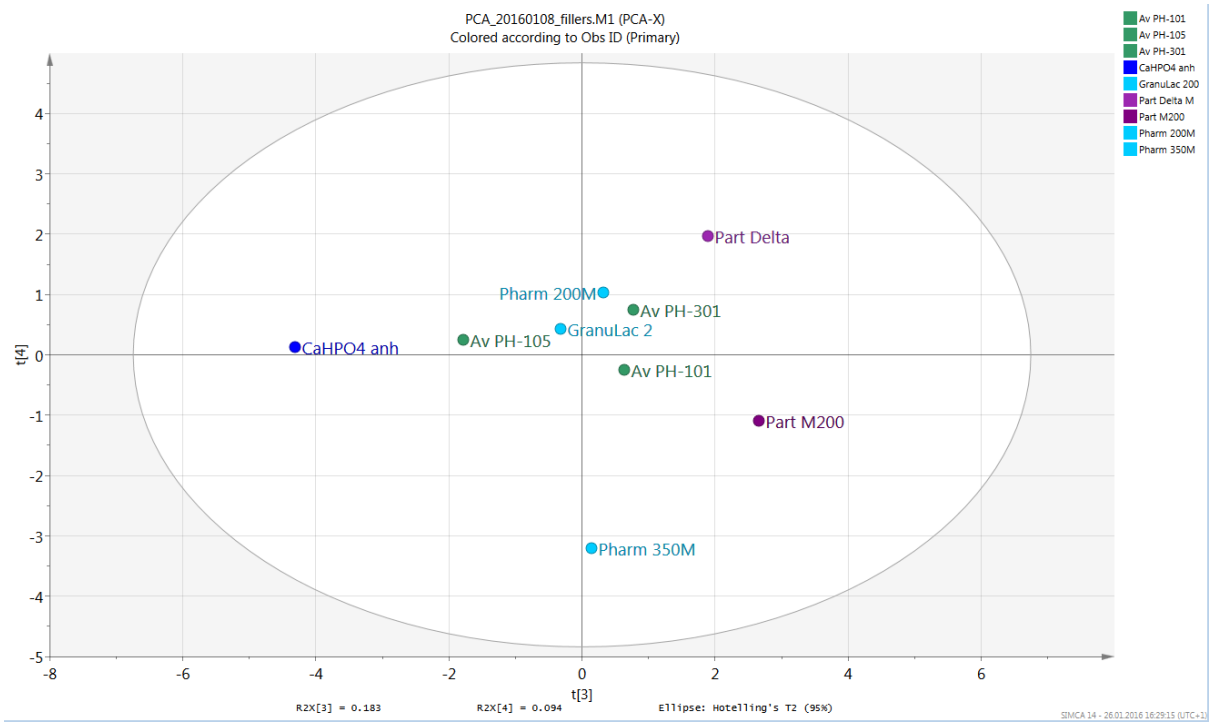

Figure 6. Scores plot PC3 vs PC4 (fillers) - Colours indicate chemical nature of fillers

The PC 1 versus PC 2 scores plot showed the relationship between the different filler types according to their principal properties (Figure 5). In the scores plot, the fillers which exhibit similar properties regarding the plotted overarching properties (i.e. loadings) were clustered, while fillers which were distinctly different in their properties were located on opposite sides of the plot. The MCC and lactose grades were grouped according to their

chemical nature, while both mannitol types did not form a cluster. The MCC grades revealed the most positive score values for the first PC. As according to the PC1 vs. PC2 loading plot (Figure 3) the first PC represented moisture-related filler properties, the MCC grades were different in their moisture-related loading values which resulted in high PC1 score values compared to all other filler types (low PC1 score values). This statement was confirmed when inspecting the raw data: Avicel grades had for example higher LOD values (3.1-4.1%) compared to other fillers (0.1-0.5%) which explains the higher PC1 score values for Avicel grades since the LOD loading values did positively contribute to PC1 (LOD value and the score value of PC1 were positively correlated) (Figure 3). The same fact was observed for degree of crystallinity where Avicel grades had low degree of crystallinity values (54-57%) compared to the other fillers which were fully crystalline. Since the degree of crystallinity was anti-correlated with the PC1 score values, a low degree in crystallinity resulted in high PC1 scores and hence explained the high PC1 score values of Avicel grades.

Plotting the PC3 against PC4 scores (Figure 6) illustrated the differences among the MCC grades: Avicel PH101 and PH301 were clustered at equal PC3 score values whereas Avicel PH105 was located at lower PC3 score values. As depicted in the PC3 vs PC4 loading plot (Figure 4) variables like D50, dissolution rate, true density, AR and compressibility index strongly loaded into PC3. Referring to the raw data of excipient characterization there was neither a distinct difference among the Avicel grades in true density (1.55-1.57g/cm^3) nor in dissolution rate (0.008 mg/sec for all Avicel grades). However, Avicel PH105 had a lower D50 (19µm) compared to Avicel PH101 (61µm) and Avicel PH301 (63µm) as well as a higher compressibility index (34.6%) and aeration ratio (42.02) compared to Avicel PH101 (25.95% and 10.76, respectively) and Avicel PH301 (23.45% and 15.11, respectively). Thus, the difference in median particle size D50, compressibility index and AR mainly explained the lower PC3 score values of Avicel PH105 compared to the two other Avicel grades. Parteck M200, a mannitol grade designed with excellent flowability [22], showed a high score value for PC2, representing flow-related properties. The superior flow properties of Parteck M200 compared to the other fillers were hence confirmed by the PCA model. Some of the fillers were located close to the origin of the PC3 versus PC4 scores plot which indicated that they had average properties in terms of density/particle size-related as well as charge and adhesion-related characteristics. In contrast to the PC1 versus PC2 scores plot, excipients were not clustered by their chemical nature in the PC3 versus PC4 scores plot. Hence, excipients of the same chemical group (e.g. lactose, mannitol, etc.) were heterogeneous with regards to their PC3/PC4 score values and thus different in their density/particle size-related properties and charge/adhesion-related properties.

Dicalcium phosphate anhydrate had a substantially higher density compared to other fillers since it had a lower score value for PC3 which was in accordance with the earlier described finding that density-related properties were mainly represented in PC3. In contrast to other fillers, Pharmatose 350M revealed a distinctly lower net charge as confirmed by its low PC4 scores value. Both, the PC 1 versus PC 2 and PC 3 versus PC 4 scores plot showed that

Pharmatose 200M and Granulac 200 were strongly correlated and had comparable properties since they were clustered (Figure 5 and Figure 6).

The PCA approach can not only be used to highlight which excipients possessed similar properties but also to identify those properties for which two fillers of interest differ the most. For example, Parteck M200 and Parteck Delta M were not clustered in the scores plots, although they were both mannitol grades. A contribution plot depicts the differences for all model terms in scaled units between two selected observations. According to the contribution score plot of Parteck Delta M and Parteck M200 (Figure 7), Parteck Delta M particularly exhibited a higher cohesive index, lower ffc value, smaller specific surface area, lower value for aspect ratio, higher value for compressibility index and broader particle size distribution. The differences in the above-mentioned properties allowed to conclude that Parteck Delta M possessed inferior flowability compared to Parteck M 200.

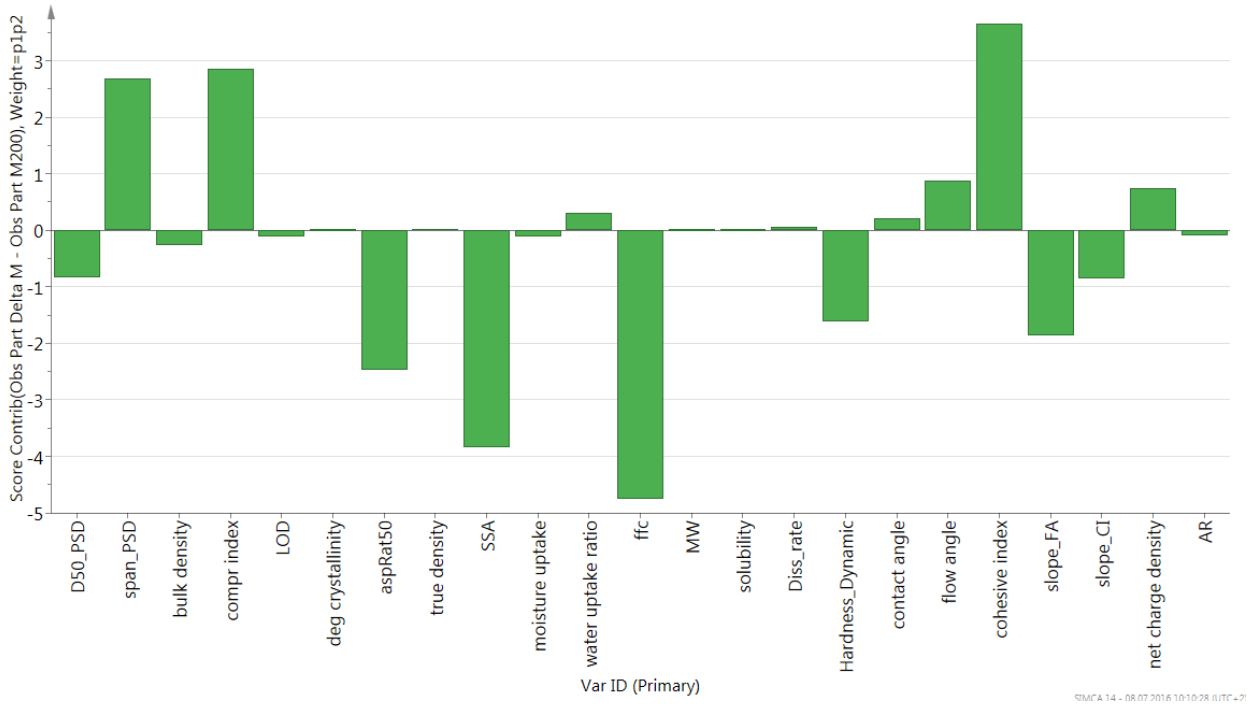

Figure 7. Contribution plot for comparison of Parteck M200 and Parteck Delta M – The larger the bar, the more the two filler differ in the given property

3.3.2.PCA of binders

Binders are commonly used in aqueous dispersions during wet granulation processes, where the physico-chemical characteristics of the dispersion are essential with regards to their influence on the product quality attributes. Therefore, no solid state characterization was performed for the binders and the data generated for the binders was mainly related to the hydrated state of the polymers in an aqueous environment. Hence, a reduced number of binder characteristics was measured compared to the fillers (Table 3). Three principal components were appropriate in order to summarize the binder properties, while all

variables were reflected in at least one of the PCs. A fourth PC did not distinctly increase the cumulative Q^2- or R^2-values and was therefore disregarded for the model.

As indicated by the R^2-bars in the summary of fit (Figure 8), the three principal components explained 93.4% of the overall variability in the binders` data set (i.e. 46.1% for 1st PC, 28.0% for 2nd PC and 19.2% for 3rd PC).

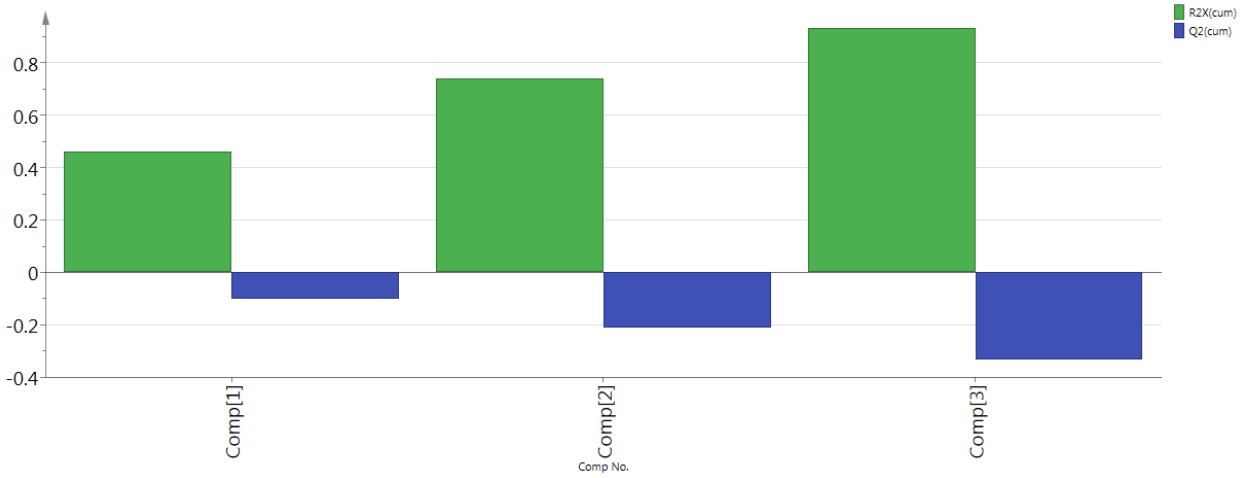

Figure 8. Summary of fit for binders

The negative Q^2 values indicated that prediction by applying the cross validation technique was not reliable for the binder data set, which might be attributed to the rather small data set used for PCA with only 5 properties characterized for 9 binders. The interpretation of the PCs for the binders was performed based on the coefficient scatter plots (Figure 9 and Figure 10) following the same approach as previously described for the fillers data set.

The first PC mainly described viscosity variability, the PC 2 mainly captured surface tension variability among the binders and the third PC was a representative of the binders` variability in glass transition temperature. Accordingly, viscosity, surface tension and glass transition temperature could be identified to be important properties while the major variation of 46.1% was explained by viscosity properties in the binder data set. Moreover, no clear correlation among the single binder properties was observed.

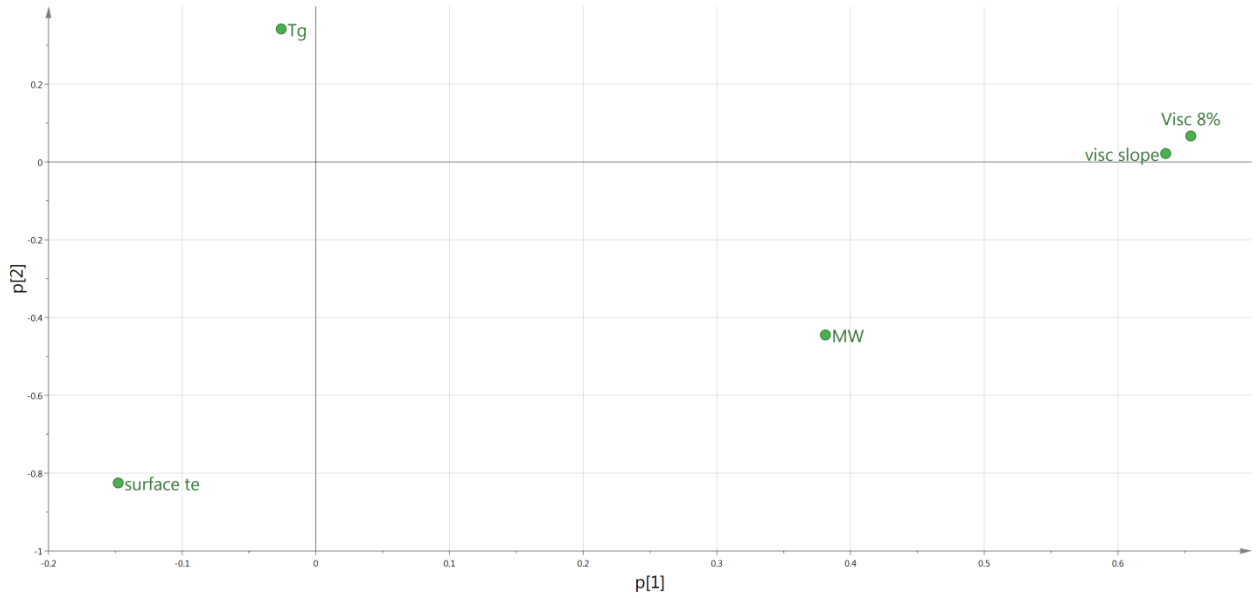

Figure 9. Loading scatter plot of binders` 1st and 2nd PC

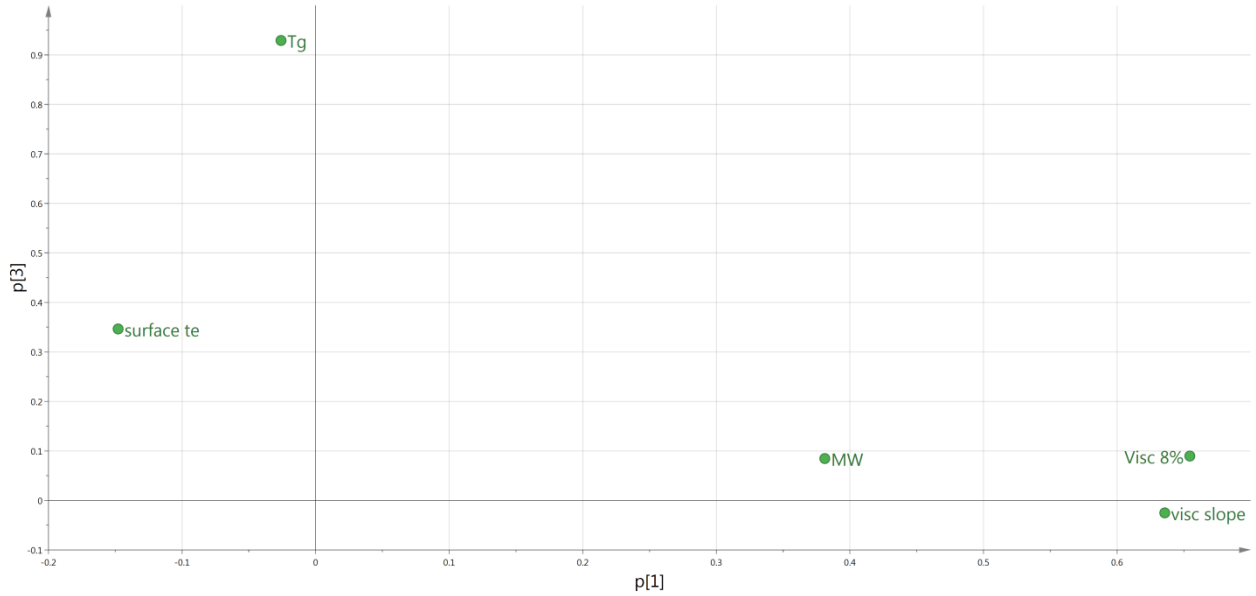

Figure 10. Loading scatter plot of binders` 1st and 3rd PC

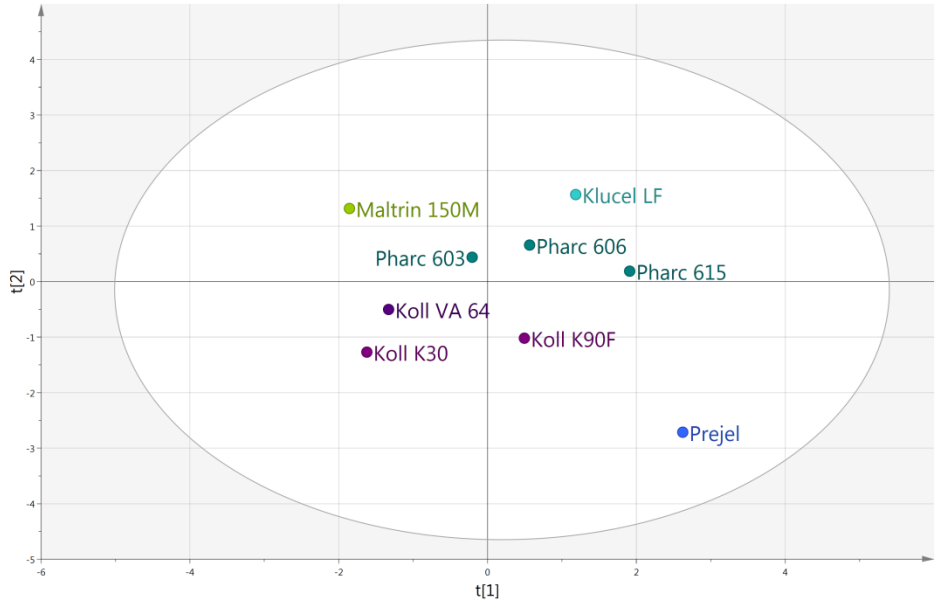

Figure 11. Scores plot PC1 vs. PC2 (binders) - Colours indicate chemical nature of binders

The PC 1 versus PC 2 scores plot showed that the binders were not clustered according to their chemical nature with respect to their principal properties explained by PC1 and PC2 (Figure 11).

Pharmacoat 615 had the highest viscosity of the three Pharmacoat grades included in this study and hence had a high positive PC1 score whereas Pharmacoat 603 with a low viscosity had a negative PC1 score value. The same fact was observed for the Kollidon polymers where Kollidon K90 had the highest PC1 score as a result of its high viscosity. Prejel had a negative PC2 score value which was in alignment with its high molecular weight for example. Due to insufficient solubility the viscosity and surface tension of an aqueous solution of Prejel could not be determined. However, according to the model Prejel should have a high viscosity which was in alignment with literature [23].

4. Conclusion

To conclude, PCA of the filler and binder data set allowed to reveal similarities and differences in excipient characteristics among materials of different chemical nature as well as between material grades. Moreover, PCA enabled to identify the excipient properties which were responsible for the differences and similarities between the excipients. The analysis also helped to understand which excipient properties were correlated or anti-correlated and which were not important in the underlying excipient property data set. Applying common pharmaceutical knowledge, the distribution of the excipients in the model space was in good agreement with the overarching properties which were assigned to the four principle components. The excipients selected for this study covered a broad range of material properties with the idea that also properties of other excipients which were not considered in this study might fall within these ranges. In addition, the database can be expanded by adding newly characterized excipients of interest. Also an expansion of the database with API data is possible. Therefore, the new excipients or APIs would need to be characterized applying the described characterization methods. In general, adding new data to the model is expected to result in an improved new model as it will be based on a larger data set with potentially more diverse excipient properties. As indicated in Figure 1, this research work is aimed to be used for a property-based selection of excipients to be processed in a continuous twin screw wet granulation process and to support a systematic investigation of formulation property impact on product and process performance. By using the principle components of the fillers and binders PCA models as factors in a DoE, the number of DOE experiments can be substantially reduced while all underlying excipient properties are still indirectly reflected and covered by the experimental design.

Appendix

Table 4. Numerical values of descriptors used for PCA of fillers

Descriptive filler characteristic (units)	Particle size distribution D50 (in µm)	Span of particle size distribution (dimensionless)	Bulk density (in g/ml)	Compressibility index (in %)	Moisture content (in %)	Degree of crystallinity (in %)	Shape of particles (dimension-less)	True density (in g/cm^3)	Specific surface area (in m^2/g)	DVS amount of water uptake (in %)	DVS water uptake ratio (in min/%)	Flowability (dimension-less)	Molecular weight (in Da)	Solubility in water (in %)	Dissolution kinetics (in mg/sec)	Dynamic Hardness (in MPa)	Wettability - Contact angle (in °)	Dynamic flow - flow angle (in °)	Dynamic flow - cohesive index (in °)	Dynamic flow - change of flow angle (dimension-less)	Dynamic flow - change of cohesive index (dimension-less)	Electrostatic charge (in µC/kg)	Cohesiveness (dimension-less)
Abreviation for variable in PCA	D50_PSD	span_PSD	bulk density	compr index	LOD	deg crystallinity	aspRat50	true density	SSA	moisture uptake	water uptake ratio	ffc	MW	solubility	Diss_ rate	Hardness_ Dynamic	contact angle	flow angle	cohesive index	slope_FA	slope_CI	net charge density	AR
Name of filler																							
Avicel PH 101	61	2.02	0.308	26.0	4.07	56.7	0.44	1.5656	1.00	11.55	9.45	3.19	36000.0	0	0.008	240	38.3	54.0	34.6	0.2675	0.1487	-4.622	10.76
Avicel PH 105	19	1.99	0.313	34.6	3.1	53.9	0.51	1.5499	1.70	11.85	6.95	1.84	36000.0	0	0.008	243	43.7	57.0	47.1	0.1358	-0.3203	-3.333	42.02
Avicel PH 301	63	2.00	0.433	23.5	3.6	57.2	0.47	1.5568	0.40	19.69	6.63	3.48	36000.0	0	0.008	200	40.3	44.1	28.0	0.1308	0.3639	-3.333	15.11
Granulac 200	33	2.81	0.543	31.5	0.5	100.0	0.62	1.5405	0.60	0.32	42.13	1.80	360.3	16	7.952	79	19.4	44.8	36.6	-0.4556	-1.1932	-3.787	29.35
Pharmatose 200M	45	2.71	0.578	32.1	0.53	100.0	0.60	1.5439	0.50	0.20	116.65	2.17	360.3	16	8.110	38	19.3	34.3	33.5	-0.4485	-1.0579	-2.560	15.95
Pharmatose 350M	30	2.64	0.51	29.9	0.43	100.0	0.62	1.5383	0.50	0.21	134.15	1.54	360.3	16	8.227	74	15.9	53.6	53.4	0.1193	0.2860	-6.560	27.80
Parteck M200	126	2.10	0.519	11.5	0.13	100.0	0.74	1.4928	3.20	0.70	53.90	7.28	182.2	15	11.561	275	43.5	35.4	10.7	0.3743	0.3428	-3.440	31.46
Parteck Delta M	65	3.54	0.46	26.1	0.1	100.0	0.50	1.5012	0.50	0.34	86.63	2.17	182.2	15	13.080	180	48.4	42.6	36.1	-0.7829	-0.4216	-2.129	29.21
Dicalcium phosphate anhydrous	19	1.70	0.901	32.0	0.27	100.0	0.71	2.8767	2.10	0.31	88.32	3.95	136.1	0	0.008	269	17.3	40.7	20.7	-0.3828	-0.6073	-2.360	89.53

Table 5. Numerical values of descriptors used for PCA of binders. (*Values could not be measured as it was not possible to fully disperse Prejel in water.)

Descriptive binder characteristic (units)	Dynamic Viscosity (in mPas)	Change in Viscosity (dimension-less)	Molecular weight (in Da)	Glass transition temperature (in °C)	Surface tension (in mN/m)
Abreviation for variable in PCA	visc 8 %	visc slope	MW	Tg	surface tension
Name of binder					
Pharmacoat 603	27.9	0.31	16000	141	45.9
Pharmacoat 606	145.0	0.35	35600	151	44.4
Pharmacoat 615	602.0	0.60	60000	158	50.3
Kollidon K30	5.2	0.12	49000	161	67.3
Kollidon K90F	89.3	0.30	2250000	178	60.3
Klucel LF	328.0	0.39	96000	182	38.9
Kollidon VA 64	4.8	0.11	58500	108	48.1
Prejel	---*	---*	76200000	125	---*
Maltrin 150M	3.3	0.08	5950	177	42.6

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CHAPTER 3

DEVELOPMENT OF A STATISTICAL MODEL TO PREDICT DRUG PRODUCT PROPERTIES – EXPERIMENTAL DESIGN TO STUDY THE IMPACT OF PHARMACEUTICAL FILLERS AND BINDERS

1. Introduction

With its potential for rapid and efficient development, cost effectiveness and improved drug product quality, continuous twin screw wet granulation is a promising alternative to batch wet granulation technologies for the pharmaceutical industry. In view of differences like the shorter granulation time between continuous wet granulation process and high shear wet granulation, the effect of excipients on process performance and product quality attributes may not necessarily be transferable. However, this understanding is of high importance in the context of a Quality by Design (QbD)-based formulation development [1]. As described in chapter 4, a number of studies have been published which investigated different formulations processed via twin screw wet granulation in order to study the influence of excipient material attributes on the drug product critical quality attributes. However, it remained challenging to compare excipients, which were very different in their characteristics in the same study due to varying requirements for the different formulations in e.g. liquid-to-solid (L/S) ratio [2]. Therefore, the above-mentioned studies included limited variation in formulation composition which allows to assume that the obtained scientific conclusions are mainly formulation specific. The objective of this study was to investigate excipients with very different material properties in one experimental design and to systematically study their impact on process and product performance in a continuous twin screw wet granulation process.

In some aspects, the objective of this study is comparable with the work described in chapter 4 as both studies aimed to generate understanding about the impact of excipients on drug product attributes by following a systematic statistical approach. The main differences and similarities of the two studies are summarized in Table 1. The results of this study were used to identify limitations in the experimental set-up and statistical approach in order to optimize the approach and to define areas of interest for further investigations for the second study which is described in chapter 4.

Table 1. Summary of differences and similarities of both Design of Experiment (DoE) studies within the PhD project (for further details the reader is referred to the Methods section of the respective chapters)

	Criteria	DoE study 1 (this chapter)	DoE study 2 (chapter 4)
Similarities	Excipient dataset	data from excipient characterization and the principal component analysis were used as basis (chapter 2)	
	Statistical tools	application of statistical methods: combination of principle component analysis (PCA) and DoE	
Differences	Statistical Design	full factorial design (enabled estimation of quadratic model term) with 5 factors	d-optimal design with 5 factors
	Selection of fillers	systematic by hand selection of fillers based on PCA score values (including dicalcium phosphate)	selection of fillers via d-optimal design based on PCA score values (dicalcium phosphate excluded)
	Selection of binders	systematic by hand selection of binders based on PCA score values; 4 binder types at fixed concentrations	by hand selection of binders; 2 binder types at varying concentrations
	Equipment type and location	Experimental trials performed on ConsiGma©-25 line at Ghent University with loss in weight liquid feeding system	Experimental trials performed on ConsiGma©-25 line at Roche Basel with mass flow meter liquid feeding system and two liquid addition ports

The general approach can be summarized as follows. A combination of principle component analysis (PCA) and Design of Experiments (DoE) was applied in order to (a) reduce the number of factors and the number of experimental batches in the DoE and (b) evaluate various formulations in the same DoE. Commonly known pharmaceutical fillers and binders for twin screw wet granulation were selected and extensively characterized with regards to their physico-chemical properties and solid state characteristics. A PCA was then performed on the resulting data set of excipient properties in order to identify the overarching properties (chapter 2). By using the overarching properties as DoE factors, suitable combinations of fillers and binders were selected for the experimental trials. The resulting statistical models were used to understand and predict the impact of overarching excipient properties on granule and tablet quality attributes. Aiming to keep the process influence as low as possible the process parameters were kept constant whenever possible.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel PH101, Avicel PH105, Avicel PH301, FMC Biopolymer, Philadelphia, USA), α-lactose monohydrate (Pharmatose 200M, Pharmatose 350M, DFE Pharma, Goch, Germany and GranuLac 200, Meggle Group, Wasserburg, Germany), mannitol (Parteck M200, Parteck Delta M, Merck, Darmstadt, Germany) and dicalcium phosphate anhydrous (FCC grade, Innophos, New Jersey, USA) were used as fillers. Hydroxypropyl methylcellulose (Pharmacoat 615, Shin Etsu, Tokyo, Japan), polyvinylpyrrolidone (Kollidon K90F, BASF, Ludwigshafen, Germany), hydroxypropyl cellulose (Klucel LF, Ashland, Kentucky, USA) and maltodextrin (Maltrin 150M, Grain Processing Corporation, Iowa, USA) were used as binders in this study. Croscarmellose sodium (Disolcel GF, Mingtai Chemical Co, Taoyuan Hsien, Taiwan), magnesium stearate (Mallinckrodt, St. Louis, USA) and colloidal silicon dioxide (Aerosil 200, Evonik, Rheinfelden, Germany) were used to prepare the final blend before tablet compression.

2.2. Definition of experimental design: combined PCA/DoE approach

2.2.1. Selection of filler and binder types

A PCA of filler and binder characteristics was used as basis for a by-hand selection of excipients to be tested in the experimental study (Table 2). Fillers and binders which are commonly used for wet granulation and which are different in chemical nature and properties were selected for excipient characterization to obtain a broad range in excipient characteristics. Further details on excipient characterization as well as on the PCA are given in chapter 2. The overarching properties of fillers were identified via PCA as moisture-related properties (PC1), flow-related properties (PC2), density/particle size-related properties (PC3) as well as charge/adhesion-related properties (PC4). For the binders the overarching properties were identified as viscosity (PC1) and surface tension (PC2). 3 out of 4 overarching filler properties were used as DoE factors (including 3 out of 4 PC avoided double selection of filler types, while the most important filler properties were still considered, see below). The 2 binder overarching properties were also used as additional DoE factors (Table 2). For clarification the reader is reminded that the terms “principle component” and “overarching property” are used synonymously. In a DoE, the experimental trials are selected based on algorithms such that different combinations of the extreme values of the factors are tested. The selected runs are thus a combination of high and low values for the studied factors. Following the same principle for this formulation DoE, high and low values were selected for the DoE factors, i.e. the principle components as depicted by the arrows in Figure 1. Applying this approach for each of the three principle components of fillers and the two principle components of the binders, fillers and binders were identified, each of which represent either a high or low value for the DoE runs. Thus a set of

6 fillers (high and low score values for 3 principle components) and 4 binders (high and low score values for 2 principle components) was selected for the experimental trials (Table 2).

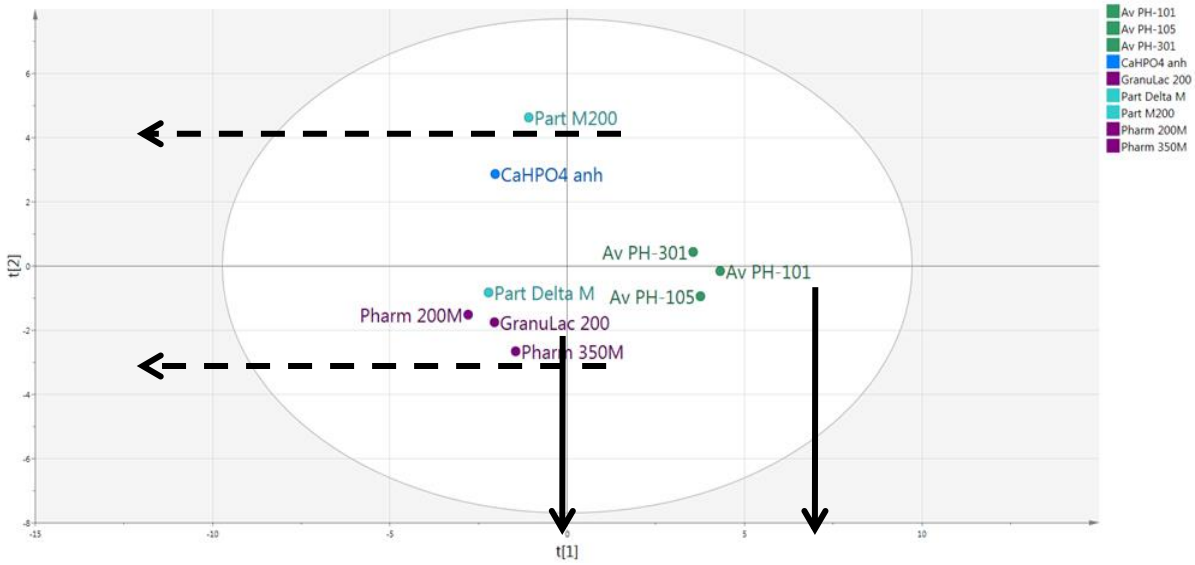


Figure 1. PC1 vs. PC2 scores plot of filler PCA (see chapter 2): selection of fillers with high and low score values

Table 2. List of selected fillers and binders as well as studied DoE factors

	DoE factors = principal components (PC)	**Low value**	**High value**
Filler	Factor 1 = PC1 filler *mositure-related properties*	Pharmatose 200M	Avicel PH101
	Factor 2 = PC2 filler *flow-related properties*	Pharmatose 350M	Parteck M200
	Factor 3 = PC3 filler *density/particle size-related properties*	Dicalcium phosphate	Parteck Delta M
Binder	Factor 4 = PC1 binder *viscosity*	Maltrin M150	Pharmacoat 615
	Factor 5 = PC2 binder *surface tension*	Kollidon K90F	Klucel LF

When excipients were selected based on their principle component (PC) score values, none of the excipients should be selected twice to represent a low or high factor setting in the DoE in order to avoid confounding of factors. If factors were confounded, the attribution of any observed effect on the response to a certain overarching filler property would be ambiguous and would thus result in a loss of important information. In order to avoid double-selection of fillers, only 3 PC (out of 4) were considered for the filler selection. In an ideal case, the factors of a DoE can be varied completely independently from each other, i.e. the factors are orthogonal and not interrelated. Although the principle components are in general orthogonal to each other, there is a deviation from perfect orthogonality when excipients are selected as factor settings. For example Pharmatose 200M with a low PC1 score value (-2.78) was selected as low set point for the factor PC1, however Pharmatose 200M has also score values for PC2 (-1.52) and PC3 (0.32) which are not zero. The information about deviation from perfect orthogonality was included in the experimental design since each excipient was defined by its score values for the principle components. Nevertheless the lack of perfect orthogonality carries the risk of confounding and had to be considered during data analysis.

2.2.2.Selection of binder concentration

In contrast to the binder type, the binder concentration was not tested as a factor in the experimental design. Hence, an appropriate binder concentration had to be defined for the experimental trials. One possibility would have been to apply all binders in the same concentration in the formulation. The shortcoming of this approach is, however, that not all selected binders have the same binding efficiency at equal concentration in the formulation. Therefore the following approach was used to reach comparable binder efficiency for all binder types:

1. Identify the recommended binder concentration range for application in wet granulation processes (based on the binder manufacturer recommendation)
2. Select target binder concentration in the formulation as 70% of the overall recommended range.

The resulting binder concentration per binder type is listed in Table 3.

Table 3. Targeted binder concentration in the formulation (remark: as described in section 3.1 the target concentration could not always be reached)

Binder type	Recommended range by manufacturer	Target binder concentration in formulation
Pharmacoat 615	2-5%	4.1%
Klucel LF	2-6%	4.8%
Maltrin M150	3-10%	7.9%
Kollidon K90F	1-3%	2.4%

2.2.3.Statistical Design of Experiments (DoE)

Five factors were studied in the experimental design. Three factors were the score values of the principal components PC1, PC2 and PC3 being derived from the filler PCA. In that way, three overarching filler properties were investigated in the DoE, while all underlying filler characteristics were still indirectly included in the experimental design. Factors 4 and 5 were the binder score values for PC1 and PC2 of the binder PCA, respectively (chapter 2). A full factorial design was computed (MODDE, Version 11.0, Umetrics®, Umeå, Sweden) to provide maximum information including interactions between fillers and binders. Thus all possible combinations of the selected fillers and binders were manufactured. In addition, the design was split up into 4 blocks such that within a block the binder type was constant. 3 center point replicates were included per block offering the opportunity to analyse data blockwise (i.e. per binder type) in case the binder effect might overrule the effect of the fillers. A center point is usually located in the origin of the experimental space. In this study however, none of the fillers was located in the origin of all PCA score plots which would be equivalent to average factor values. Parteck Delta M had score values for PC1 and PC2 which were close to average and was thus selected as filler for the center point runs (3 runs per block). Even if not representing average factor values for all 3 filler factors, the center point will still provide information about the reproducibility. Avicel PH105 was in addition selected as filler for external model verification purposes since this filler was not selected for the DoE experiments, but as part of the PCA its score values were available for prediction purposes. As depicted in Figure 2 each block finally consisted of 9 runs, resulting in a total of 36 experiments (Table 4). The center points were randomized within each block.

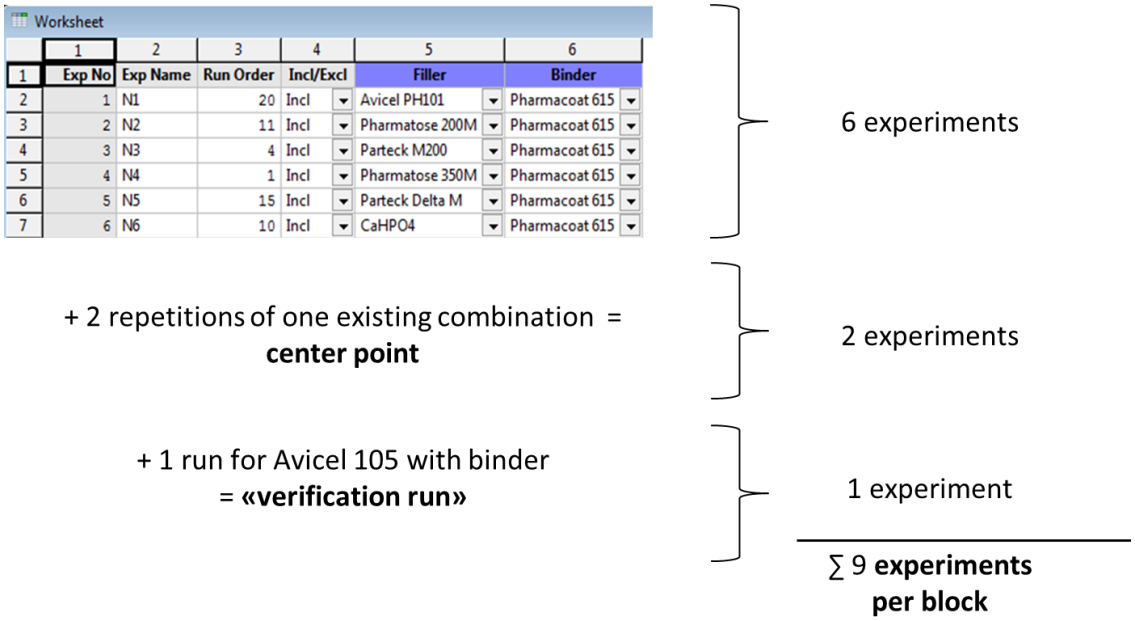


Figure 2. Compilation of the experimental runs per block (example shown for Pharmacoat binder; Parteck Delta M was used for the center points)

Table 4. List of experimental batches

Batch number = run order	Filler type	Binder type
1	Parteck Delta M	Pharmacoat 615
2	Avicel PH101	Pharmacoat 615
3	Pharmatose 200M	Pharmacoat 615
4	Parteck M200	Pharmacoat 615
5	Parteck Delta M	Pharmacoat 615
6	Pharmatose 350M	Pharmacoat 615
7	CaHPO4	Pharmacoat 615
8	Avicel PH105	Pharmacoat 615
9	Parteck Delta M	Pharmacoat 615
10	Parteck Delta M	Klucel LF
11	CaHPO4	Klucel LF
12	Avicel PH101	Klucel LF
13	Parteck Delta M	Klucel LF
14	Parteck M200	Klucel LF
15	Avicel PH105	Klucel LF
16	Pharmatose 350M	Klucel LF
17	Parteck Delta M	Klucel LF
18	Pharmatose 200M	Klucel LF
19	Avicel PH101	Maltrin M150
20	Pharmatose 200M	Maltrin M150
21	Parteck Delta M	Maltrin M150
22	Avicel PH105	Maltrin M150
23	CaHPO4	Maltrin M150
24	Parteck Delta M	Maltrin M150
25	Parteck M200	Maltrin M150
26	Pharmatose 350M	Maltrin M150
27	Parteck Delta M	Maltrin M150
28	Pharmatose 200M	Kollidon K90F
29	Parteck Delta M	Kollidon K90F
30	Avicel PH101	Kollidon K90F
31	CaHPO4	Kollidon K90F
32	Parteck M200	Kollidon K90F
33	Parteck Delta M	Kollidon K90F
34	Avicel PH105	Kollidon K90F
35	Parteck Delta M	Kollidon K90F
36	Pharmatose 350M	Kollidon K90F

2.3. Manufacturing of DoE batches

Continuous twin screw wet granulation technology was applied for the production of granules using the ConsiGma®-25 unit (GEA Pharma Systems, Collette®, Wommelgem, Belgium). Consisting of a twin screw granulator followed by a six-segmented fluid bed dryer and a so-called Granule Conditioning Unit which contained a cone mill, the machine allowed continuous wet granulation from powder (pre-blend) to dried and milled granules [3]. The tablet compression of the dried granulate was performed off-line after addition of the extra-granular phase (blending was performed in batch mode). After manufacturing, granules and tablets were characterized via selected in-process control (IPC) tests. Figure 3 provides an overview of the process flow including the IPC tests.

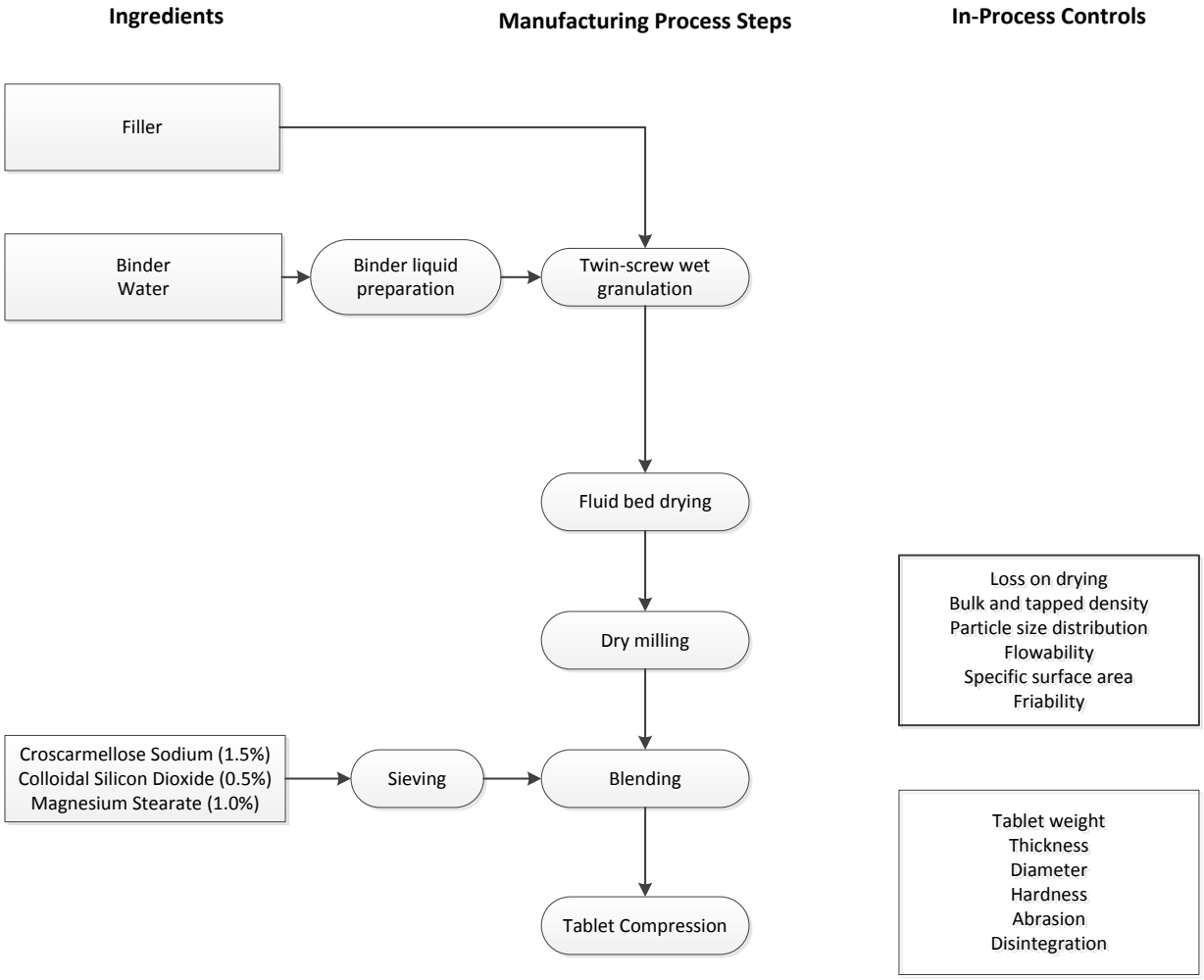


Figure 3. Process flow chart including IPC tests

2.3.1.Granulation

In this study, it was required to minimize the influence of process parameters on product attributes since the objective was to gain information on the impact of excipient properties on the product critical quality attributes. Consequently process parameters were set to fixed values wherever possible. However, variations in the formulation composition required the adjustment of some process parameters in order to obtain adequate granulation conditions (i.e. avoid under- or over-granulation). Especially the water content which is needed during wet granulation can vary depending on the filler type in the formulation. A systematic approach for the selection of the most appropriate settings was applied for the parameters “water content” and “screw speed” to ensure optimal and consistent granulation conditions for every formulation composition (Figure 4).

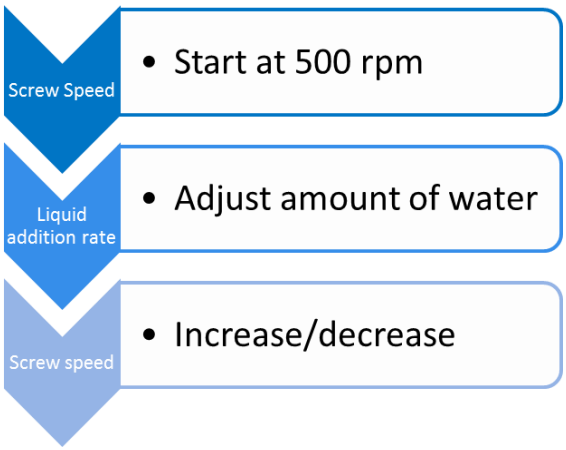


Figure 4. Standardized procedure to determine the process parameter settings “water content” and “screw speed” in order to create ideal granulation conditions for each batch

Therefore, prior to the manufacturing of a batch, the appropriate water content and second, the optimal screw speed was identified. For identification of the appropriate water content, granules were produced at a fixed screw speed of 500rpm and granule samples were collected at different water contents: starting from very dry and powdery granules the water content was increased stepwise until granules were over-wetted. The collected granule samples were visually examined with regards to particle size and examined by hand regarding their state of agglomeration and binding (e.g. strength of granules). After having identified the most optimal setting for “water content”, the screw speed was adjusted accordingly to optimize the granule particle size, if needed.

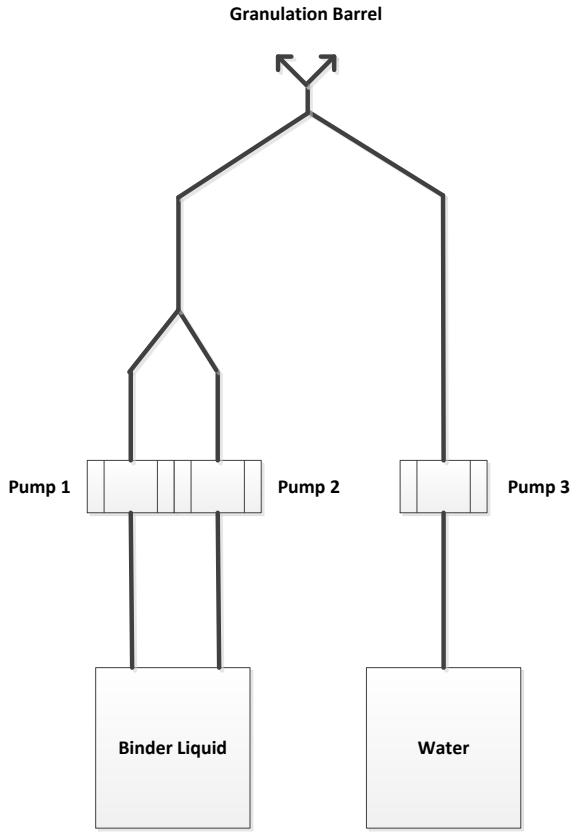


Figure 5. Set-up of liquid feeding system for granulation

As depicted in Figure 5 the binder liquid feeding system was set-up to ensure consistent binder concentration in the formulation, while the water content could be adjusted separately. The liquid mass flow was controlled via loss-in-weight principle for the binder liquid and via pump speed for water. Tubings with inner diameter of 3.2mm and nozzles with diameter of 1.6mm were used. Powder mass feed rate and binder liquid feed rate were selected to reach the target binder concentration in the formulation. The granulation jacket temperature was set to 25°C. Both granulation screws were each equipped with 2 blocks of 6 kneading elements in an angle of 60°, each block separated by a conveying zone (Figure 6).

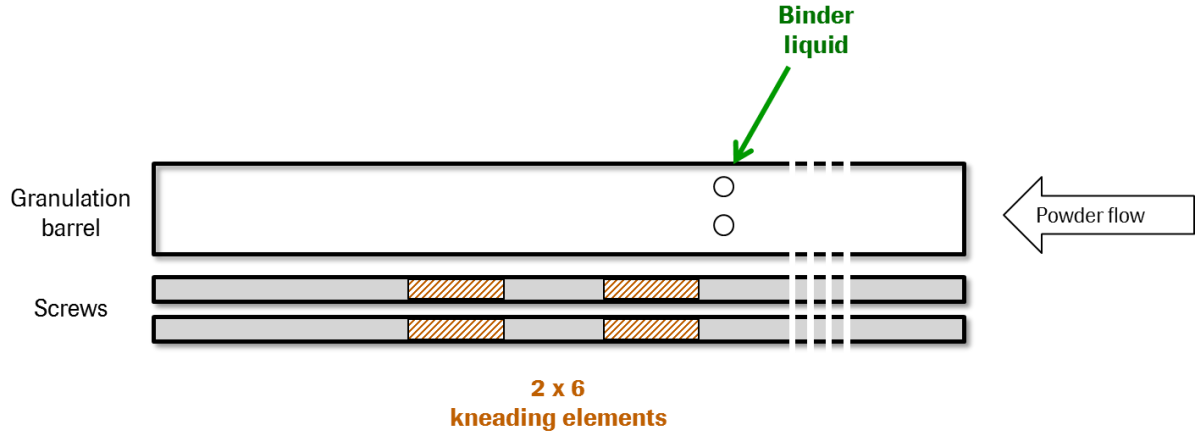


Figure 6. Scheme of applied screw configuration: kneading elements (orange) and conveying zone (grey)

The inlet air temperature of the fluid bed dryer was set to 60°C. The drying time in the fluid bed dryer was adjusted to reach a target granule LOD (loss on drying) of 0-1.5% for lactose/mannitol and 2.5-4.5% for microcrystalline cellulose. The target LOD was defined to correspond to the LOD of the filler starting material in order to obtain a residual granule moisture which is in equilibrium at ambient conditions. This approach made sure that there is no significant water uptake or water loss of the granules during storage. The inlet air flow in the fluid bed dryer was adjusted in order to ensure optimal fluidization conditions to account for the varying weight of granules, e.g. depending on the water content that was used for granulation. For the dry milling of granules a sieve size of 1.575mm and a rotation speed of 1000rpm was used.

2.3.2.Final blend preparation

Prior to tablet compression, an extra-granular phase was added to the granules. The extra-granular phase consisted of 0.5% colloidal silicon dioxide, 1.5% croscarmellose sodium and 1.0% magnesium stearate. Silicon dioxide was added to provide sufficient flowability to the blend, while Magnesium stearate was selected as most common lubricant to ensure robust tablet compression without sticking/picking. Silicon dioxide and croscarmellose sodium were sieved (1.0mm mesh size) for delumping purpose and mixed with the granules for 1 minute. Magnesium stearate was sieved (also for delumping, 0.5mm mesh size), then an approximately 10-fold amount of the granule blend (compared to the magnesium stearate amount) was added and mixed for another 3 minutes. Finally the two blends were united and mixed for another 3 minutes. Two blenders of different sizes were used (Turbula T2C and Turbula T10B, Glen Mills, Clifton, NJ, USA).

2.3.3.Tablet compression

A Korsch XL 100 tablet press (Korsch, Berlin, Germany) was instrumented with four pairs of 9mm flat-faced punches and operated at a speed of 30rpm. Process parameters were fixed if possible, in order to minimize their influence on the tablets characteristics. The target tablet weight was 300mg. Tablets were compressed at forces of 5, 10, 15, 20 and 25kN. In addition, tablets with a target hardness of 75N were compressed for each batch in order to allow comparison of tablet attributes at comparable tablet hardness.

2.3.4.Characterization of granule attributes

Granule samples were collected and characterized by the test methods described below (also Figure 3 for an overview).

Particle Size Distribution

By means of sieve analysis the particle size distribution of granules was measured. Sieves of 1000, 710, 500, 315, 250, 180, 125 and 90µm and an amplitude of 2mm (continuous mode, 3 minutes) were applied. The sample size was 30g. The fine fraction (in %) was calculated as the amount of granules below 125µm.

In addition, dry laser diffraction (Malvern Mastersizer 2000, Malvern Instruments, Malvern, UK) was used for the determination of the particle size distribution. At least two measurements were performed per sample. The median particle size (D_{50} in µm) was calculated.

Flowability and bulk density

Flowability of granules was characterized by means of ring shear testing (Ring Shear Tester RST-XS, Dr. Dietmar Schulze, Wolfenbüttel, Germany) applying a pre-shear of 1000 Pa. The three most suitable normal loads of each measurement were automatically chosen by the device, whereas the first normal load was repeated as a fourth normal load measurement point. The flow function coefficient (ffc), which is the ratio of consolidation stress to unconfined yield strength, was used to characterize flowability [4].

The granule bulk density (in g/ml) was calculated as the volume *V* in the shear cell over the mass *m* of the powder contained in the shear cell.

Moisture content

Loss on drying (in %) was measured with an infrared dryer (Mettler LP16, Mettler-Toledo, Greifensee, Switzerland) in combination with a balance (Mettler PM480 Delta Range, Mettler-Toledo, Greifensee, Switzerland). A drying temperature of 90°C was applied until the weight variation was below 2mg within 30 sec. LOD was used to define the appropriate drying time in the fluid bed dryer.

Specific Surface Area

The specific surface area (in m^2/g) was determined via nitrogen adsorption (Tristar II 3020, Micrometrics, Norcross, USA) in the validity range of the BET-isotherm. The samples were degassed at room temperature over-night before conducting the measurements (n=2).

Friability

Friability of granules was measured (n=3) using a friability tester (PTF E Pharma Test, Hainburg, Germany) as described by Vercruysse et al [5]. Before measurements, the fine fraction of the granules was removed with a 250µm sieve. Afterwards 10.0g of the granules (I_{wt}) were filled into the drum together with 200 glass beads of 4mm diameter. At a speed of 25rpm a 10 minute run was performed. The generated granule size fraction below 250µm was again removed via sieving and the residual amount of granules was weighed (F_{wt}). The friability (in %) was calculated as $((I_{wt} - F_{wt})/I_{wt}) * 100$.

2.3.5.Characterization of tablet attributes

Tablet mass, height, diameter and hardness were measured for all compression forces as well as for the samples with a target hardness of 75N. Additionally, abrasion was determined for tablets samples at 10kN compression force and samples with 75N target hardness. Disintegration time was determined for tablets with 75N target hardness.

Tablet hardness and solid fraction

Tablet thickness (n=10), diameter (n=10), weight (n=20) and hardness (n=10) were determined for all compression forces as well as for the 75N hardness samples with an automatic tablet testing system (Sotax HT 100, Sotax AG, Aesch, Switzerland). Tablet solid fraction was calculated from tablet mass (m in g), volume (V in cm^3) and true density (ρ_{true} in g/cm^3) as $(m/V)/ \rho_{true}$. True density of the final blend before compression was measured using a helium pycnometer (AccuPyc 1330, Micrometrics, Norcross, USA). Five purges at 19.5 psig and five runs at 19.5 psig were conducted in one measurement (n=2).

Abrasion

100g of de-dusted tablets (m_1 in g) with target hardness of 75N were filled into a Weis-Fogh drum (Friabilator AE-1, Biomation, Jugenheim, Germany) which rotated 1250 times at a speed of 100rpm. After the stress test tablets were de-dusted again, the remaining tablet weight was determined (m_2 in g) and abrasion (in %) was calculated as $((m_1-m_2)/ m_1)*100$.

Disintegration

The disintegration time (in sec) of the 75N target hardness tablets (n=6) was determined using a disintegration tester (basket method; Sotax DT2, Sotax AG, Aesch, Switzerland) with automatic endpoint detection. Demineralized water with a temperature of 37°C was used as disintegration medium.

Compression force

The compression force (in kN) which was needed to reach a target tablet hardness of 75N was recorded and used as an indicator for tabletability.

2.4. DoE analysis and model development

2.4.1.Statistical models to generate understanding of excipient impact on responses

As summarized in Table 5 selected granule and tablet critical quality attributes were used as responses for the statistical model.

Table 5. Overview of model responses

Granule attributes	Tablet attributes
Bulk density	Disintegration time
Particle size D50	Tablet abrasion
Fine fraction <125 µm	Solid fraction @75N
Flowability	Compression force @75N
Friability	
Specific surface area	

Using the software Modde (Version 11.0, Umetrics®, Umeå, Sweden), multiple linear regression (MLR) models were fitted. More information about MLR models is given in chapter 4.

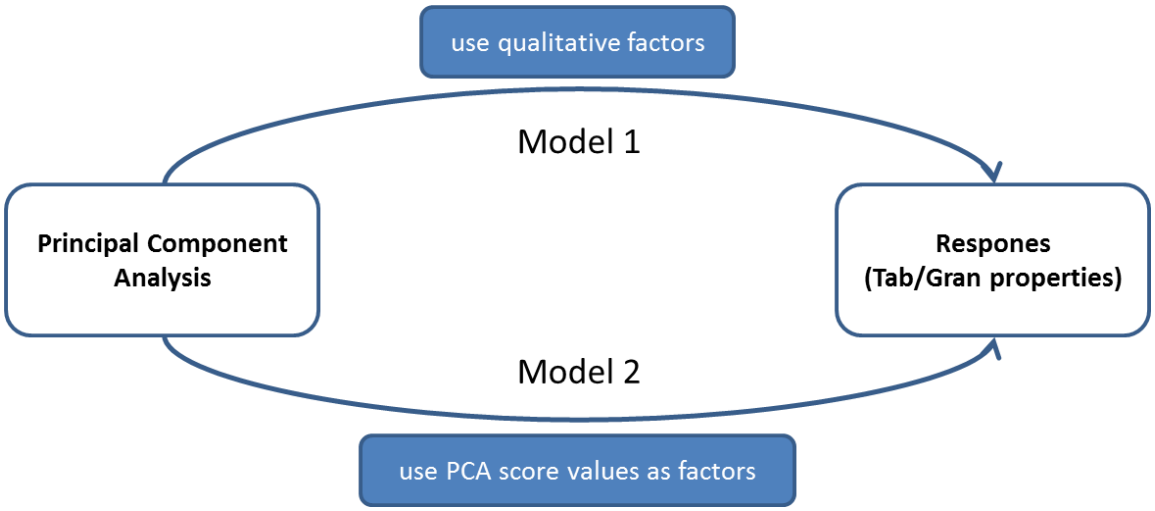


Figure 7. Options for statistical models: model 1 is based on qualitative factors and model 2 on quantitative factors

As depicted in Figure 7 two types of MLR models were fitted, both model types including only the main model terms (main effects) but different type of factors. The expressions "model 1" and "model 2" are used to group the number of underlying MLR models per response for a facilitated discussion. Model 1 was calculated using qualitative factors for fillers and binders, i.e. the names of the filler and binder types. Thus, no information about the filler and binder properties was included in the model. Being the simplest type of model it provided valuable information if a filler or binder influenced the granule and tablet properties and to what extent. A logarithmical transformation of responses was performed if needed in order to convert a non-normal into a normal distribution since the latter is in general expected to result in better model estimates and statistics [6]. For model 1 all experimental batches were considered, including the batches with Avicel PH105 which were actually produced for model verification purposes. However, since model 1 was not suitable for prediction purposes due to the qualitative factors, Avicel PH105 was included to increase the underlying dataset for the model.

For a more in-depth understanding which overarching filler and binder properties were responsible for the impact on granule and tablet properties, model 2 was calculated. By using the filler and binder score values from the PCAs, the overarching excipient properties were reflected as factors in the model to gain understanding which overarching property – and to what extent - had an impact on the product quality attributes. Again a logarithmical transformation of responses was performed where needed.

2.4.2. Optimization and verification of statistical models

Since MLR models are in general fitted per response, it is possible to optimize the model of every response separately to achieve higher R^2 and Q^2 values as this results in a better

model fit and potentially in more precise predictions. Models can be optimized by adding model terms (e.g. interaction terms, quadratic terms) or by removing statistically insignificant model terms as long as this results in higher Q^2 values [6]. A full factorial design in general allows the addition of interaction model terms. Moreover the software indicates if non-linear relations occur. However, in order to receive clear information about non-linear relations of factors, different designs with more experimental runs are needed. With the selected full factorial design, quadratic terms are most probably confounded and can thus not be used for model interpretation. Although in some cases the addition of quadratic terms might lead to optimized models with larger Q^2 values and potentially stronger predictive model power.

External model verification is a suitable way to assess the models' predictive power. The purpose of external model verification is to test if the model is also valid for data that was not included in the models. Model 2 with quantitative factors (main model terms) were optimized towards the highest Q^2 values per response by including interaction terms and quadratic terms as well as by removing insignificant main model terms. The addition of all interaction model terms (10 model terms) was not possible for an MLR model since the number of 36 experimental runs resulted in an ill-conditioned data matrix due to the lack of degree of freedom (too many factors and insufficient number of experimental runs). After model optimization, confounding of some factors was observed. Thus, the simpler models with only main model terms (i.e. not optimized) were used to understand the impact of factors on responses (section 3.2.2). Avicel PH105 was selected as filler (Figure 2) for model verification purpose and was combined with all 4 binder types of this study, resulting in 4 verification batches that were not included in the experimental design. Based on the factor settings, values for the responses were predicted. The predicted values were then compared with the observed experimental values of the 4 verification batches which were measured after production of granules and tablets. The difference of predicted values to observed values (P/O difference in %) was calculated.

3. Results and Discussion

3.1. Limitations of the DoE regarding binder concentrations

Pre-trials were performed (data not shown) to test if the binder liquids can be prepared and pumped at the required concentrations. The trials revealed that the maximum binder concentration in the granule formulation was limited: first, the binder solubility in aqueous solutions was limited and second, there was a limitation in pumpability and control of constant liquid flow for highly concentrated and therefore highly viscous binder liquids. Due to the low water uptake capacity of pure lactose, batches which contained lactose as filler represented the worst case for wet granulation, since lactose only tolerated a minimal amount of water for granulation. For this study the selection of excipients was based on the principle component score values (see 2.2.1). Consequently binder types with extreme

properties were selected, for example high viscosity binder types such as Pharmacoat 615 or Kollidon K90. In order to work with comparable binder concentrations in the formulation for each binder type, the maximum achievable concentration with lactose was used as set-point for each DoE block. Table 6 shows the targeted binder concentration and the concentration that was maximal achievable in the given set-up.

Table 6. Targeted and observed binder concentrations in the formulations. (*maximal concentration that was achievable in the given set-up)

Binder type	Binder target concentration in formulation (see Table 3)	Actual binder concentration in formulation*	% of target	Is actual binder concentration within recommended
Pharmacoat 615	4.1%	0.71%	17%	no
Klucel LF	4.8%	0.98%	20%	no
Maltrin M150	7.9%	6.92%	86%	yes
Kollidon K90F	2.4%	1.51%	63%	yes

The target concentration was reached for none of the binder types, however for Maltrin and Kollidon the achieved concentration was still within the binder concentration range recommended by the manufacturer for wet granulation processes.

Although the by-the-manufacturer recommended minimal binder concentration was not reached for Pharmacoat and Klucel, it was still possible to granulate all batches with these binder types. An exception were batches with dicalcium phosphate (DCP) as filler in combination with Pharmacoat (batch 7), Klucel (batch 11) and Kollidon (batch 31) which were insufficiently granulated, resulting in high granule friability, low D_{50} and large amount of fines. Tablets were compressed for batch 7, 11 and 31 by applying higher compression forces compared to other batches. The tablet properties of batches produced with DCP such as abrasion and disintegration time were comparable with other batches. DCP in combination with Maltrin as binder resulted in good granule quality. From these findings it was concluded that when using a high DCP content as filler in a formulation, higher binder concentrations might be needed to obtain granules of good quality.

Overall, granules and tablets of adequate quality were produced for all other batches although the originally targeted binder concentrations were not reached.

In view of the interpretation of model results it must be taken into account that the binder concentration is neither comparable for all binder types (as it was originally planned for this DoE), nor is the binder concentration represented as factor in the design. Different binder concentrations had to be applied in the formulations due to the pumpability limitations. To account for this limitation, the binder concentration was added to the models as an uncontrolled factor (data not shown). However, the factor “binder concentration

(uncontrolled)" was confounded with the binder type. The explanation for the observed confounding is that the binder concentration was always varied together with the binder type and thus no additional information was given to the model by adding the binder concentration as uncontrolled factor. Overall it was assumed that some of the responses might have come out differently if the binder was present in the originally targeted concentration in the formulation and that the effect of binders might potentially be underrepresented in the models due to the lower binder concentrations in the formulation. Moreover, some response models were dominated by the DCP batches due to its low quality granules (e.g. with a high friability as described above) which might have decreased the model quality for the respective responses.

It must be stated that the limitations regarding the maximal achievable binder concentration in the formulation originated from the experimental set-up where formulations with one filler type were used. Some formulations contained lactose as filler with a very low water uptake capacity which was the limiting factor when defining the binder concentration for the experimental trials.

3.2. Impact of studied factors on granule and tablet responses

More detailed explanations about the discussed statistical plots and model parameters can be found in chapter 4.

3.2.1. Model 1 (qualitative factors)

The models with qualitative factors – summarized as model 1 for facilitated discussion - were used to investigate if, and if yes to what extent, the fillers and binders which were selected in this study had an impact on the granule and tablet properties.

The coefficient plots were used for interpretation of results as they display the change in the response when a factor is varied from the average to the high set point. The error bars represent the 95% confidence intervals. Variables were scaled and centred for comparability. Figure 8 shows coefficient plots of three selected responses. A positive bar expresses an increase in the response value if the respective filler or binder was used, while a negative bar expresses a decrease in the response. If the depicted error bar crosses zero, the coefficient was not considered for interpretation for the lack of statistical significance. It was observed that Avicel PH101 and Avicel PH105 resulted in improved granule flowability (expressed as higher ffc values), whereas Pharmatose 350M and Parteck Delta M resulted in granules with reduced flowability. The binder type did not impact the flowability of granules. The use of fillers like Parteck M200 and binders like Pharmacoat and Klucel increased the specific surface area (SSA) of granules. In contrast, Pharmatose 200M and 350M as well as the binder Maltrin decreased SSA. A potential reason for the different effects of the binder types on the granule SSA might be attributed to the applied binder concentrations in the formulation: low concentrations of Pharmacoat (0.71%) and Klucel (0.98%) were present in contrast to higher concentrations for Maltrin (6.92%). Both Avicel

grades and Kollidon increased the median granule size (expressed as D_{50}), while dicalcium phosphate and Pharmacoat yielded smaller D_{50} values.

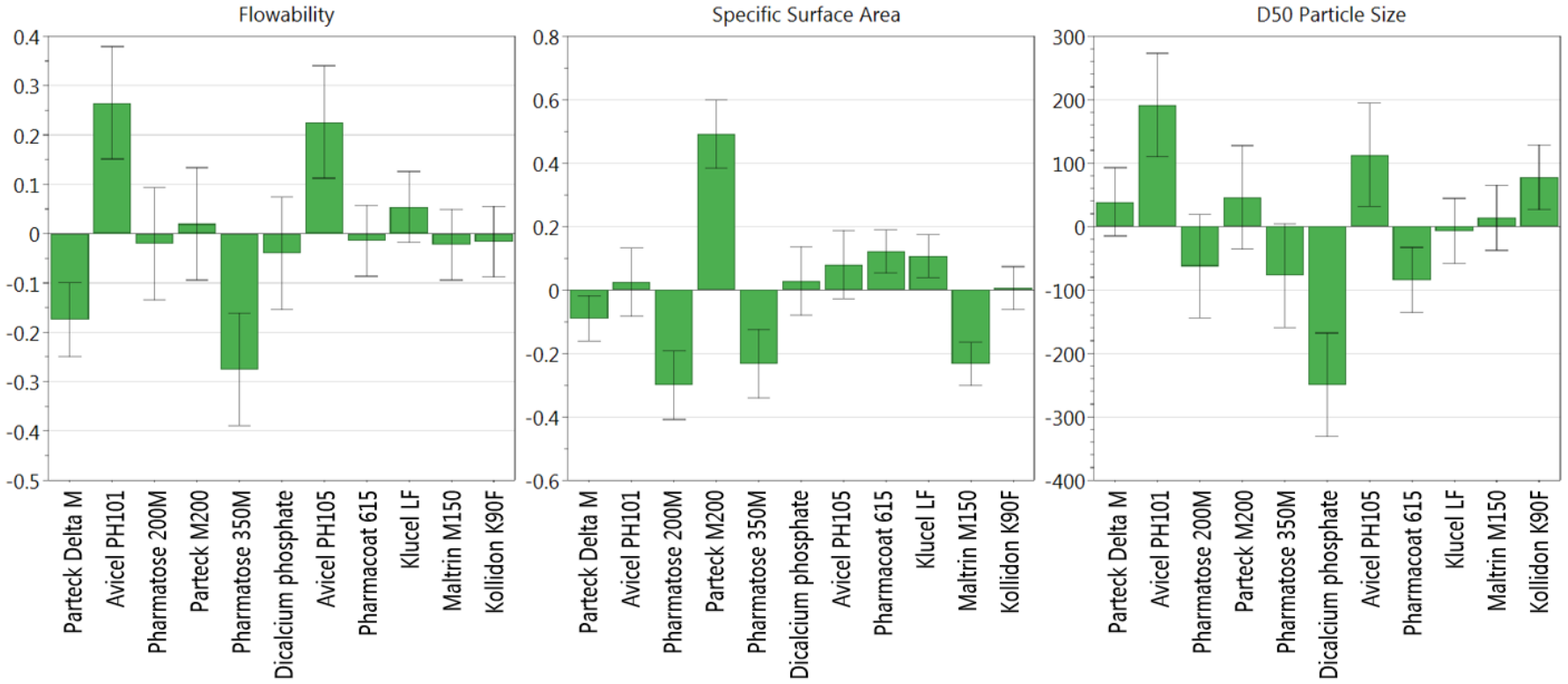


Figure 8. Coefficient plots (scaled and centered) of selected granule responses from model 1 with qualitative factors: flowability (left), specific surface area (middle) and median particle size (right)

Table 7 provides a summary of the significant coefficients of fillers and binders which were observed for all granule and tablet properties (information was taken from the coefficient plots). Overall the fillers revealed a stronger influence on the responses compared to the binders. The filler Pharmatose 200M impacted only a minority (3 out of 10) of the responses. Almost every filler and binder type (9 out of 11) impacted the response disintegration time. No impact of binders was observed on bulk density, flowability and tablet solid fraction. For the interpretation of binder impact, however it must be taken into account that the conclusions can only be seen in context of the limited binder concentration that was used in this DoE (Table 6). The outcome might be different if higher binder concentrations would have been investigated.

Being based on qualitative factors, model 1 provides a good overview which impacts and trends can be achieved by using specific filler or binder types in a formulation. The gained knowledge can for example be applied for the selection of excipients in early development phase of a drug product in order to compensate for unfavourable API properties.

Table 7. Overview of responses for model 1 – significant impact of fillers and binders on responses (information extracted from coefficient plots; arrows indicate the change in the response when the respective filler/binder is used)

Filler/binder type	Bulk density	Fria-bility	Flow-ability	SSA	Fine fraction	D50	Comp. force	Abra-sion	Disint. time	Solid fraction
Avicel PH101	↓	↓	↑	---	↓	↑	---	---	↓	---
Avicel PH105	↓	↓	↑	---	↓	↑	↓	---	↓	---
Pharm 200M	---	---	---	↓	---	---	↑	---	---	↑
Pharm 350M	---	---	↓	↓	↑	---	---	---	↑	↑
Parteck M200	---	---	---	↑	---	---	↓	↓	↑	↓
Parteck Delta M	↓	---	↓	↓	---	---	↓	↑	↑	---
Dicalcium phos.	↑	↑	---	---	↑	↓	↑	---	---	↓
Pharmacoat	---	↑	---	↑	↑	↓	↑	---	↓	---
Klucel	---	---	---	↑	---	---	---	---	↓	---
Maltrin	---	---	---	↓	---	---	---	↑	↑	---
Kollidon	---	↓	---	---	↓	↑	---	↓	↑	---

3.2.2. Model 2 (quantitative factors)

The models with quantitative factors - summarized as model 2 for facilitated discussion - were build in order to generate a better understanding regarding the influence of excipient properties on granule and tablet characteristics. It is possible to link the drug product attributes with the excipient characteristics, as the overarching properties were represented as model factors. In some cases it was also possible to make the link via the overarching properties with to the underlying excipient properties.

When evaluating the impact of model factors on the responses, in general two aspects are of interest: the statistical significance and the magnitude of change in the responses. The magnitude of change in the response indicated to what degree the granule and tablet properties could be influenced by varying the respective factors. As depicted in Figure 9 the variations in the range of the responses was considered relevant and hence, the different filler and binder combinations revealed a relevant impact on the granule and tablet properties. This observation suggested that the main granule and drug product attributes can be influenced to a relevant degree by selecting the right fillers and binders in the formulation. Accordingly, the formulation understanding generated by this DoE might be utilized for a QbD-based formulation design towards a product with the defined quality target product properties.

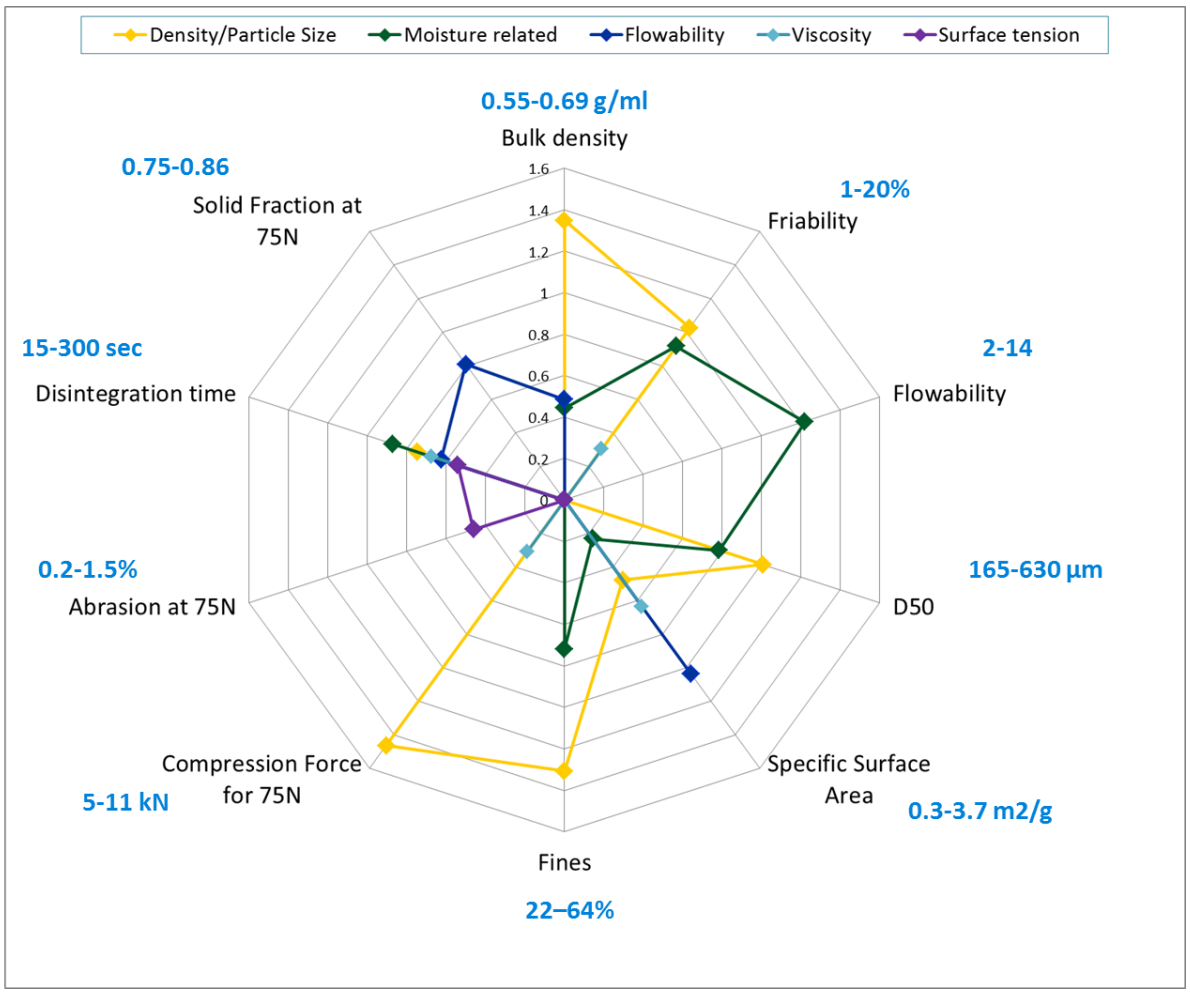


Figure 9. Spider plot: significant impact of factors (i.e. the overarching properties of fillers and binders) on the responses (model 2) – overall observed variation of the response values are depicted in blue

Next to the variation in the responses, Figure 9 depicted the significant impacts of the factors on the responses. The values were received from the normalized coefficient plots. To make the coefficients comparable when responses have different ranges, the coefficients were normalized by dividing the coefficients by the standard deviation of the respective response. All coefficients were plotted as positive values in the spider plot. The larger the

coefficient value of a factor was for a response, the more influence the factor had on this response. Overall it was observed that the filler factors had a dominating impact on the responses compared to the binder factor impact. Again it is emphasized that the limitations in experimental design regarding binder concentration might bias this overall outcome (see above). According to the coefficient values, the filler factor density/particle size-related properties (PC3) revealed the strongest influence (7 responses), followed by the moisture-related properties (PC1) (7 responses but smaller coefficients) and the flow-related properties (PC2) (4 responses). It was thus concluded, that variations in density and particle size-related filler properties as well as variations in moisture-related properties were mainly responsible for the changes in the critical quality attributes (CQA) of granules and tablets. The filler properties did not impact the tablet abrasion.

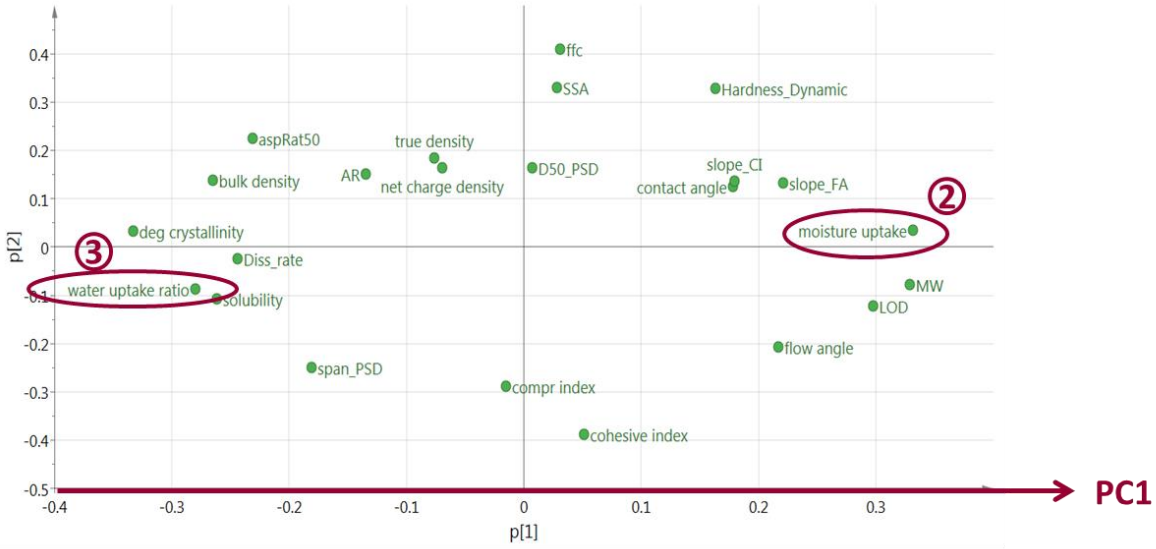
The binder factor viscosity (PC1) had a stronger influence on the granule and tablet properties compared to the factor surface tension (PC2). From a technological point of view it seems reasonable that the binder properties impacted product CQAs like granule friability, specific surface area, disintegration time, compression force and abrasion. The binder liquids' surface tension might for example impact the wettability of dry powder and consequently have an impact on the specific surface area of granules. Wettability of dry powders during the granulation process might be of importance - especially for short granulation times of less than 10 seconds in twin screw wet granulation – and a PhD project is on-going at Ghent University with focus on the impact of different binders and surfactants on granules produced via twin screw wet granulation [7]. The conclusions regarding binder influence have to be seen in the context of the binder concentration below target and the different binder concentrations per binder type. It must moreover be considered, that for example the viscosity factor always varied together with the binder concentration and type in the formulation and it cannot be clearly stated if any impact (e.g. on specific surface area, friability,…) originates from viscosity properties, binder concentration, binder type or even a combination thereof. In order to investigate the impact of binder concentration separately from the viscosity further studies are needed, where the binder concentration is included as a factor in the experimental design.

The significant impact of filler properties (taken from model 2) on the product CQAs are summarized in Table 8 which also indicates if the factor and response are positively or negatively correlated. The arrows depict if an increase or decrease in the response was noted when varying the factor from average to high values.

Table 8. Overview - significant impact of filler factors on responses (arrow up: increase in response, arrow down: decrease in response; coefficients of model 2 were used)

Response	PC1 (moisture-related)	PC2 (flow-related)	PC3 (density/particle size-related)
Fine fraction	↓	---	↓
PSD D50	↑	---	↑
Bulk density	↓	↑	↓
Flowability	↑	---	---
Friability	↓	---	↓
Specific surface area	↑	↑	↑
Disintegration time	↓	↑	↑
Tablet abrasion	---	---	---
Solid fraction @75N	---	↓	---
Compression force @75N	---	---	↓

Aiming to obtain a more detailed understanding for specific responses, the fillers` underlying properties (for further information and characterization methods see chapter 2) can be linked with the model responses (i.e. granule and tablet properties) via the principal components. Two examples thereof are presented below. Model 2 showed that with high PC1 factor values for the fillers, the granule fine fraction decreased (number 1 in Figure 10). On the level of the PCA a high PC1 loading value is associated with for example a high moisture uptake value (i.e. more water absorption during DVS measurements; number 2 in Figure 10). Thus, it can be concluded that a high water uptake capacity of the filler resulted in less fines in the granules. Also a lower water uptake ratio (i.e. the filler absorbs water quickly; number 3 in Figure 10) reduced fines in the granules. In conclusion, fillers which quickly absorb larger amounts of water seem to support a more effective granulation which resulted in less fines.



Response	PC1 (moisture-related)	PC2 (flow-related)	PC3 (density/particle size-related)
Fine fraction	↓	---	↓

Figure 10. Example for the link between underlying filler properties, principle components and the response "fine fraction of granules" (important information in the PCA loading plot is highlighted in red)

3.3. External model verification

External model verification was performed to assess the models' predictive power and to test if the models were also valid for data that was not included in the models. Model 2 with quantitative factors (main model terms) was optimized towards the highest Q^2 values per response by removing insignificant main model terms and by including interaction terms as well as quadratic terms. The summary of fit of the optimized model 2 is shown in Figure 11. Further explanations of the model indicators are given in chapter 4.

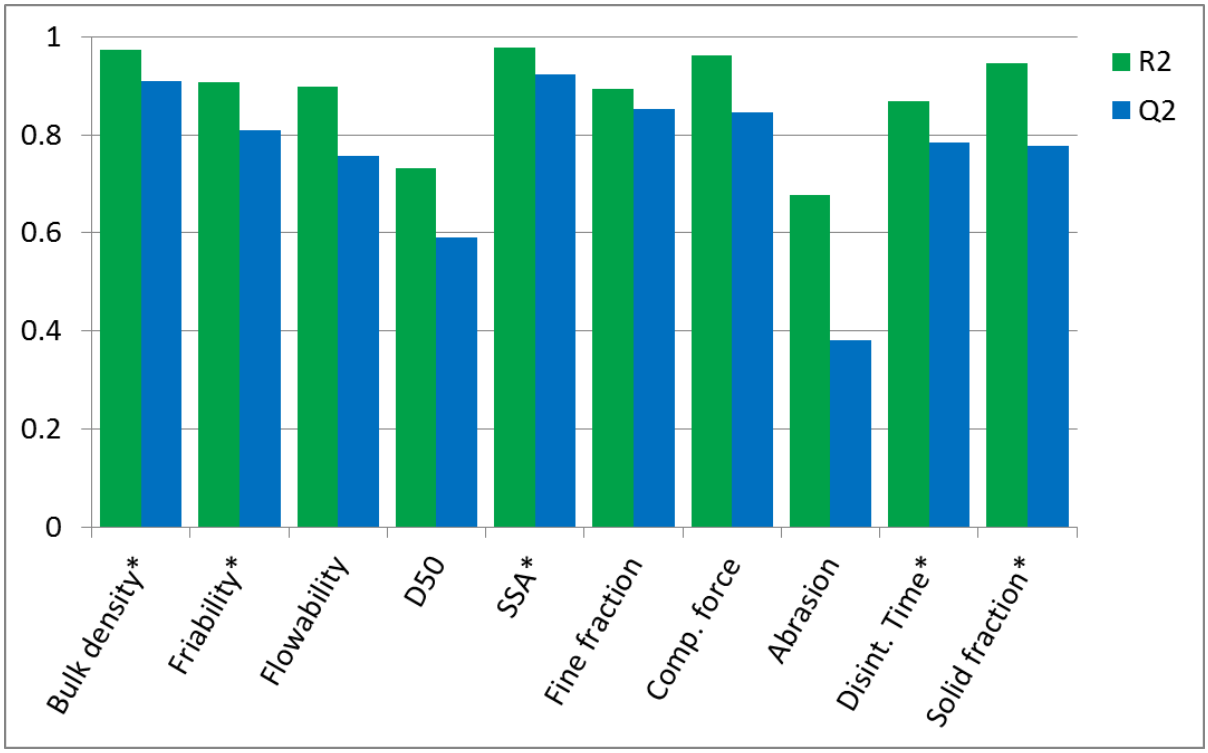


Figure 11. Model 2 - summary of fit (green bars – R2, blue bars – Q2, the * indicates that the response was log transformed)

Overall the model fit (R^2) was good. A Q^2 bar > 0.5 indicates that the model has a good predictive power, except for the response abrasion. For the majority of responses (except for D50 and tablet abrasion) a low variation for the three center points was observed which indicates a good reproducibility (see replicate plot of solid fraction as an example in Figure 12).

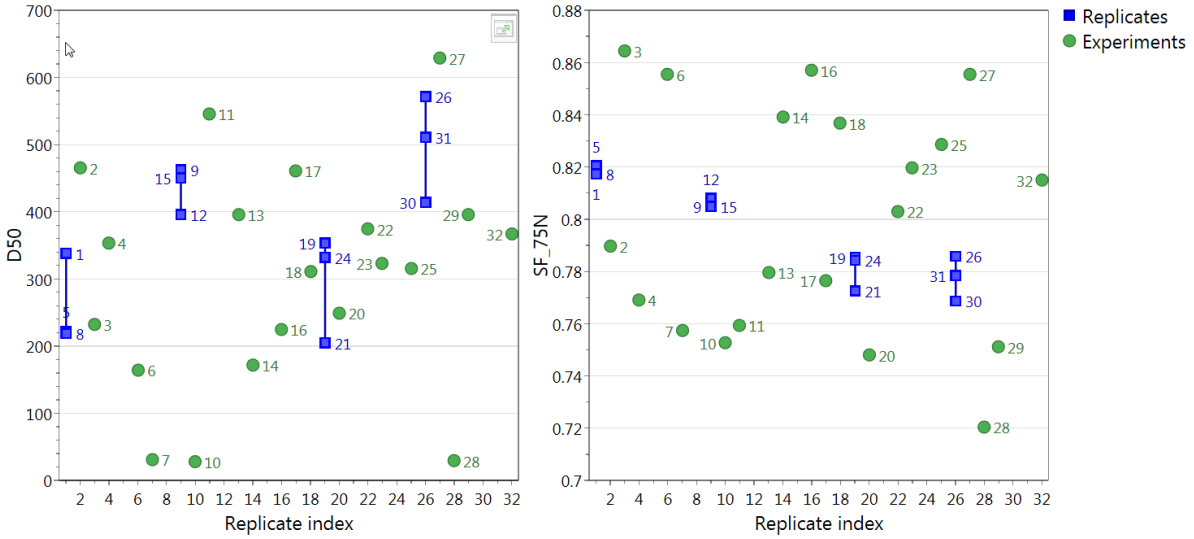


Figure 12. Replicate plot for the responses D50 (left, example for larger variation of replicates) and solid fraction (right, example for small variation of replicates). Numbers indicate the batch number and the blue boxes highlight the center points (3 center points per binder block)

For the responses D50 and tablet abrasion a part of the variation in the response seems to be insufficiently explained by the models which is indicated by a low R^2 value. A potential reason might be the rather high variability of center point replicates which hindered sufficient differentiation in the overall response range in relation to the large center point variability (Figure 12 left).

The difference of predicted values to observed values (P/O difference in %) was calculated to assess the predictive powder of model 2.

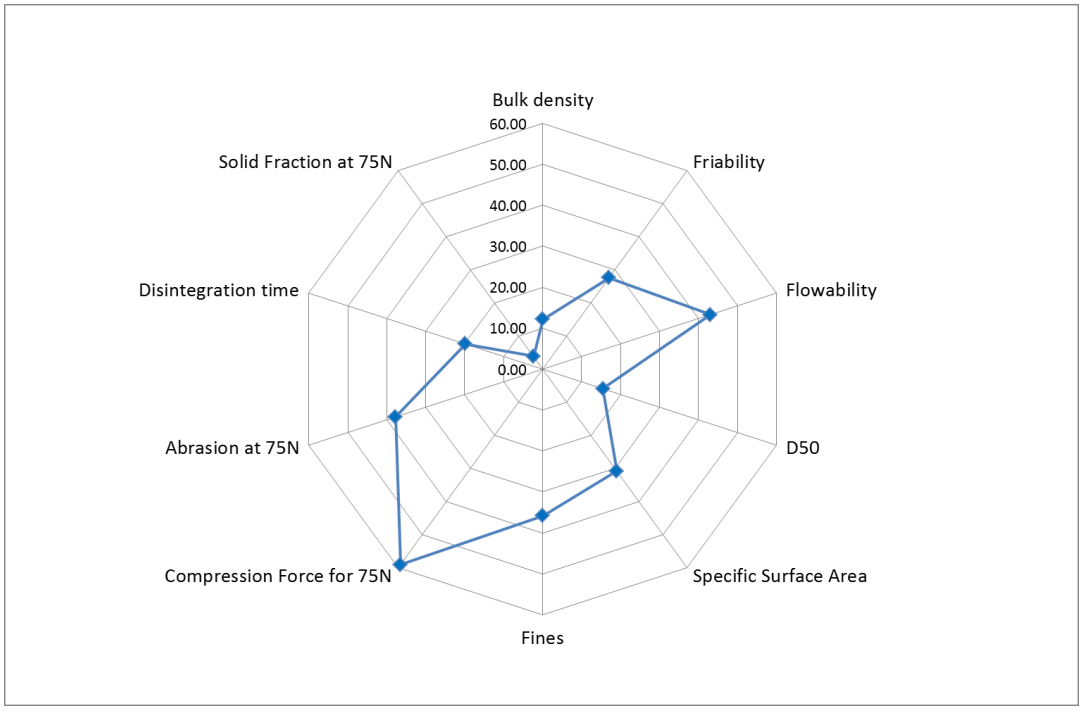


Figure 13. Spider plot: difference of predicted vs observed values per response (average of 4 verification batches; the axis shows the deviation from predicted to observed in %)

The spider plot in Figure 13 visualizes the P/O difference per response. For 4 out of 10 responses (i.e. bulk density, D50, disintegration time and solid fraction) the P/O difference was below 20%. The most precise predictions were observed for solid fraction. In contrast to the finding that the model for the response D50 had the lowest Q^2 value (which indicates the model predictive power, Figure 11) the prediction was close to the experimental results. Poor predictions were obtained for compression force although the summary of fit plot indicated a good model fit and a strong predictive power. A potential explanation might be that factors which strongly influenced the tabletability (i.e. the compression force) were not included in the model (e.g. the binder concentration). Overall the models' predictive power was considered acceptable and some limitations regarding predictability might be attributed to the limitations in binder concentration.

4. Conclusion

The impact of a broad range of filler and binder characteristics on granule and tablet properties was investigated in this study based on a set of 36 experimental trials due to the combination of PCA with DoE. Via statistical MLR models a good understanding of formulation impact on drug product CQAs was achieved. Dicalcium phosphate as filler however, resulted in low quality granules (e.g. with a high friability) for some of the compositions. Thus, some response models were biased by the DCP batches which might have decreased the model quality. In conclusion, DCP being an insoluble and abrasive filler might require special granulation conditions compared to other fillers which were manufactured in this study. The limitations regarding non-comparable binder concentrations of different applied binder types might have affected the DoE outcomes, especially regarding the impact of binder PCs. Further experimental studies would be needed in order to better understand the impact of binder concentration and binder properties on granule and tablet quality attributes. Although the targeted binder concentration in the formulation was not reached, granules and tablets of good quality were manufactured for the majority of formulations. Based on this observation we assume that potentially lower binder concentrations might be needed for effective granulation in continuous wet granulation processes compared to batch high shear or fluid bed wet granulation processes. Meaningful variations in the granule and tablet responses were observed, suggesting that the concept of minimizing the process parameters' impact on the responses by working with fixed process parameter settings seemed to work. Overall the models' predictive power was acceptable and can be used for future formulation design like formulation optimization and troubleshooting. The statistical models can help to select fillers with appropriate properties to optimize granule or tablet properties towards the quality target product profile.

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CHAPTER 4

A NOVEL APPROACH TO SUPPORT FORMULATION DESIGN ON TWIN SCREW WET GRANULATION TECHNOLOGY: UNDERSTANDING THE IMPACT OF OVERARCHING EXCIPIENT PROPERTIES ON DRUG PRODUCT QUALITY ATTRIBUTES

1. Introduction

Continuous twin screw wet granulation is a promising alternative to batch wet granulation technologies for solid dosage form manufacturing in the pharmaceutical industries due to its potential for an accelerated development process with a lean scale up and savings in drug substance [1]. Considering the difference in granulation process, and in particular the shorter granulation time of a continuous wet granulation process, compared to high shear wet granulation, the effect of excipients on process performance and product quality attributes may not necessarily be transferable. This understanding however is of fundamental importance as basis for a quality by design (QbD)-based formulation development [2]. A number of studies have been published which investigated different formulations processed via twin screw wet granulation in order to study the influence of excipient material attributes (e.g. particle size or water binding capacity) on the drug product's potential critical quality attributes (pCQAs) (e.g. granules particle size distribution and tablet tensile strength). Mainly, excipients like lactose [3],[4], microcrystalline cellulose [5], dicalcium phosphate, or mixtures thereof were used. Some formulations also contained active pharmaceutical ingredients (API), focusing on variation in API particle size [5], API hydrophobicity [6] or drug load [7]. For a tabular overview the reader is referred to the review of M. Tezyk [8]. By including hydroxypropyl methylcellulose as hydrophilic matrix former in formulations, Vanhoorne et al. and Thomson and O`Donnel showed that controlled release formulations with sustained release over 16-20 hours were also processable via continuous twin screw wet granulation [9], [10]. However, it remains challenging to compare excipients with very different characteristics in the same study since the resulting formulations require e.g. different liquid-to-solid (L/S) ratios in order to obtain granules of good quality [11]. Therefore the above-mentioned studies focused on a limited variation in formulation composition, hence the obtained scientific conclusions can mainly be considered formulation specific.

For this reason, an important driver for this research work was to include excipients (fillers and binders) with different material properties in one experimental design and to systematically study their impact on process and product performance of a continuous twin screw wet granulation process. DoE is generally limited in the number of factors which can be studied due to limitations in the number of experiments that can be performed. Therefore, one of the main challenges was to investigate a broad range of excipient properties which might potentially impact the drug product's pCQAs as factors in the same DoE study. As previously described by the authors in [12], principle component analysis (PCA) was used to reduce large data sets of excipient characteristics (1 data set for fillers and 1 data set for binders) to a limited number of overarching properties (i.e. the principal components). These overarching properties explained most of the variability of the original excipient property data sets: 4 principal components (PCs)

explained 98.4% of the overall variability in the filler data set, while 93.4% of the overall variability in the data set of binders was covered via 3 PCs. Moreover, PCA of the filler and binder data set allowed revealing similarities and differences in filler and binder characteristics among materials of different chemical nature as well as between material grades. PCA also enabled to identify those properties which were mainly responsible for these differences and similarities of the excipients. PCA and DoE were combined with the intention to understand the influence of excipient (filler and binder) characteristics and formulation composition upon granule and tablet attributes after continuous twin screw wet granulation. The objective was to develop statistical models which are capable of predicting the pCQAs after granulation and tableting for a certain combination of filler and binder as well as to select an optimal combination of filler and binder leading to desired drug product characteristics based on the models predictions.

Figure 1 depicts the step-wise systematic approach that was followed in this study [13]. The performance and results of steps 1-4 were published in [12], while steps 5-8 are presented in this publication. First, pharmaceutical fillers and binders suitable for twin screw wet granulation were selected and extensively characterized with regard to their physico-chemical properties and solid state characteristics (steps 1 & 2). PCA was then performed on the resulting data sets of excipient properties (1 PCA on filler data set and 1 PCA on binder data set) in order to identify the overarching properties, i.e. PCs (steps 3 & 4). Using these overarching properties as DoE factors, suitable combinations of fillers and binders can be selected based on an experimental design (step 5). In this study two commonly used low viscosity grade binders were selected. The resulting statistical DoE models were used to understand and predict the impact of the overarching excipient properties on granule and tablet quality attributes. In addition, the process performance of the selected formulations was evaluated (steps 6-8).

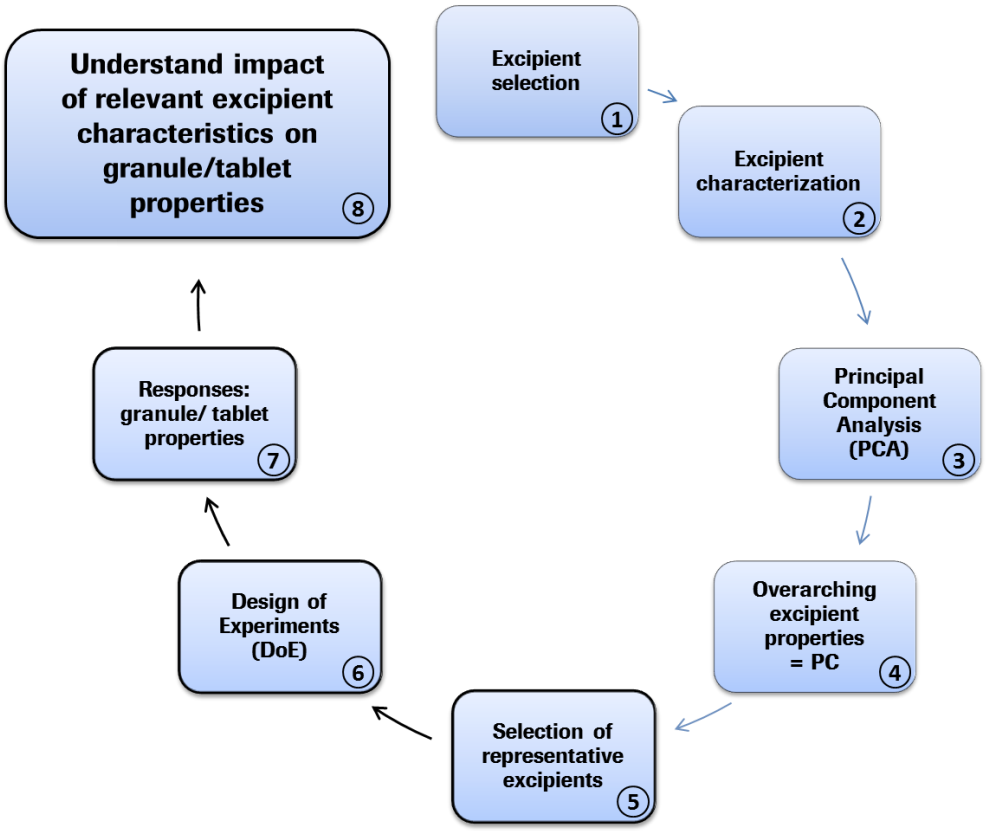

Figure 1. Stepwise overview of the systematic approach to generate formulation understanding

2. Material and Methods

2.1. Materials

Microcrystalline cellulose (Avicel PH101, Avicel PH105, Avicel PH301, FMC Biopolymer, Philadelphia, USA), α-lactose monohydrate (Pharmatose 200M, Pharmatose 350M, DFE Pharma, Goch, Germany and GranuLac 200, Meggle Group, Wasserburg, Germany) and mannitol (Parteck M200, Parteck Delta M, Merck, Darmstadt, Germany) were used as fillers. Hydroxypropyl methylcellulose (Pharmacoat 603, Shin Etsu, Tokyo, Japan) and polyvinylpyrrolidone (Kollidon K30, BASF, Ludwigshafen, Germany) were used as binders in this study. Croscarmellose sodium (Disolcel GF, Mingtai Chemical Co, Taoyuan Hsien, Taiwan), magnesium stearate (Mallinckrodt, St. Louis, USA) and colloidal silicon dioxide (Aerosil 200, Evonik, Rheinfelden, Germany) were used to prepare the final blend for tablet compression.

2.2. Experimental design

2.2.1. Identification of filler and binder types

The intention in this study was to investigate formulations which consisted of one filler and one binder. The selection of fillers included commonly used types suitable for wet granulation with differences in chemical nature (e.g. lactose, MCC, mannitol) and properties, such as water solubility or compression behavior (brittle/plastic). Further variability in excipient characteristics was obtained by selecting filler grades differing in particle size (e.g. Pharmatose 200M vs. Pharmatose 350M) and density (e.g. Avicel PH101 vs. Avicel PH301). The 8 selected fillers were extensively characterized as described in a previous paper [12]. Using PCA, the overarching properties of the filler data set were identified.

Kollidon K30 (PVP) and Pharmacoat 603 (HPMC) were selected as commonly used and low viscosity binder grades for wet granulation.

2.2.2. Selection of binder concentration

The binder concentration range for the DoE was defined at 1-2% (in the dry granules) based on the outcome of preliminary trials (data not presented). Due to the short granulation time, the binders were added as aqueous dispersions. The pre-trials revealed that the maximum binder concentration which could be added in the granule formulation was limited. First, the binder solubility in the aqueous dispersions is limited. Secondly, there is a limitation in pumpability and control of constant liquid flow for highly concentrated, highly viscous binder dispersions depending on the applied set-up of tubing and pumps (section 2.3.1). Due to the limited water uptake capacity of pure lactose, this formulation was considered as the worst case for wet granulation, as it requires a low water content for granulation. For this lactose formulation, a binder concentration in the formulation of maximum 2% could be reached for both binder types. Although 2% binder concentration is well below the maximal concentration for HPMC and PVP recommended by the suppliers (i.e. 2-5%), the pre-trials showed that a binder concentration range of 1-2% resulted in pronounced differences in granule properties (e.g. granule PSD and granule friability). Hence, the selected concentration range was considered sufficiently discriminating. Furthermore, with a concentration range of 1-2% a controlled and reproducible pumpability was ensured.

2.2.3. Factors of the DoE

5 factors were studied in the experimental design. 3 factors were the score values of the 3 principal components (PC) derived from the PCA of the fillers data set which consisted of the fillers' physico-chemical and solid state properties [12]. These 3 PCs together defined the filler type in the formulation where PC1 represented the moisture-related, PC2 the flow-related and PC3 the density/particle size-related filler properties. In that way, three overarching filler

properties were investigated in the DoE, while all underlying filler characteristics were indirectly included in the experimental design.The fourth qualitative factor defined the binder type (PVP or HPMC). The fifth factor represented the binder concentration in the dry granules varying between 1 and 2%. The binder types were not represented by their PCA score values in the experimental design and thus not selected by their overarching properties as this approach leads to the selection of high viscosity grade binders which had limitations regarding pumpability during processing (data not presented).

2.2.4.Statistical design

Based on these 5 factors, a d-optimal interaction design for screening purpose was selected (MODDE, Version 11.0, Umetrics®, Umeå, Sweden) resulting in 27 experiments including 3 center point experiments (Table 1).

D-optimal designs are used when a non-standard experimental design needs to be created (e.g. irregular experimental regions, multi-level qualitative factors or a combination of process and mixture factors). In this design, the constraints resulted from the fact that only specific combinations of factors 1, 2 and 3 (i.e. specific combinations of score values) could be selected since these factors represent the overarching filler properties which could not be chosen arbitrarily. Figure 2 demonstrates how the numerical values of the DoE factors (which are the score values of the principal components) were derived from the PCA scores plot. As shown for Pharmatose 350M as an example, every filler type has specific values for the principal components which results in a fixed combination of DoE factors 1, 2 and 3. A perfect orthogonality, e.g. by combination of score value 1 for factor 1 (PC 1), score value 0 for factor 2 (PC 2) and score value 1 for factor 3 (PC 3) is not possible since this combination does not correspond to a filler.

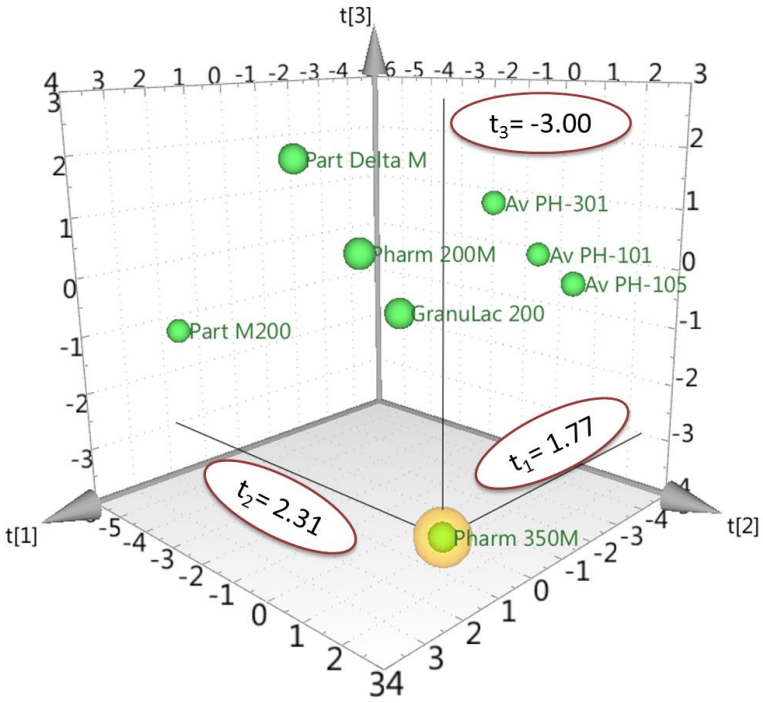

Figure 2. 3-dimensional PCA scores plot of the fillers. Each filler is located in this space according to its overarching properties (PC1, PC2 and PC3). Pharmatose 350M is highlighted as an example. Its t_1, t_2 and t_3 are the score values to be used as DoE factor values for Pharmatose 350M.

By applying the selected d-optimal design, the experiments were defined in a way that the factor ranges were maximally covered [13]. The asset of this d-optimal design was that the factors 1, 2 and 3 (which represent the fillers score values of the overarching properties) enabled to link the DoE with the original filler PCA model and underlying filler data set in order to understand the impact of filler properties upon the pCQAs of granules and tablets, being responses of the DOE (see further). A limitation of the selected design was that confounding partially occurred between 2-factor interaction terms as well as between main factor and 2-factor interaction terms. However, no confounding above the default threshold of 0.3 was present between the main model terms [14]. Confounding of factors can be attributed to a deviation from perfect orthogonality of the factors and impedes the assignment of an observed effect to one of the confounded factors. The DOE responses which were selected for the statistical model are described in detail in section 2.4.

2.2.5. Experimental runs

Table 1 provides an overview of the experiments. The center point was run in triplicate (experiment number 19-21).

Table 1. DoE design matrix

Experiment number (not run order)	Filler type	Binder type (factor 4)	Binder concentration in granules (factor 5)	Filler principal component 1 (factor 1)	Filler principal component 2 (factor 2)	Filler principal component 3 (factor 3)
1	Avicel PH301	Kollidon	1.5%	-3.37	-0.70	0.98
2	Avicel PH105	Pharmacoat	1.5%	-3.84	1.14	-0.30
3	Avicel PH301	Pharmacoat	2.0%	-3.37	-0.70	0.98
4	Avicel PH301	Kollidon	1.0%	-3.37	-0.70	0.98
5	Parteck M200	Pharmacoat	1.0%	1.83	-5.56	-1.18
6	Avicel PH105	Pharmacoat	2.0%	-3.84	1.14	-0.30
7	Avicel PH105	Kollidon	1.0%	-3.84	1.14	-0.30
8	Granulac 200	Pharmacoat	1.0%	2.20	1.71	0.21
9	Avicel PH101	Kollidon	2.0%	-4.31	-0.14	0.02
10	Parteck M200	Pharmacoat	2.0%	1.83	-5.56	-1.18
11	Parteck M200	Kollidon	1.0%	1.83	-5.56	-1.18
12	Parteck Delta M	Pharmacoat	2.0%	2.76	-0.28	2.18
13	Parteck Delta M	Kollidon	1.0%	2.76	-0.28	2.18
14	Pharmatose 200M	Kollidon	1.0%	2.94	1.51	1.09
15	Pharmatose 350M	Pharmacoat	1.0%	1.77	2.31	-3.00
16	Pharmatose 350M	Pharmacoat	2.0%	1.77	2.31	-3.00
17	Pharmatose 350M	Kollidon	1.0%	1.77	2.31	-3.00
18	Pharmatose 350M	Kollidon	2.0%	1.77	2.31	-3.00
19	Avicel PH301	Pharmacoat	1.5%	-3.37	-0.70	0.98
20	Avicel PH301	Pharmacoat	1.5%	-3.37	-0.70	0.98
21	Avicel PH301	Pharmacoat	1.5%	-3.37	-0.70	0.98
22	Avicel PH101	Pharmacoat	1.0%	-4.31	-0.14	0.02
23	Parteck Delta M	Pharmacoat	1.0%	2.76	-0.28	2.18
24	Granulac 200	Kollidon	2.0%	2.20	1.71	0.21
25	Parteck Delta M	Kollidon	2.0%	2.76	-0.28	2.18
26	Parteck M200	Kollidon	2.0%	1.83	-5.56	-1.18
27	Pharmatose 200M	Pharmacoat	2.0%	2.94	1.51	1.09

2.3. Manufacturing of DoE batches

The DoE batches were manufactured via continuous twin screw wet granulation followed by fluid bed drying (using a six-segmented fluid bed dryer). The tablet compression of the dried granulate was performed in batch mode after addition of the extra-granular phase. Granules and tablets were characterized via IPC tests. Figure 3 provides an overview of the process flow, including the IPC tests that were performed for granules and tablets.

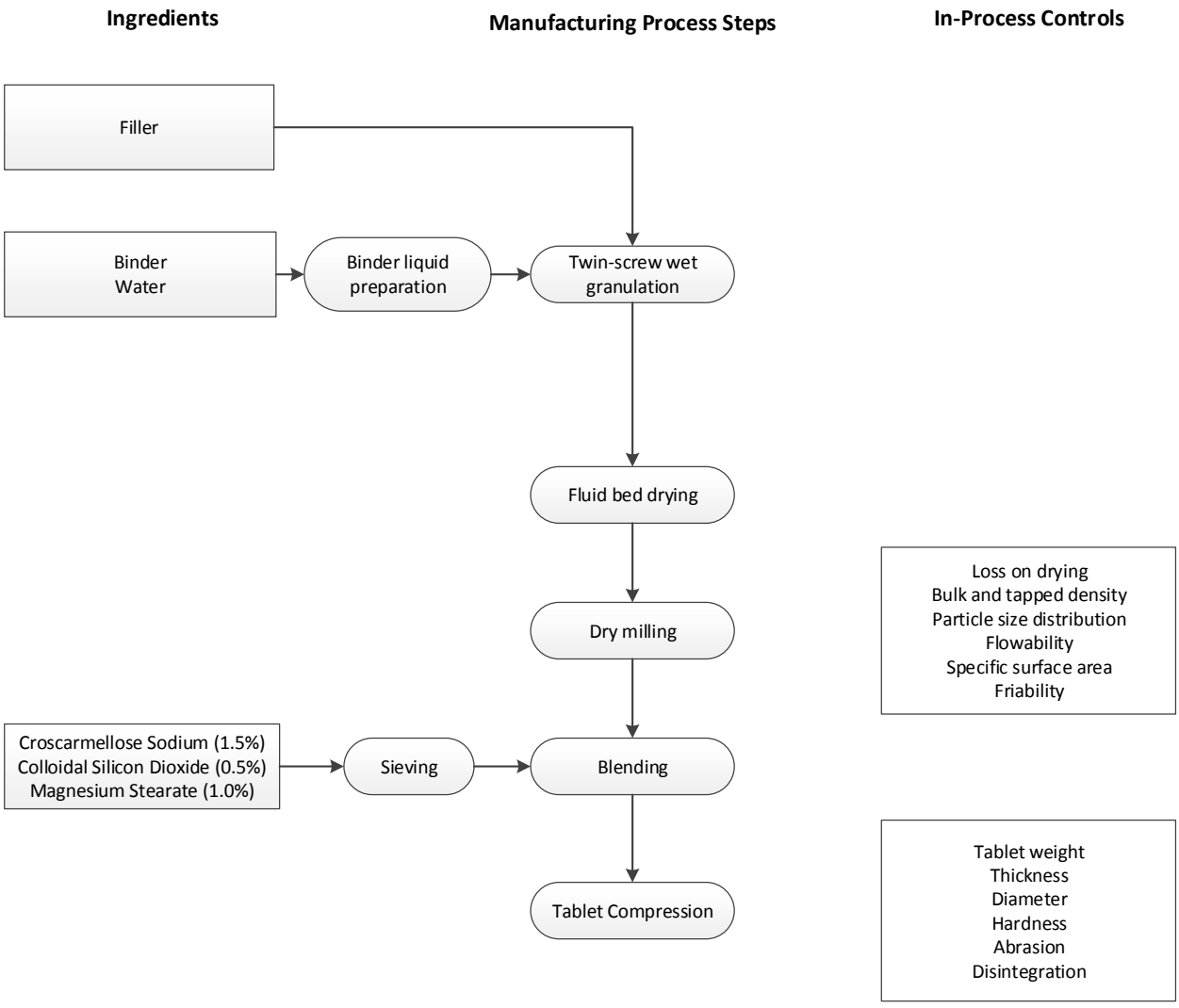

Figure 3. Process flow chart for the manufacturing of DoE batches including IPC tests

2.3.1.Granulation

The ConsiGma®-25 technology (GEA Pharma Systems, Collette®, Wommelgem, Belgium) was used for the manufacturing of the granules. This technology consisted of a twin screw granulator linked to a six-segmented fluid bed dryer and a granule conditioning unit with a cone mill [15].

Process parameters setting for granulation

Since the objective of this study was to understand the influence of the formulation composition on the product and process performance it was important to minimize the influence of process variables as well as of raw material variability on granule quality. Therefore, the same lots of excipients were used throughout the DoE study. Also the process parameters were set to the same fixed values wherever possible. Granulation was conducted at a granulation jacket temperature of 25 °C. The temperature of the inlet air in the fluid bed dryer was set to 50 °C. For dry milling of the granules a sieve size of 1.575 mm and a rotating speed of 1000 rpm was used. For all experiments a screw configuration of 2x6 kneading elements in an angle of 60° was used, while a block of 6 kneading elements was positioned after each liquid entry port in the granulation barrel (Figure 4). Binder liquid was added via the first and water via the second entry port of the barrel. Although the viscous binder liquid and water were separately added during granulation, the miscibility of both phases in the granulation barrel was visually confirmed during pre-trials with coloured binder liquid (data not shown).

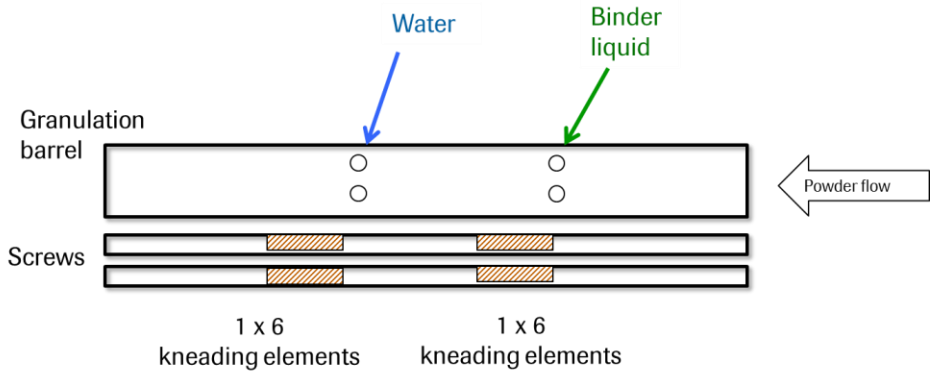

Figure 4. Scheme of the position of the liquid addition ports and kneading elements in the granulation barrel

Other granulation parameters, however, were adjusted due to variations in formulation composition in order to avoid under- or over-granulation and to obtain a proper product. Especially the water content needed for wet granulation varied depending on the filler type in the formulation. A systematic approach for the selection of the most appropriate settings was applied for the parameters “water content” and “screw speed” in order to ensure optimal granulation conditions for each formulation: prior to the manufacturing of a batch, first, the appropriate water content and secondly, the optimal screw speed was identified. For the

identification of the appropriate water content, granules were produced at a fixed screw speed setting and granule samples were collected at different water contents, starting from very dry and powdery granules and increasing the water content stepwise until granules were over-wetted. The collected granule samples were visually examined with regard to particle size and examined by hand regarding their state of agglomeration and binding. The binder liquid feeding system (Figure 5) was set-up to ensure consistent binder concentration in the formulation as it was possible to adjust the water flow rate independently of the granulation liquid flow rate. Once the most appropriate setting for “water content” was identified, in a next step the screw speed was adjusted accordingly to optimize the granule particle size, where needed. The decision on acceptable granule size was taken based on operator experience and the objective was to achieve comparable wet granule sizes for all manufactured batches. Powder mass feed rate and binder liquid feed rate were selected to reach the target binder concentration in the formulation. The ratio of powder feed rate over screw speed was kept constant at 0.02 (e.g. 10 kg/h powder mass flow over 500 rpm screw speed) for all batches to achieve a consistent barrel filling degree. The drying time in the fluid bed dryer was adjusted to reach a target LOD (loss on drying) of the granules which corresponded to the original LOD of the filler in the formulation. This approach was used in order to obtain a residual moisture in the granules which is in equilibrium at ambient conditions. The target LOD was defined as 0.5-1.0% for lactose and mannitol and 3.0-4.0% for microcrystalline cellulose. The inlet airflow was adjusted to ensure optimal fluidization conditions to account for the varying weight of granules depending on the water content that was used for granulation. The binder liquid was fed to the granulation barrel using peristaltic pumps. Tubings with inner diameters varying from 1.6 to 6.4 mm were selected as appropriate for the water and binder liquid addition in order to reach the target feed rate. Nozzles with diameters of 0.8 to 2.4 mm were applied to guarantee a constant liquid flow at the target liquid feed rate.

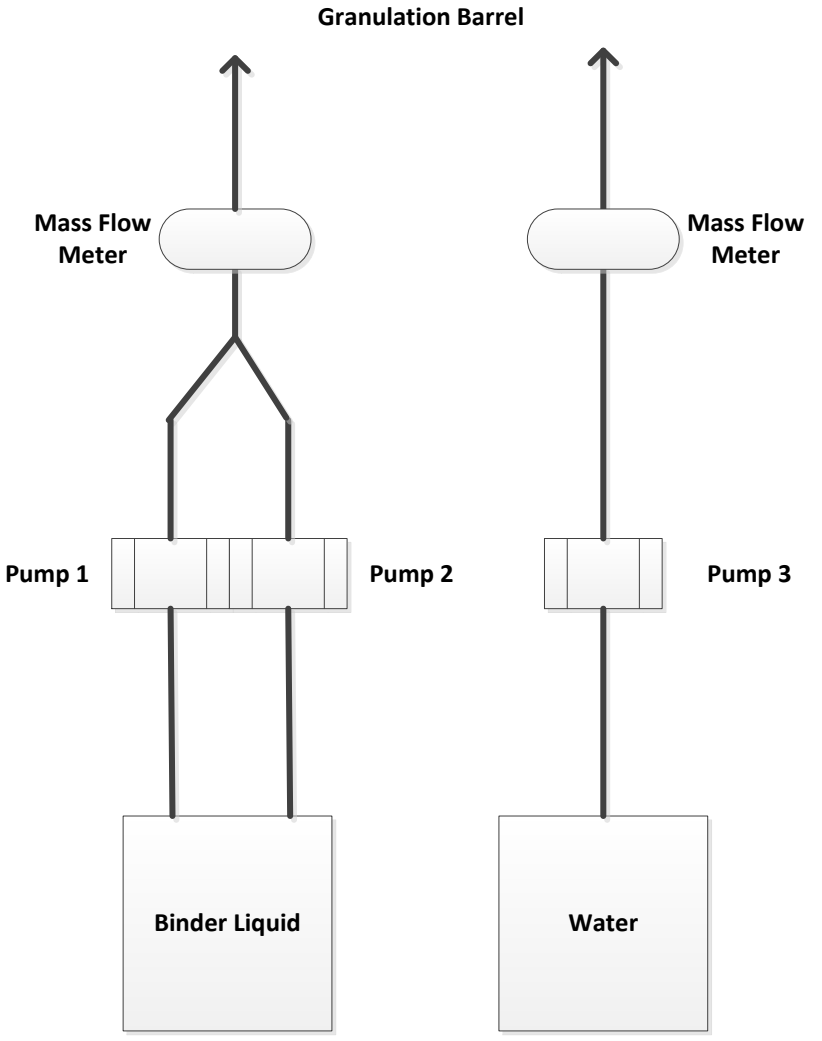

Figure 5. Scheme for set-up of binder liquid and water addition

2.3.2.Final blend preparation

Extragranular phase was added to the granules prior to tablet compression. 0.5% silicon dioxide, 1.5% croscarmellose sodium and 1.0% magnesium stearate were selected as extragranular excipients for all DoE batches. Silicon dioxide was added to provide sufficient flowability to the blend, magnesium stearate was selected as most common lubricant to ensure smooth tablet compression and prevent sticking. Croscarmellose sodium was added for adequate tablet disintegration. A croscarmellose concentration of 1.5% was selected in order not to overrule the effects of the formulation composition on disintegration time and secondly, obtain disintegration times which were in a realistic range according to pharmacopoeial requirements. Silicon dioxide and croscarmellose sodium were sieved (1.0 mm mesh size) and mixed with the milled granules in a tumble blender (Turbula T10B, Willy A. Bachofen, Muttenz,

Switzerland) at 24 rpm for 5 minutes. Magnesium stearate was sieved (1.0 mm mesh size), added to the blend and further mixed for 3 minutes.

2.3.3.Tablet compression

Tablet compression parameters were fixed for all batches in order to minimize their influence on the tablet characteristics. Tablets were compressed using a rotary press (Korsch XL200, Berlin, Germany) which was equipped with 4 pairs of 9 mm flat-faced punches running at 30 rpm. Tablets with a mass of 300 mg were compressed at forces of 8, 15 and 22 kN. In addition, tablets with a target hardness of 75 N were compressed for each batch in order to allow comparison of tablet attributes at a standardized hardness.

2.3.4.Characterization of granule attributes

Samples of the produced granules were collected per batch and characterized by the test methods described below.

Particle Size Distribution

The particle size of granules was analysed using sieve analysis. Sieves of 1400, 1000, 710, 500, 355, 250, 180, 125 and 90 µm were used. A motion amplitude of 2mm (continuous mode) was applied for 5 minutes. The sample size was 100 g. The median particle size D63.2 in µm was calculated based on mass according to the Weibull distribution. Moreover the fine fraction was calculated as % of granules below 125 µm, the yield fraction as % of granules between 125 and 710 µm, and the coarse fraction as % of granules above 710 µm.

Bulk and tapped density

The volume of 100 g granules after 0 taps ($volume_{bulk}$) and 1250 taps ($volume_{tapped}$) was determined using a tapping machine (J. Engelsmann, Ludwigshafen a. Rhein, Germany). Considering the sample mass, bulk density (mass/$volume_{bulk}$ in g/ml) and tapped density (mass/$volume_{tapped}$ in g/ml) were calculated as well as the Hausner Ratio ($density_{tapped}$/$density_{bulk}$) [16].

Flowability

Flowability of granules was characterized by means of ring shear testing (Ring Shear Tester RST-XS, Dr. Dietmar Schulze, Wolfenbüttel, Germany) applying a pre-shear of 1000 Pa. The three most suitable normal loads were chosen automatically for each measurement by the device, whereas the first normal load was repeated as a fourth normal load measurement point. The flow function coefficient (ffc), which is the ratio of consolidation stress to unconfined yield strength, was calculated [17].

Moisture content

A halogen moisture analyser (Mettler Toledo HR83, Mettler-Toledo, Greifensee, Switzerland) was used to measure loss on drying (LOD) (n=1, in %) at a drying temperature of 90°C until the weight variation was below 2 mg within 30 sec.

Specific Surface Area (BET method)

In the validity range of the BET-isotherm, the specific surface area (in m^2/g) was measured by means of nitrogen adsorption (Tristar II 3020, Micrometrics, Norcross, USA) (n=2). Prior to measurements, the samples were over-night degased at vacuum.

Friability

The friability of granules was measured using a friability tester (PTF E Pharma Test, Hainburg, Germany) as described by Vercruysse et al. [18]. The fine fraction of the granules was removed prior to the measurements using a 250 µm sieve. Afterwards 10.0 g of the granules (I_{wt}) were filled into the drum together with 200 glass beads of 4 mm diameter. At a speed of 25 rpm a 10 minute run was performed. The generated granule size fraction below 250 µm was again removed and the residual amount of granules was weighed (F_{wt}). The friability was calculated as $((I_{wt} - F_{wt})/I_{wt}) * 100$ in %.

2.3.5.Characterization of tablet attributes

Tablet mass, height, diameter and hardness were measured for 8, 15 and 22 kN compression forces as well as for the samples with a target hardness of 75 N. Additionally, disintegration time and abrasion were determined for tablets with 75 N target hardness.

Tablet hardness and solid fraction

Tablet thickness, diameter, weight and hardness were determined for a sample of 10 tablets processed at each compression force as well as the 75 N hardness samples with an automatic tablet testing system (Sotax HT 100, Sotax, Aesch, Switzerland). Tablet solid fraction was calculated from tablet mass (m in g), volume (V in cm^3) and true density (ρ_{true} in g/cm^3) as $(m/V)/\rho_{true}$. True density of the final blend before compression was measured using a helium pycnometer (AccuPyc 1330, Micrometrics, Norcross, USA). Five purges at 19.5 psig and five runs at 19.5 psig were conducted in one measurement (n=2).

Abrasion

100 g of de-dusted tablets (m_1 in g) with target hardness of 75 N were filled into a Weis-Fogh drum (Friabilator AE-1, Biomation, Jugenheim, Germany) which rotated 1250 times at a speed of 100 rpm. After the stress test, tablets were de-dusted again, the remaining tablet weight was determined (m_2 in g) and abrasion (in %) was calculated as $((m_1-m_2)/ m_1)*100$.

Disintegration

The disintegration time (in sec) of the 75 N target hardness tablets (n=6) was determined using a disintegration tester (basket method; Sotax DT2, Sotax AG, Aesch, Switzerland) with automatic endpoint detection. Demineralized water with a temperature of 37°C was used as disintegration medium.

Compression force

The compression force (in kN) which was needed to reach a target tablet hardness of 75N was recorded and used as an indirect measure for tablet hardness.

2.4. DoE analysis and model development

The above-described granule and tablet attributes were used as DoE responses (Table 2).

Table 2. List of granule and tablet model responses

Granule responses	Tablet responses
Bulk density	Disintegration time
Tapped density	Tablet abrasion
Hausner ratio	Solid fraction of tablets with 75 N hardness
Particle size D63.2	Compression force needed to reach 75 N target tablet hardness
Fine fraction <125 µm	Ejection force at 15 kN compression force
Yield fraction 125-710 µm	
Coarse fraction 710-1400 µm	
Flowability	
Friability	
Specific surface area	
Torque granulation barrel	

Multiple linear regression (MLR) models were fitted for each response using Modde (Version 11.0, Umetrics®, Umeå, Sweden). Responses were thus studied independently from each other. A logarithmic transformation of responses was performed if needed in order to convert a non-normal into a normal distribution since the latter is a general requirement for linear regression [14]. Orthogonally scaled and centred variables were used in the coefficient plots to achieve comparability of factors.

The models were fitted and optimized for two purposes. First, the models were fitted with main model terms in order to understand which factors (i.e. the formulation properties) influence the responses (i.e. granule and tablet properties) (section 3.3.1). Although the statistical design allowed the inclusion of interaction model terms, it was not beneficial for this purpose to include interaction model terms due to confounding among the main and interaction model

terms. Second, the models were fitted for prediction and model verification purpose. Here the addition of interaction model terms can be beneficial to improve the model fit. The models were optimized by removing statistically insignificant model terms as long as this resulted in larger Q^2 values [6] (results see sections 3.2 and 3.4). As specific parameters (i.e. inlet air flow in the fluid bed dryer, LOD of dry granules and inlet air humidity in the fluid bed dryer) introduced uncontrolled variability during the experiments, these parameters were added to the DoE as uncontrolled factors (one uncontrolled factor at a time).

3. Results and Discussion

3.1. Process performance

A total of 31 formulations (27 DoE batches plus 4 batches for external model verification purpose, Table 1 and Table 6) were manufactured via continuous wet granulation in this study.

Typically formulations designed for wet granulation processes consist of a blend of multiple fillers (e.g. two complementary fillers like MCC and lactose). In this study, however, formulations in their most simple form were used with the objective to obtain more pronounced effects of the different filler types on the product characteristics. For the majority of batches, no manufacturing issues were observed as appropriate granules and tablets could be produced. During wet granulation, limitations were observed when processing formulations with Avicel PH301 as filler. Although these formulations yielded granules, the granulator had to be restarted several times as the process was automatically interrupted when the maximum screw torque was exceeded. This observation might be attributed to the higher density of Avicel PH301 compared to the two other Avicel grades since the density is the property which is different for Avicel PH301 compared to Avicel PH105 and PH101. This observation is in contrast to the expectation that the higher density of Avicel PH301 results in a lower filling degree of the granulation barrel which might result in a reduced screw torque. Potentially, despite the differences in the overall barrel filling degree for the Avicel grades according to their different densities, comparable filling levels might be achieved in the kneading element area: At the kneading elements (where most friction occurs) the smallest space is available between screw elements and granulation barrel wall which would result in equal amounts of powder for all grades regardless of the powder density. When the space around the kneading elements is fully filled with wetted powder, this would results in a higher mass of Avicel PH301 (due to higher density of Avicel PH301 of 0.433 g/ml compared to Avicel PH101 of 0.308g/ml and Avicel PH105 of 0.313g/ml) which potentially results in higher resistance and friction in the kneading element area and thus in higher screw torque. As expected, it was more difficult to obtain a stable and consistent granulation liquid flow with increasing viscosity of the binder liquid. Particularly binder solutions with a high viscosity (e.g. for formulations with 2% HPMC binder

concentration) required a suitable selection of tubing size and assessment of appropriate pump speed with pre-trials in order to ensure a consistent flow at the target binder liquid flow rate. Although the majority of batches showed a reasonable to good tablet compression performance (maximal observed ejection force of approx. 360 N), some formulations were limited in the process performance during tablet compression. For batch 15 (Pharmatose 350M + 1% Pharmacoat) and batch 31 (Pharmatose 350M + 1.5% Pharmacoat; one of the model verification batches, section 3.4) high ejection forces (up to 1600 N) were observed. Batch 31 did not allow to compress tablets at 15 kN compression force or higher since tablets broke during ejection from the die. However, batches with Pharmatose 350M + 2% Pharmacoat or with Kollidon (at any concentration) could be processed into tablets without difficulties. Some formulations revealed sticking tendencies (Batch 5, 10, 15, 17) or showed lamination at 22 kN compression force (batch 2, 6, 7). The three latter formulations for which lamination was observed at 22kN, contained Avicel PH105 as filler. Although MCC undergoes plastic deformation during compression, it was assumed that the high compression force of 22 kN at a tablet weight of 300 mg resulted in over-compression. Over compression (i.e. excessive compaction pressure) during tabletting causes a flattening out of granules which reduces the bonding-ability due to flat granule surfaces without irregularities [19]. Therefore, the compacts tend to laminate. Avicel PH105 is designed as the most compressible MCC quality among the grades included in this study. Hence, the state of over-compression is expected to be reached at lower compression forces compared to the other MCC grades (Avicel PH101 and PH301) [20].

3.2. Quality of the statistical models

An overview of the model parameters R^2 and Q^2 after model optimization is given in Figure 6.

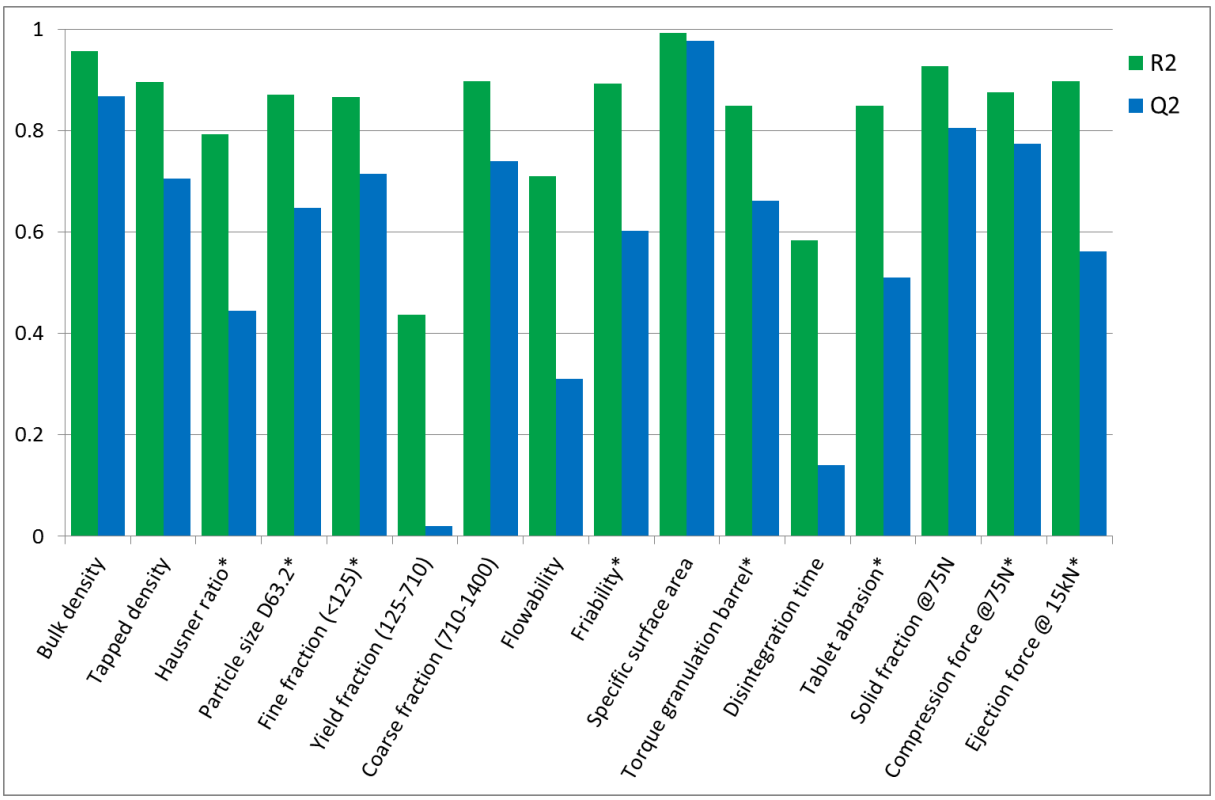

Figure 6. Summary of fit: R^2 (green bars) and Q^2 (blue bars) of the optimized models (the * indicates that the response was log transformed)

R^2 is an indicator for the model fit and describes how well the variation in a response can be explained by the model terms. The closer the value is to 1, the better the model fit is. Overall the models had a good fit (R^2) for all responses. However, assessment of model quality should also take Q^2 into account which indicates the predictive power of the model. Q^2 is defined as $1 - (\frac{PRESS}{SS_{tot}})$ where *PRESS* is the prediction residual sum of squares calculated based on all model samples and SS_{tot} is the total sum of squares of the responses [14]. A $Q^2 > 0.5$ generally indicates that the model has a good predictive power. The model predictability is further discussed in section 3.4.

For all responses (except for disintegration time) a good reproducibility was obtained since the variation of the center point experiments per response was low and much smaller than the overall variability of the DoE experiments. An example for a replicate plot is shown in Figure 7.

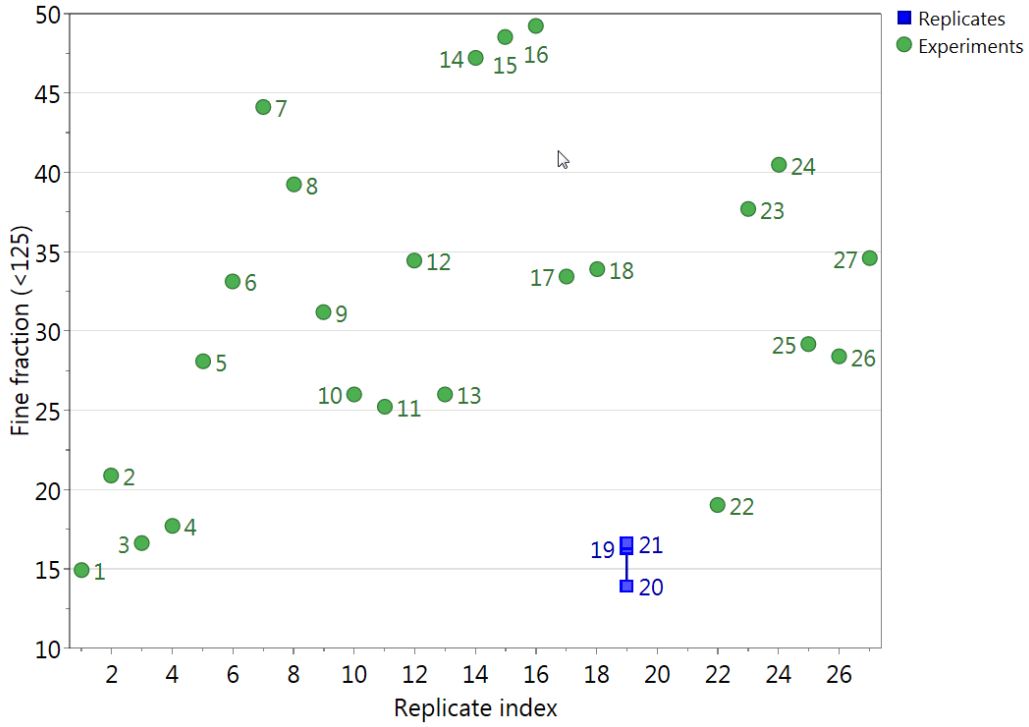

Figure 7. Replicate plot of the response "Fine fraction" of granules. Replicates are highlighted in blue (number 19, 20 and 21)

In this study, it was observed that the variation of factors in the defined experimental space resulted in relevant variation of the granule and tablet characteristics for the majority of responses (Table 3), which was a good foundation to obtain meaningful quality models.

Table 3. Numerical values of granule and tablet responses for the DoE runs. (*measurement values are missing)

Experiment number	Filler type	Binder type	Binder concentration in granules	Bulk density (in g/ml)	Tapped density (in g/ml)	Hausner ratio	Particle size D63.2 (in µm)	Fine fraction (<125 µm) (in %)	Yield fraction (125-710 µm) (in %)	Coarse fraction (710-1400 µm) (in %)	Flowability (ffc)	Friability (in %)	Specific surface area (in m^2/g)	Torque granulation barrel (in Nm)	Disintegration time (in sec)	Tablet abrasion (in %)	Solid fraction @75N	Compression force @75N (in kN)	Ejection force @15kN (in N)
1	Avicel PH301	Kollidon	1.5%	0.57	0.68	1.19	594	14.9	55.6	29.5	4.4	2	0.4	4.7	36	0.4	0.81	7.5	46
2	Avicel PH105	Pharmacoat	1.5%	0.53	0.64	1.21	454	20.9	59.8	19.4	5.4	7	1.0	3.3	24	0.6	0.79	6.5	38
3	Avicel PH301	Pharmacoat	2.0%	0.63	0.75	1.19	587	16.6	53.6	29.9	7.0	3	0.4	11.1	217	0.5	0.89	15.0	44
4	Avicel PH301	Kollidon	1.0%	0.61	0.75	1.23	550	17.7	55.7	26.6	3.6	3	0.5	8.4	169	1.0	0.88	15.0	47
5	Parteck M200	Pharmacoat	1.0%	0.56	0.63	1.13	373	28.1	55.9	15.7	4.0	10	3.3	2.1	93	0.4	0.82	9.5	365
6	Avicel PH105	Pharmacoat	2.0%	0.53	0.68	1.28	366	33.1	51.3	15.7	5.4	6	1.0	3.3	103	0.8	0.80	7.0	43
7	Avicel PH105	Kollidon	1.0%	0.48	0.66	1.38	281	44.1	43.2	12.6	3.5	9	1.0	3.2	88	1.0	0.80	7.0	42
8	Granulac 200	Pharmacoat	1.0%	0.60	0.69	1.15	284	39.2	50.2	10.6	4.3	24	0.5	2.1	97	0.7	0.86	13.0	158
9	Avicel PH101	Kollidon	2.0%	0.45	0.56	1.24	420	31.2	47.3	21.7	10.2	4	1.0	3.6	19	0.8	0.73	5.0	39
10	Parteck M200	Pharmacoat	2.0%	0.55	0.62	1.13	384	26.0	57.7	16.2	4.2	9	3.3	2.0	113	0.2	0.80	8.0	80
11	Parteck M200	Kollidon	1.0%	0.57	0.64	1.12	422	25.2	54.2	20.4	4.1	7	2.9	2.8	119	0.2	0.79	7.0	113
12	Parteck Delta M	Pharmacoat	2.0%	0.51	0.65	1.27	360	34.4	50.8	15.0	4.6	8	0.6	1.8	94	0.8	0.82	8.0	168
13	Parteck Delta M	Kollidon	1.0%	0.51	0.60	1.18	445	26.0	51.7	22.0	4.3	4	0.8	3.6	114	0.6	0.83	7.0	62
14	Pharmatose 200M	Kollidon	1.0%	0.53	0.64	1.21	202	47.2	47.3	5.6	2.8	18	0.2	1.7	106	0.5	0.88	15.0	92
15	Pharmatose 350M	Pharmacoat	1.0%	0.55	0.66	1.20	207	48.5	46.9	4.6	2.4	66	0.4	1.4	104	*	0.86	22.0	1378
16	Pharmatose 350M	Pharmacoat	2.0%	0.56	0.65	1.16	210	49.2	45.7	5.0	3.7	28	0.4	1.3	161	0.5	0.85	11.0	129
17	Pharmatose 350M	Kollidon	1.0%	0.53	0.63	1.19	253	33.4	58.0	8.5	2.8	18	0.3	3.1	104	1.3	0.87	15.0	87
18	Pharmatose 350M	Kollidon	2.0%	0.56	0.64	1.14	351	33.9	49.7	16.2	6.4	11	0.4	3.0	160	0.5	0.83	9.0	119
19	Avicel PH301	Pharmacoat	1.5%	0.60	0.71	1.18	556	16.3	56.5	27.2	*	2	0.4	5.7	248	0.5	0.88	14.0	45
20	Avicel PH301	Pharmacoat	1.5%	0.62	0.74	1.19	643	13.9	52.4	33.7	6.0	5	0.4	10.1	210	0.5	0.89	14.0	43
21	Avicel PH301	Pharmacoat	1.5%	0.63	0.74	1.17	553	16.6	57.1	26.3	6.0	3	0.4	8.1	153	0.5	0.88	14.5	46
22	Avicel PH101	Pharmacoat	1.0%	0.52	0.62	1.19	537	19.0	53.5	27.7	3.7	1	1.1	3.4	142	0.6	0.83	10.0	51
23	Parteck Delta M	Pharmacoat	1.0%	0.49	0.58	1.18	281	37.7	52.7	9.5	3.4	18	0.7	1.4	99	0.5	0.86	10.5	77
24	Granulac 200	Kollidon	2.0%	0.59	0.71	1.20	294	40.5	45.8	13.6	5.2	15	0.5	1.4	177	0.7	0.82	8.0	176
25	Parteck Delta M	Kollidon	2.0%	0.52	0.60	1.15	490	29.2	44.9	25.9	2.2	1	0.5	4.6	161	0.7	0.81	6.5	195
26	Parteck M200	Kollidon	2.0%	0.57	0.65	1.14	421	28.4	51.1	20.4	6.4	5	2.7	3.2	168	0.2	0.76	5.5	176
27	Pharmatose 200M	Pharmacoat	2.0%	0.58	0.68	1.17	305	34.6	53.7	11.6	5.1	17	0.3	1.6	266	0.6	0.87	11.5	118

3.3. Impact of studied factors on granule and tablet responses

In order to avoid confounding in the model terms (see above), linear models with main model terms only were selected to evaluate if, and to what extent, the studied factors (i.e. fillers overarching properties, binder type and concentration) had an impact on the responses (i.e. granule and tablet properties) (section 2.4). The results which are discussed in section 3.3 are based on the main term models. A list of the effects per response is given in Table 4.

Table 4. Overview of main term model effects for untransformed responses (remark: no information on statistical significance is provided in this table; for statistical significance of factors see Table 5)

Response	Filler PC1 (factor 1)	Filler PC2 (factor 2)	Filler PC3 (factor 3)	Binder type (factor 4)	Binder concentration (factor 5)
Bulk density	0.00	-0.01	0.00	-0.02	0.01
Tapped density	-0.01	0.00	0.00	-0.02	0.01
Hausner ratio	-0.02	0.02	0.01	0.02	0.00
Particle size D63.2	-53.59	-39.72	55.35	12.22	33.34
Fine fraction (<125)	4.05	3.97	-3.49	0.33	-0.79
Yield fraction (125-710)	-0.69	-1.43	-0.12	-2.74	-1.86
Coarse fraction (710-1400)	-3.41	-2.50	3.65	2.37	2.71
Flowability	-0.51	-0.18	-0.02	0.26	1.96
Friability	3.83	4.15	-7.05	-8.07	-7.22
Specific surface area	0.05	-0.67	-0.35	-0.08	-0.06
Torque granulation barrel	-1.08	-0.27	0.81	0.18	0.34
Disintegration time	5.36	0.89	9.82	-21.95	34.73
Tablet abrasion	-0.02	0.13	-0.01	0.10	-0.11
Solid fraction @75N	0.00	0.01	0.01	-0.03	-0.03
Compression force @75N	0.16	1.08	-0.74	-3.02	-3.59
Ejection force @ 15kN	50.62	22.17	-115.47	-120.96	-118.73

3.3.1. Overview: impact of factors on responses

The coefficient plot (Figure 8) displays the factors' regression coefficients per response including 95% confidence intervals. The coefficients reflect the change in the response when a factor is varied from its average setpoint to its high setpoint while keeping the other factors at their center point. The confidence intervals indicate whether the coefficients can be considered statistically different from zero. These statistically insignificant terms can be removed from the model during model optimization.

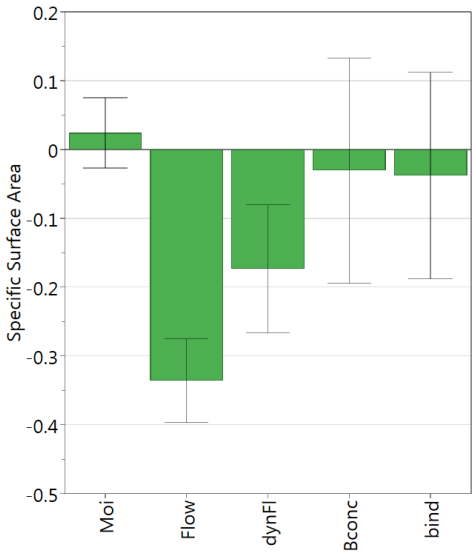

Figure 8. Coefficient plot for the response specific surface area: Increasing the factors "flow-related properties (PC2)" and "dynamic flow (PC3)" resulted in a reduction of granule specific surface area

Table 5. Overview of the factor impacts on responses: arrows in green indicate a significant and pharmaceutically relevant impact, arrows in black indicate a significant but pharmaceutically not relevant impact (models with main model terms were used for this table)

Response	PC1 (moisture-related)	PC2 (flow-related)	PC3 (dynamic flow & others)	Binder concentration	Binder type
Particle size D63.2	↓	↓	↑	---	---
Fine fraction	↑	↑	---	---	---
Yield fraction	---	↓	---	---	---
Coarse fraction	↓	↓	↑	---	---
Bulk density	---	---	---	---	---
Tapped density	---	---	---	---	---
Hausner ratio	↓	↑	---	---	---
Flowability	↓	---	---	↑	---
Friability	↑	↑	↓	(↓) borderline	↓
Specific surface area	---	↓	↓	---	---
Disintegration time	---	---	---	---	---
Tablet abrasion	---	↑	---	---	---
Solid fraction @75N	---	↑	---	---	↓
Compression force @75N	---	---	---	↓	↓
Torque granulation barrel	↓	---	---	---	---
Ejection force @ 15kN	↑	---	↓	---	---

Table 5 summarizes the significance and pharmaceutical relevance of the coefficients of the models (with main model terms) for the different responses. The coefficient plots were used to obtain the information which is summarized in the table. Overall, the impact of filler properties on the granule and tablet responses appear to be more dominant compared to the impact of binder type and concentration. Binder type or concentration only revealed a relevant influence on granule flowability (using a higher binder concentration improved granule flowability) and friability (using Kollidon as binder reduced granule friability) as well as on tablet compression force as an indicator for tabletability (a higher binder concentration and Kollidon as binder both resulted in lower compression forces). Among the overarching properties of the fillers, the moisture-related properties (1st PC) and the flow-

related properties (2nd PC) of the fillers showed a dominant impact on the responses compared to the dynamic flow properties of the filler (3rd PC).

3.3.2. Responses without pharmaceutically relevant impact of fillers and binders

The influence of some factors proved to be statistically significant on some responses (bulk and tapped density, Hausner ratio, yield fraction, torque in the granulation barrel, disintegration time and solid fraction). However, the changes in the responses were not considered pharmaceutically relevant (i.e. the impact was significant but the observed change was rated too small to be of practical relevance).

None of the studied factors had a significant influence on the responses bulk and tapped density, respectively. Moreover, limited variation within the response range was obtained for bulk density (0.45-0.63 g/ml) and tapped density (0.56-0.75 g/ml) as well as for solid fraction (0.73-0.89) (Table 3). However, as the experimentally observed values of these responses were within common target ranges (e.g. 0.4-0.7 g/ml for bulk density, 0.6-0.8 g/ml for tapped density and 0.7-0.9 for solid fraction), optimization of those responses is therefore not necessary. Since a change in the formulation factors did not influence these granule and tablet properties, the advantage is that other responses can be optimized while those responses remain within the desired range. Prior to tablet compression, 1.5% of croscarmellose sodium was added to the extra granular phase. This disintegrant concentration was considered sufficient for all manufactured formulations since the tablet disintegration time was below 5 minutes for all batches. This might be the reason why the studied filler and binder properties did not show a significant influence on disintegration time. Furthermore, the addition of a disintegrant might have overruled a potential small influence by fillers and binders. An efficient way of influencing the disintegration time is expected via proper selection of disintegrant type and concentration rather than by varying filler and binder properties.

The screw torque is a resulting process parameter and can thus be considered as a response in the DoE, as it cannot be actively controlled. Especially in view of long runs, a high screw torque might be unfavourable. None of the studied formulation properties significantly affect the screw torque. The only formulations which had an elevated screw torque during processing contained Avicel PH301 (Table 3).

3.3.3. Factor impact on individual responses

Granule particle size distribution (PSD)

The granule PSD is of high relevance for the downstream process performance and the potential critical quality attributes of the final drug product. The granule PSD has for example an impact on granule flowability and this directly could impact tablet mass and content variation [21], [22]. High fraction of fines can also lead to segregation issues during tablet compression, which might result in content uniformity issues. Furthermore granule PSD can impact the compressibility of the product as well as dissolution performance [23],

[24]. Therefore the PSD of the granules is considered as a key response which is often in focus during formulation and process design.

The statistical granule diameter obtained from the Rosin-Rammler distribution function (D63.2) [25] was significantly impacted by the three overarching filler properties: by changing the factors PC1 or PC3 from their lowest to highest setpoint, the D63.2 changed by 40-55 µm for each factor. As D63.2 is calculated cumulatively, it contains information about the shift in particle size distribution. The models revealed that fillers with high PC1 and/or PC2 score values increased the granules fine fraction (by approx. 4% per factor) and at the same time decreased the amount of coarse granules (by approx. 3% per factor). Fine and coarse fractions were thus anti-correlated.

Figure 9 is derived from the scores plot of the fillers PCA [12] and was supplemented with information from the DoE. It shows that lactose grades yielded smaller D63.2 values, while Avicel PH301 increased D63.2. However, changes in D63.2 were probably mainly attributed to changes in the particle size distribution. This assumption was based on the finding that yield fraction was not impacted in a relevant way (see below), while fine and coarse fraction were impacted by the same factors (PC1, PC2 and PC3) as D63.2. Interestingly, no correlation of D63.2 with the filler water uptake behaviour, filler solubility or filler particle size D50 was observed (graphs not shown). Therefore, it could be concluded that granule particle size was neither affected by the original particle size of the filler nor by its water solubility or water uptake behaviour in the selected experimental set-up. It is expected that at a fixed L/S ratio, excipient properties like particle size and water uptake revealed an effect on granule particle size. In this study, however, the L/S ratio was defined in order to assure effective granulation for each formulation and to avoid over- or under-granulation. The differences in L/S ratio might be the reason that the excipient properties did not show a relevant impact on granule particle size. No relevant formulation impact was observed on the yield fraction: PC2 was the only factor that significantly impacted the yield fraction. However, an increase/decrease of 1.5% yield fraction was not considered relevant. Thus, it was assumed that the yield fraction can mainly be adjusted by granulation process parameters like screw speed instead of changing the formulation parameters.

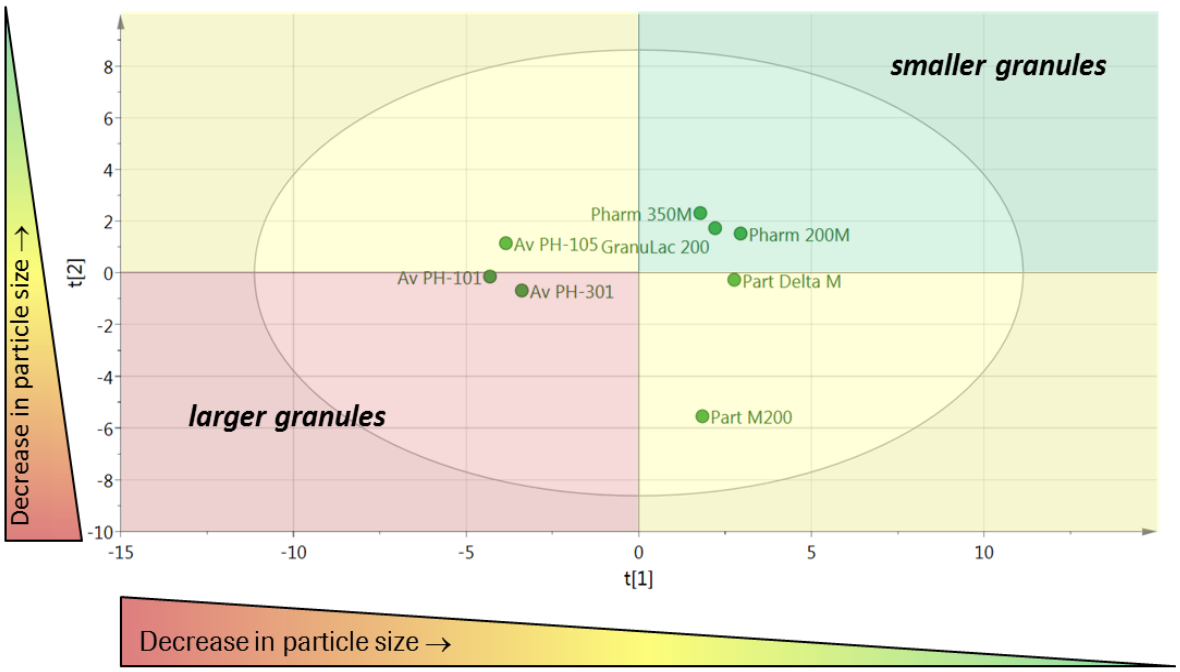

Figure 9. Adopted scores plot from the filler PCA to visualize how the selection of a filler type will influence granule particle size

Granule flowability

The filler properties had a negligible influence on granule flowability (effect of max. 0.5 units), while a higher binder concentration could improve the flowability (effect of 2.0 units) regardless of the binder type that was used. The binder concentration studied in this design ranges from 1-2% and further investigation would be needed to understand if the effect is even more pronounced at higher binder concentrations.

Granule friability

The granule friability was used as indicator for granule strength. Using PVP as binder reduced the granule friability (effect of approx. 8%) and a trend was observed that friability decreased when using higher binder concentrations (effect of approx. 7%). Since all overarching filler properties impacted the granule friability, friability can be substantially lowered by selecting the right filler properties, i.e. a low PC1 and PC2 score values in combination with a high PC3 score value. A correlation (R^2=0.6) was found between the granule fine fraction and friability (Figure 10): friable and therefore weak granules resulted in a higher amount of fines.

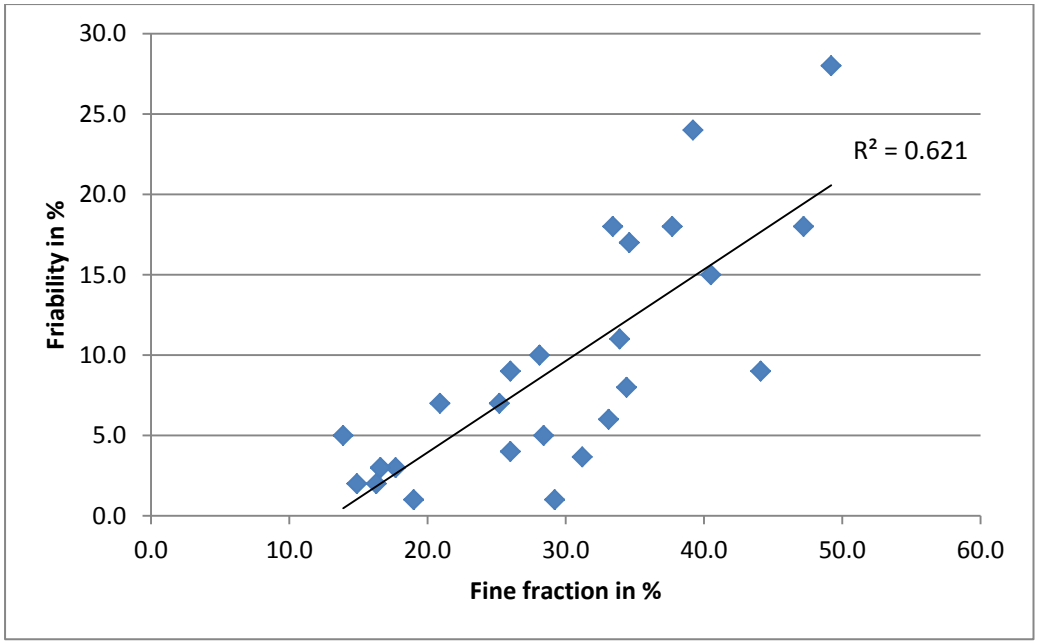

Figure 10. Correlation plot fine fraction (%) vs. friability of granules (%)

Tabletability

The compression force needed to compress tablets to a defined hardness of 75 N was used as an indicator for tabletability. The filler factors did not show a relevant impact on the tablet hardness according to the model, while the binders had a considerable effect. Using PVP as binder as well as higher binder concentrations improved the tabletability, i.e. a lower compression force was needed to reach the target tablet hardness (reduction by approx. 3 kN). In order to better understand why the fillers do not have a relevant effect on the tabletability, the compression force required to reach target hardness was plotted against the filler types, grouped by filler grades (Figure 11).

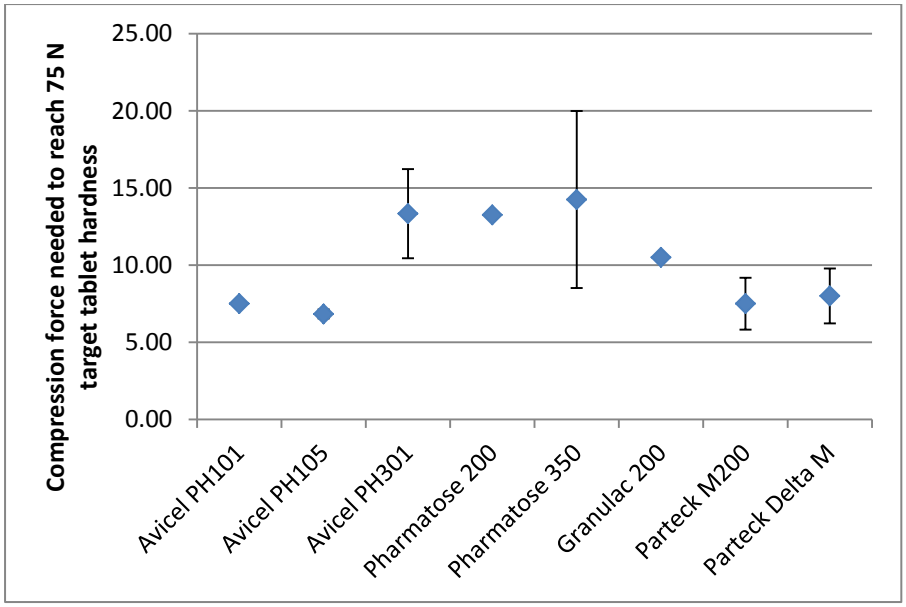

Figure 11. Tabletability (compression force needed to reach target tablet hardness) grouped by filler type. Error bars indicate absolute standard deviation values if available.

Tablets with MCC or mannitol showed a comparable tabletability, while tablets with lactose were inferior considering this response. This observation is in good agreement with previous findings and can be explained with the deformation characteristics of the materials [26]. Avicel PH301, however, shows a significantly lower tabletability compared to other MCC grades, and its tabletability is similar to that of the investigated lactose grades. This observation might be linked to the higher bulk density and lower specific surface area (i.e. reduced surface available for particle bonding) of Avicel PH301 compared to other MCC grades.

Tablet abrasion

PC2 (flow-related properties) was the only factor which showed a relevant impact on tablet abrasion: using Parteck M200 with a low PC2 score value as filler reduced the tablet abrasion (by 0.12%).

Uncontrolled factors

The approach that was used for this study aimed to keep the influence of process parameters on the granule and tablet quality attributes as low as possible to avoid that the impact of formulation parameters (PC1, PC2, PC3 of fillers, binder type and binder concentration) would be overruled by the impact of the process parameters. However, some process parameters needed to be adjusted to account for the different formulation properties (section 2.4), in order to ensure a good processability. Hence, some process parameters and IPC test results were added – one by one - as uncontrolled factors to the design and their influence upon the studied responses was evaluated. As none of the uncontrolled factors (i.e. inlet air flow, inlet air humidity in the fluid bed dryer and LOD of dry granules) had an impact upon the studied responses, the results confirmed that the

necessary adaptations of the process parameters to account for formulation needs did not significantly influence drug product attributes and that the experimental approach taken in this study was valid.

3.4. Verification of developed DOE models

The purpose of external model verification is to investigate the model applicability for granulation and tabletting experiments with formulations that were not included in the model but that were processed using factor settings within the experimental space. The formulations selected for external model verification are listed in Table 6:

Table 6. Selected formulations for external model verification

Experiment number	Filler type	Binder type (factor 4)	Binder concentration in granules (factor 5)	Filler principal component 1 (factor 1)	Filler principal component 2 (factor 2)	Filler principal component 3 (factor 3)
28	Avicel PH101	Kollidon K30	1.0%	-4.31	-0.14	0.02
29	Avicel PH101	Pharmacoat 603	2.0%	-4.31	-0.14	0.02
30	Parteck M200	Pharmacoat 603	1.5%	1.83	-5.56	-1.18
31	Pharmatose 350M	Pharmacoat 603	1.5%	1.77	2.31	-3.00

As previously described, the models with interaction terms revealed confounding among the factors which impedes to understand which factor is responsible for an observed effect. Nevertheless, the models can be used for predictions. Based on the factor settings of the 4 verification experiments (Table 6), the response values were predicted using the optimized interaction models. These predicted values were compared with the observed experimental values which were generated using the granules and tablets manufactured in the verification runs (Table 7).

Table 7. Observed and predicted values per verification batch (*for batch 31, no tablets with target hardness of 75N could be manufactured as tablets broke during ejection at compression forces above 15kN (see 3.1)

Response	Batch 28 (Avicel PH101 and Kollidon K30)			Batch 29 (Avicel PH101 and Pharmacoat 603)			Batch 30 (Parteck M200 and Pharmacoat 603)			Batch 31 (Pharmatose 350M and Pharmacoat 603)		
	observed experimental value	predicted value	95% confidence interval	observed experimental value	predicted value	95% confidence interval	observed experimental value	predicted value	95% confidence interval	observed experimental value	predicted value	95% confidence interval
Bulk density (in g/ml)	0.46	0.47	0.44 - 0.49	0.45	0.50	0.47 - 0.52	0.54	0.55	0.53 - 0.57	0.52	0.56	0.54 - 0.58
Tapped density (in g/ml)	0.58	0.59	0.55 - 0.63	0.56	0.59	0.55 - 0.63	0.62	0.63	0.59 - 0.66	0.63	0.65	0.63 - 0.68
Hausner ratio	1.26	1.27	1.23 - 1.31	1.24	1.21	1.17 - 1.24	1.15	1.13	1.10 - 1.16	1.21	1.17	1.14 - 1.21
Particle size D63.2 (in µm)	558.4	418.4	335.6 - 521.7	349.4	479.5	392.5 - 585.7	364.5	372.8	312.4 - 444.8	207.2	233.7	196.0 - 278.6
Fine fraction (<125 µm) (in %)	33.3	28.7	23.5 - 35.1	35.0	21.6	18.3 - 25.5	27.4	28.2	23.3 - 34.0	47.5	42.5	35.2 - 51.3
Yield fraction (125-710 µm) (in %)	46.7	52.1	48.9 - 55.3	50.5	53.0	50.5 - 56.1	58.4	55.8	51.6 - 60.1	47.1	48.8	44.0 - 53.6
Coarse fraction (710-1400 µm) (in %)	20.2	22.9	18.4 - 27.5	14.6	25.6	21.5 - 29.7	14.4	15.7	11.9 - 19.5	5.3	6.3	2.5 - 10.1
Flowability (ffc)	11.6	3.8	2.4 - 5.1	6.1	7.7	6.4 - 9.0	4.4	4.2	2.9 - 5.4	1.6	3.0	1.6 - 4.4
Friability (in %)	4	2	1 - 4	3	2	1 - 4	9	11	7 - 19	28	37	23 - 61
Specific surface area (in m^2/g)	1.0	1.0	0.8 - 1.2	1.0	1.0	0.9 - 1.2	3.3	3.3	3.1 - 3.4	0.2	0.4	0.3 - 0.6
Torque granulation barrel (in Nm)	4.2	3.6	2.5 - 5.3	4.3	4.7	3.4 - 6.5	1.9	1.9	1.4 - 2.7	1.5	1.6	1.1 - 2.2
Disintegration time (in sec)	31	62	-4 - 129	95	95	35 - 155	121	135	100 - 170	121	127	80 - 173
Tablet abrasion (in %)	0.7	0.9	0.6 - 1.2	0.7	0.6	0.4 - 0.7	0.2	0.3	0.2 - 0.4	*	0.7	0.5 - 1.1
Solid fraction @75N	0.76	0.80	0.77 - 0.82	0.79	0.80	0.78 - 0.82	0.80	0.81	0.79 - 0.83	*	0.86	0.84 - 0.87
Compression force @75N (in kN)	6.0	7.1	6.0 - 8.5	7.0	6.9	5.9 - 8.1	8.0	8.5	7.1 - 10.1	*	15.5	13.1 - 18.4
Ejection force @15kN (in N)	47	23	13 - 42	40	27	15 - 50	649	202	136 - 300	1138	338	216 - 528

In order to evaluate and verify the predictive quality of the models for data that were not included in the models, the difference between the predicted values (P) and the observed values (O) was calculated for each response for the 4 verification experiments using the following equation: (O – P /O)*100. The spider plot in Figure 12 provides an overview of the model verification assessment per response.

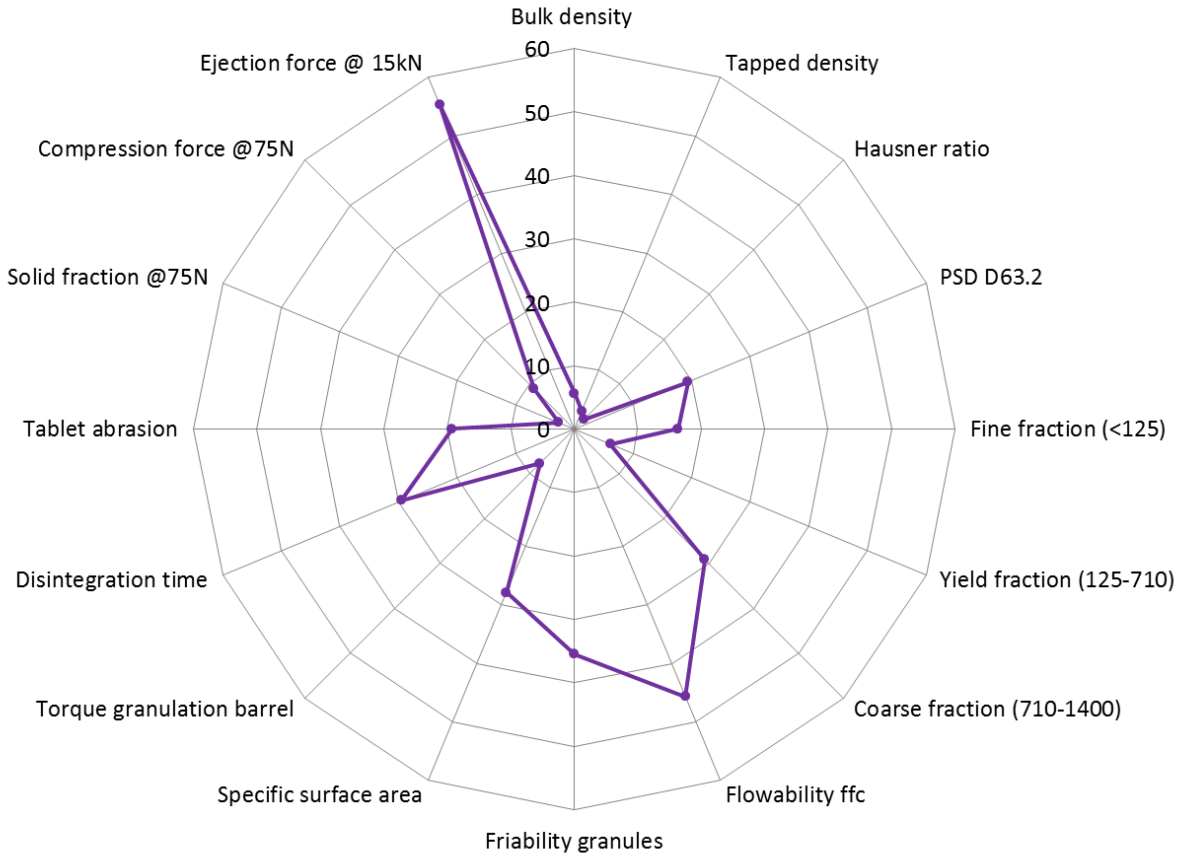

Figure 12. Spider plot: comparison of observed and predicted results per response. A higher percentage is indicative of a large deviation between observed and predicted values. The average deviation of the four verification runs is plotted.

The majority of the predictions were in alignment with expectations, indicating that high Q^2 model values resulted in a low P/O difference. There are some responses, however, where low Q^2 values resulted in limited differences between observed and predicted values (e.g. Hausner ratio, yield fraction or disintegration time), while the opposite was also observed (e.g. specific surface area or ejection force). A possible reason that predictions for the response ejection force resulted in a large P/O difference might be that parameters which distinctly influenced the ejection forces (such as concentration of lubricant in the formulation) were not included as factors in the experimental design and can thus not be explained by the model. Despite the limited variations in the response disintegration time (below 5 minutes for all samples) in combination with a low reproducibility of the centre points for this response, the P/O difference for this response was still acceptable. The low precision in the measurement method of granule flowability might be responsible for the

large P/O difference that was observed for flowability. With a low Q^2 value for the response flowability, the model indicated limited predictive power which was confirmed by a high P/O difference.

Despite these observations discussed above, the models provided good prediction results for granule and tablet responses and the external model verification confirmed the applicability of the existing model also for formulations which were not included in the statistical design, but composed of material included in the excipients PCA (see [12] for further details on the PCA).

4. Conclusion

By combining PCA with DoE, the number of design factors and subsequently the number of experimental batches was reduced while a broad experimental space of filler characteristics was investigated in the same statistical design. The application of statistical models enabled to link granule and tablet characteristics with the overarching properties using DoE and with the underlying excipients characteristics using PCA (Figure 11). Thus, a good understanding was generated regarding how formulation impact the quality attributes of granules and tablets. The formulation understanding presented in this research work, as well as the statistical models can be used to support a lean formulation development: for example, excipients with appropriate characteristics can be selected in order to compensate for unfavourable API properties and thus the number of required experimental runs can be reduced. Furthermore, the predictive power of the model can be used for formulation optimization and troubleshooting, by selecting fillers and binders with appropriate properties to improve suboptimal granule or tablet characteristics. The scope of this study is limited to binary placebo formulations consisting of one filler and one binder type. In order to understand potential non-linear effects of filler mixtures on drug product properties, further studies would be required which could follow a similar approach. Furthermore, an understanding of the impact of the API properties on the drug product pCQAs is also of interest. One approach would be to characterize the API according to the applied methods for fillers and update the PCA model by including the API properties. Based on the resulting three principle component values for the API, the statistical model should allow qualitative predictions of the API effect on the drug product pCQAs.

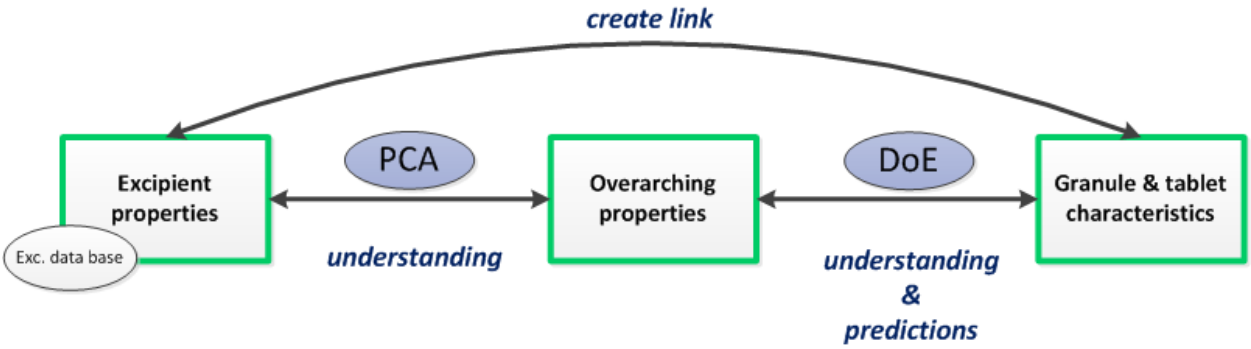

Figure 11. Combined PCA/DoE approach

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CHAPTER 5

INVESTIGATING PROCESSABILITY AND MIXING BEHAVIOUR OF AQUEOUS BINDER LIQUIDS IN VIEW OF A CONTINUOUS WET GRANULATION PROCESS – A SUMMARY OF PRELIMINARY TRIALS

1. Introduction

Pharmaceutical binders are commonly used for wet granulation processes in order to enhance agglomeration of particles. Similar to batch wet granulation, in a continuous twin screw wet granulation process, binders can either added as powders to the dry blend of excipients or be added as aqueous solutions to the granulation process [1],[2],[3]. Given the short granulation time in a continuous twin screw wet granulation process (typically <10 seconds), it is questionable whether the binder can be fully dissolved within the limited granulation time when added as dry powder. Undissolved binder could not support the granule formation and thus the application of dissolved binder in form of a binder liquid is expected to support granulation more efficiently [2]. As described in chapter 3 and 4, the manufactured formulations in the experimental designs of this PhD project consisted of binary filler/binder mixtures. The filler represented the majority of the formulation and thus had a dominant influence on the formulation properties: for example the water content which was needed for wet granulation highly depended on the filler properties. Hence, it was important to select the appropriate liquid-to-solid (L/S) ratio for each formulation in order to avoid over- or under-granulation whereas the binder concentration in the granules had to be at the defined target values for all formulations. Particularly lactose is limited in water-uptake capacity, hence the amount of binder liquid which can be added during wet granulation is limited. This results in highly concentrated and therefore often highly viscous binder liquids to reach the targeted binder concentration in the formulation.

This chapter summarizes the learnings from preliminary trials which were performed before the manufacturing of Design of Experiments (DoE) batches in order to ensure consistent binder liquid pumpability during the granulation experiments. The binder types and binder concentrations for the described pretrials were selected in view of the DoE scope. The first objective of these pretrials was to ensure controllable and constant liquid flow of the binder liquids which were in scope for the DoE study by applying simple test methods. It was important to understand if the binder liquids which are needed to reach the targeted binder concentration in the formulation can be prepared and pumped without any issues and which tubing sizes and pump speeds are suitable to deliver the binder liquid at the appropriate feed rates. Another objective was to confirm a homogeneous distribution of water and binder liquid in the granules when applying a liquid feeding system set-up where water and binder liquid feed rates can be adjusted independently. As described earlier, the experimental design required to adjust the water feed rate separately from the binder liquid feed rate to account for the different water uptake capabilities of the binder types during wet granulation and to ensure good granulation conditions (i.e. avoid over- or under-granulation). A static mixer as well as the approach to add binder liquid and water via two different injection ports to the granulation barrel was therefore investigated. Both, an insufficient binder concentration and inhomogeneous binder distribution in the granules may result in more fines in the

granulate or poor mechanical properties of the granules and should therefore be avoided.

2. Materials

The binder types for this study were selected in view of the DoE (chapter 4): hydroxypropyl methylcellulose (Pharmacoat 603, Shin Etsu, Tokyo, Japan) and polyvinylpyrrolidone (Kollidon K30, BASF, Ludwigshafen, Germany) study. Indigo carmine (Blue Indigotine MN2, Sancolor, Barcelona, Spain) was used as water-soluble colorant. Microcrystalline cellulose (Avicel PH105, FMC Biopolymer, Philadelphia, USA) was used as filler for granulation.

Peristaltic pumps and platinum-cured silicone tubings (Pumpsil, Watson-Marlow, Wilmington, USA) with inner diameters of 3.2-6.4mm were used in combination with nozzles from 0.8-3.2mm.

3. Binder liquid preparation

Experimental trials were performed with aqueous dispersions of Kollidon K30 and Pharmacoat 603. In order to define the maximum binder liquid concentration to be investigated in this study, the following assumptions were made:

- based on previous trials, lactose can tolerate a maximum of approximately 10g/min water during granulation at a powder feed rate of 10kg/h due to its high degree of crystallinity and water solubility. Lactose can be considered as worst case filler regarding water uptake capacity.
- the selected binder types were recommended by the suppliers to be used in concentrations ranging from 2-5% in the formulation for wet granulation processes.
- a binder concentration of 5% in the formulation was selected as a worst case target: if this concentration can be reached all lower concentrations should be achievable as well.

Based on these assumptions the required binder liquid concentration was approximately 50% (m/m) in order to reach a binder concentration in the formulation of 5% when granulating lactose at a powder feed rate of 166.7g/min (=10kg/h). Equations 1 and 2 depict the mathematical relation between feed rates and concentrations where $bind\ conc_{form}$ (in %, m/m) is the binder concentration in the formulation (dry granules), $bind\ liq_{FR}$ is the feed rate of the binder liquid (in g/min), $bind\ dry_{FR}$ is the feed rate of the pure binder (in g/min), *conc bind liq* is the concentration of the binder liquid (in %, m/m) and $filler_{FR}$ is the feed rate of the filler (in g/min).

$$bind\ conc_{form} = \frac{binder\ dry_{FR}}{binder\ dry_{FR} + filler_{FR}} \qquad \text{[Eq. 1]}$$

$$bind\ conc_{form} = \frac{bind\ liq_{FR} * conc\ bind\ liq}{binder\ dry_{FR} + filler_{FR}} \qquad \text{[Eq. 2]}$$

By applying equation 1, first the required feed rate of dry binder was calculated to reach 5% binder concentration in the formulation for a powder feed rate of 166.7 g/min. Second, the required concentration of the binder liquid was calculated for a water feed rate of 10g/min. The resulting binder liquid feed rate was then calculated via equation 2. Hence, it was practically investigated, if a maximum targeted binder liquid concentration of 50% (m/m) could be prepared and processed for the selected binder types.

For Kollidon K30 it was possible to prepare the binder liquid at the maximum targeted concentration of 50% (m/m). In addition, binder liquids with Kollidon concentrations of 30% and 40 % (m/m) were prepared for further pumpability testing. In contrast, the maximum concentration which was still considered as a liquid when using Pharmacoat 603 was 30% (m/m). As depicted in Figure 1 (right and middle), for Pharmacoat 603 it was neither possible to prepare binder liquids at a concentrations of 50% nor at 40%.

Figure 1. Pictures of Pharmacoat 603 binder liquids at different concentrations (% m/m). Right picture: state before obtaining a binder concentration of 50%.

In conclusion, for granulation of mixtures combining lactose as filler and Pharmacoat 603 as binder, the targeted concentration of 5% binder in the formulation could not be obtained.

4. Pumpability of binder liquids

As a next step, the pumpability of the prepared binder liquids was tested to investigate if the required pump rates can be reached to enable the targeted binder concentration in the formulation. It was important to select the appropriate tubing sizes and pump speeds to ensure a controllable and consistent liquid flow. The number of pump heads was selected accordingly, as high viscosity liquids might need increased pressure within the tubing system to achieve sufficient liquid flow.

As for Pharmacoat 603 the targeted binder concentration of 5% binder in the formulation was not achievable in combination with lactose due to insufficient binder solubility (see above), the maximum feed rates for binder liquid concentrations of 10, 20 and 30% (m/m) were evaluated. From these results the maximum achievable binder concentration in the formulation for the DoE study could be calculated. For Kollidon K30 concentrations of 30, 40, and 50% (m/m) were used for pumpability testing. The tubings were assembled as depicted in Figure 2 and the mass flow (in g) after 60 seconds was measured.

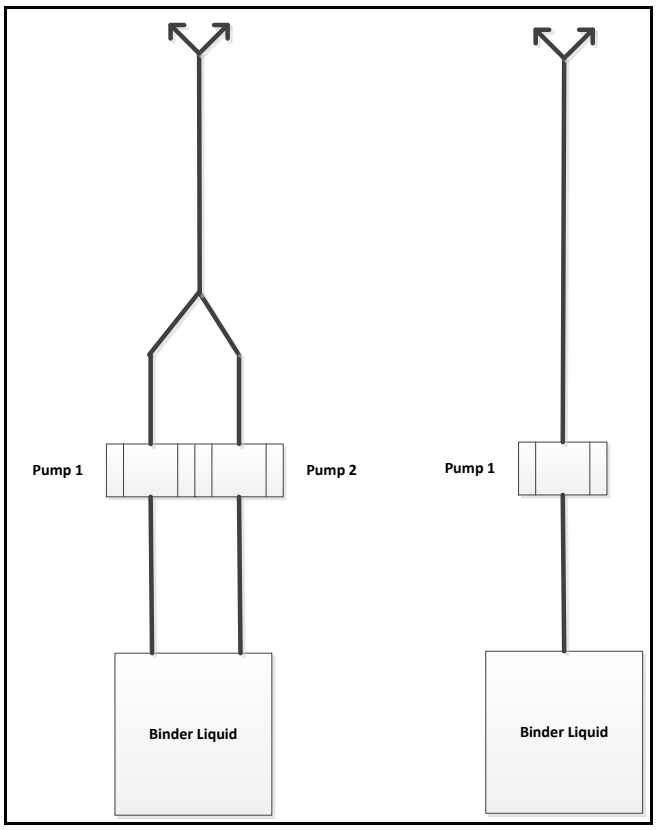

Figure 2. Assembly of binder feeding system (left: two pump heads, right: one pump head)

Independent of the tubing size or the number of pump heads used, the 30% solution of Pharmacoat 603 was not pumpable. Although a Pharmacoat solution at a concentration of 20% could be pumped using a tube with an inner diameter of 3.2 mm, the pump speed did not allow to control the liquid flow rate. Hence, it is not recommended to work under such

conditions during manufacturing due to the very limited control over the liquid flow rate (Figure 3).

The same was observed for Kollidon K30 at a concentration of 40%. For Pharmacoat 603 in a concentration of 10% and Kollidon K30 in a concentration of 30% the liquid flow rate could be controlled in function of the pump speeds (Figure 3).

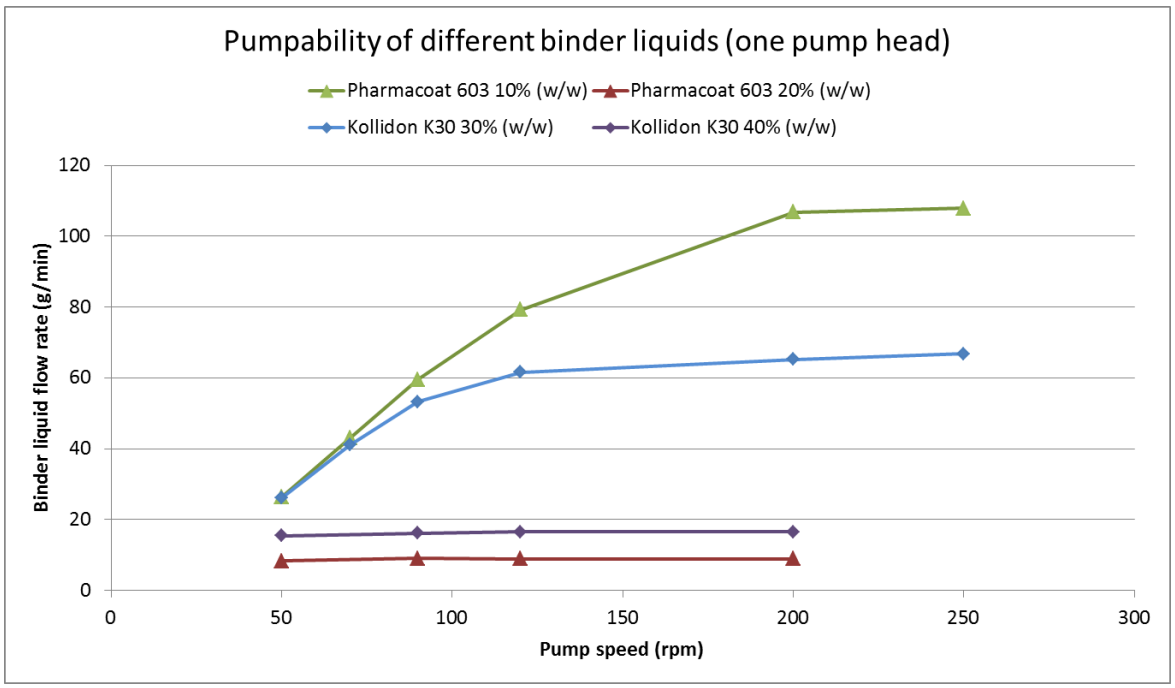

Figure 3. Results of pumpability trials - liquid mass flow as a function of pump speeds (tubing size 3.2mm)

Using two pump heads instead of one, the liquid flow rate could be increased whenever the binder liquid flow was within a controllable range, meaning that a change in pump speed (rpm) resulted in an change in liquid flow rate (e.g. Kollidon K30 at 30% concentration, Figure 4). However, no increase in liquid flow rate was observed when changing from one to two pump heads for Kollidon K30 at 50% concentration, which was already expected since a limited control over the flow rate already occurred for a concentration of 40%.

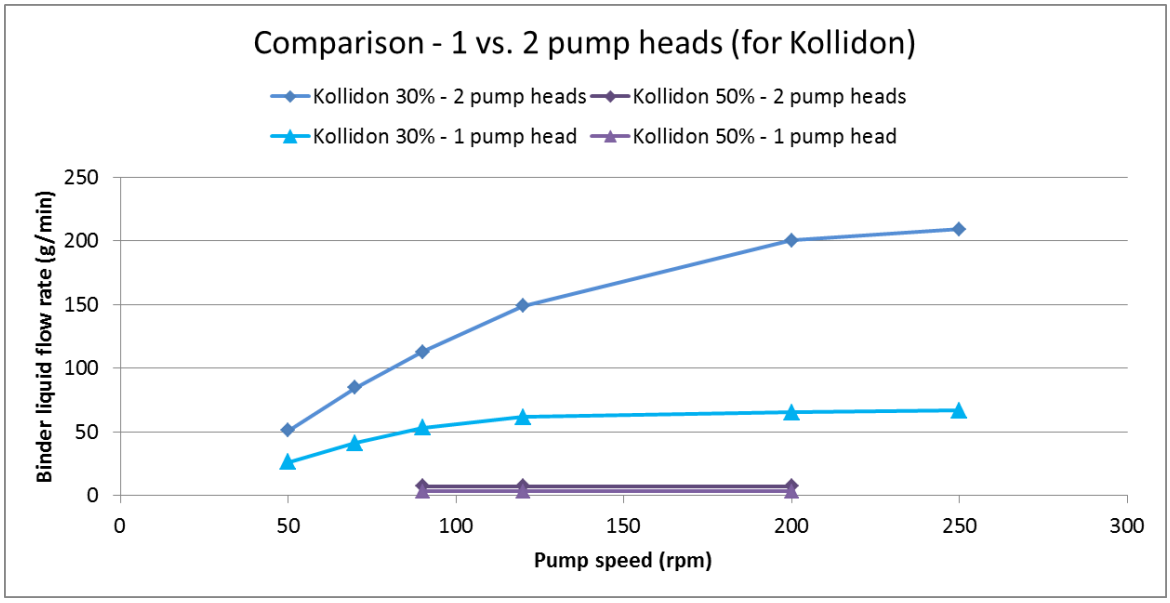

Figure 4. Liquid flow rates for Kollidon K30 at different concentrations using 1 or 2 pump heads

Overall, Kollidon K30 was pumpable in controllable ranges at higher binder liquid concentrations compared to Pharmacoat 603, meaning that the liquid flow rate can also be controlled for higher concentrations via changing the pump speed and that target flow rates can be achieved. The mass flow at equal binder concentration, pump speed and tubing configuration was higher for Kollidon K30 compared to Pharmacoat 603 which can be attributed to the different viscosities of the binder types.

The adjustment of the pump head screws (Figure 5), which prevent the tubing from moving inside the pump head, was found to impact the maximum achievable flow rates for highly viscous binder liquids. The recommended screw positions on the pump heads in function of the tubing diameter could even partially block the tubings so that the liquid flow was hindered. In order to achieve the required flow rate, it was thus preferred to adjust the screw settings with a rotating pump while monitoring the liquid flow rates.

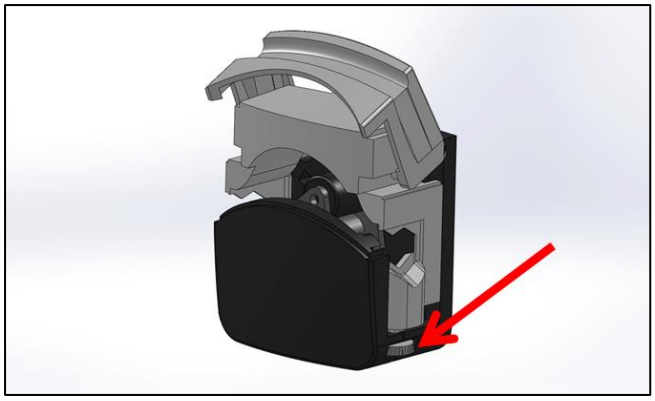

Figure 5. Picture of peristaltic pump (source: Watson Marlow). The red arrow points towards the pump head screws

A challenge during these trials was the limited reproducibility of the influence of parameter settings (e.g. number of pump heads, tubing inner diameter, pump speed) for highly concentrated binder liquids. In order to ensure consistent flow at target flow rate for highly viscous binder liquids during the DoE experiments, the following proceeding was applied (Figure 6):

1. Check the flow rate with recommended settings (based on previous experience, e.g. pretrials)
2. If the target flow rate could not be reached with the selected settings, the tubings' inner diameter, pump head screws, number of pump heads or pump speed needed to be adjusted

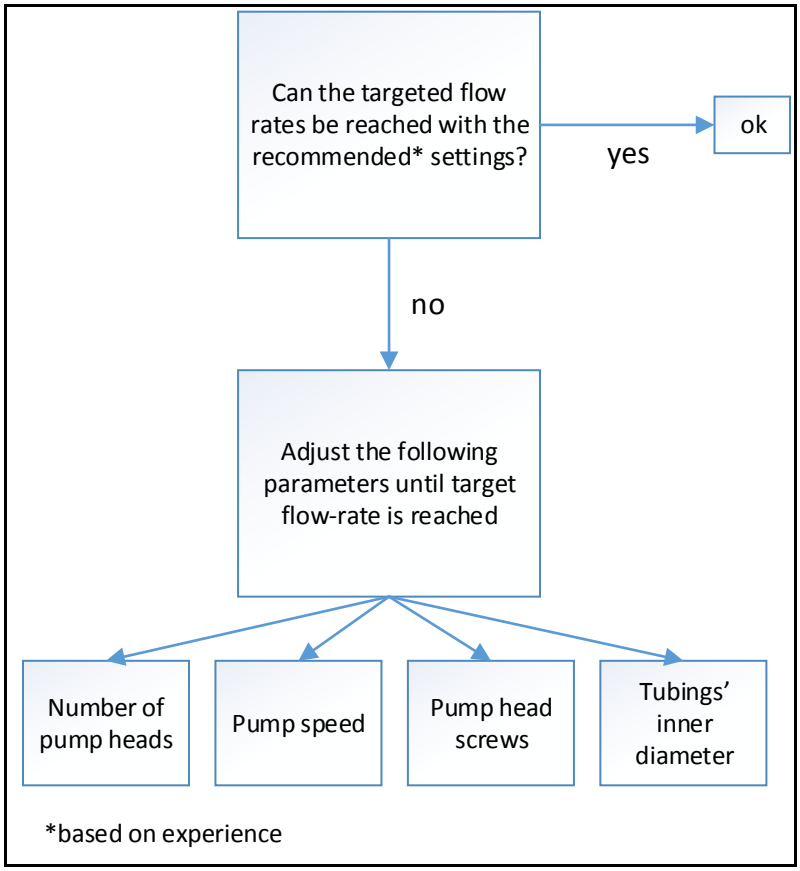

Figure 6. Flow diagram: How to ensure a consistent binder liquid flow at target flow rate

5. Mixing capability of a static mixer for water and binder liquid

One objective of the pretrials was to confirm if water and (highly viscous) binder liquids were homogeneously mixed before the liquids are fed to the granulation barrel when using a liquid feeding system set-up where water and binder liquid feed rates can be adjusted independently. The independent adjustment of the water feed rate was needed to account for the different water uptake capabilities of different formulations in the continuous wet granulation process. For these miscibility trials, the water was colored with indigo carmine (blue) for a better differentiation between the liquids. As depicted in Figure 7, a static mixing tool was integrated in the tubing system to enhance the mixing of binder liquid (Kollidon K30 in 45% (m/m) concentration was selected as highly viscous binder liquid) and water before entering the granulator. The static mixer consisted of a glass tube which contained a metal baffle to cause turbulent flow. The pump speed was set to 35 rpm for water and to 50 rpm for binder liquid.

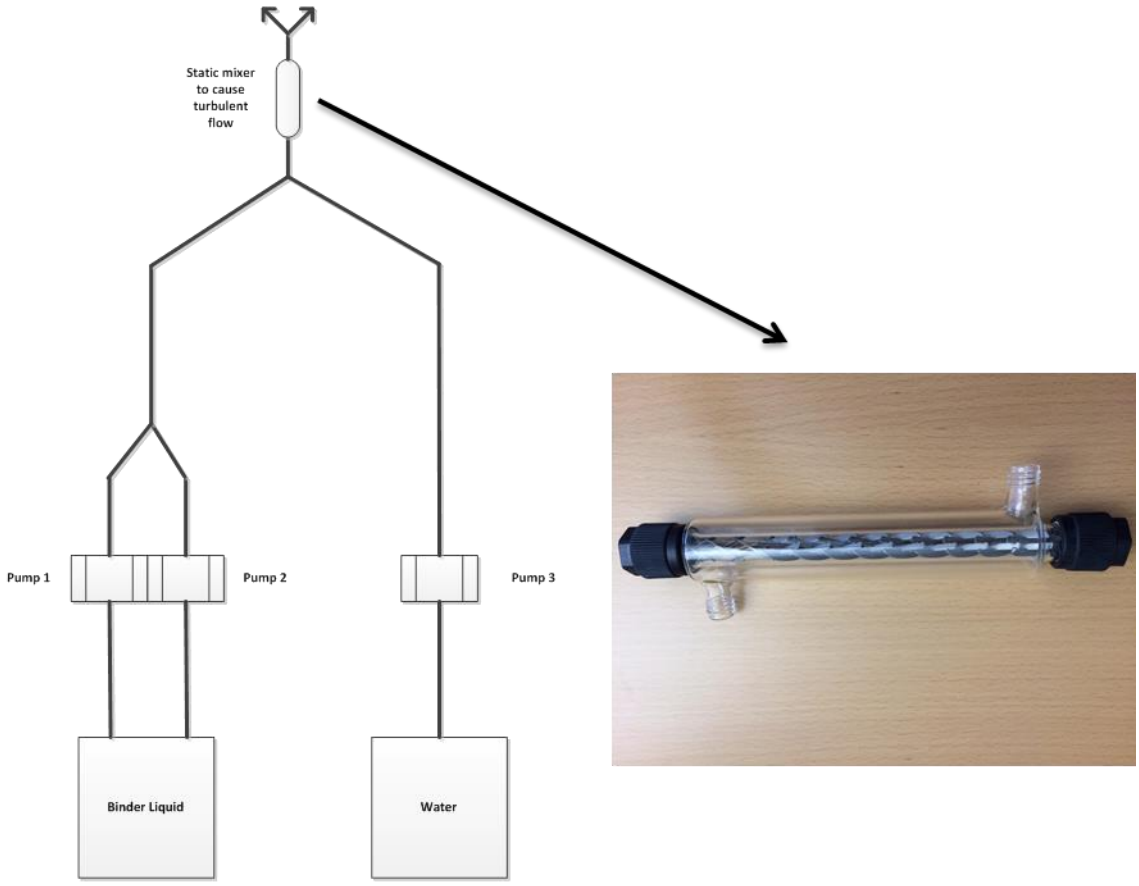

Figure 7. Experimental set-up of combined water and binder liquid feeding system including static mixer

By applying the static mixer device it was shown that binder liquid and water were homogeneously mixed, supported by the metal baffle in the mixer (Figure 8). The yellow streaks gradually disappeared over the distance of the mixer, indicating that binder liquid and water were homogeneously mixed.

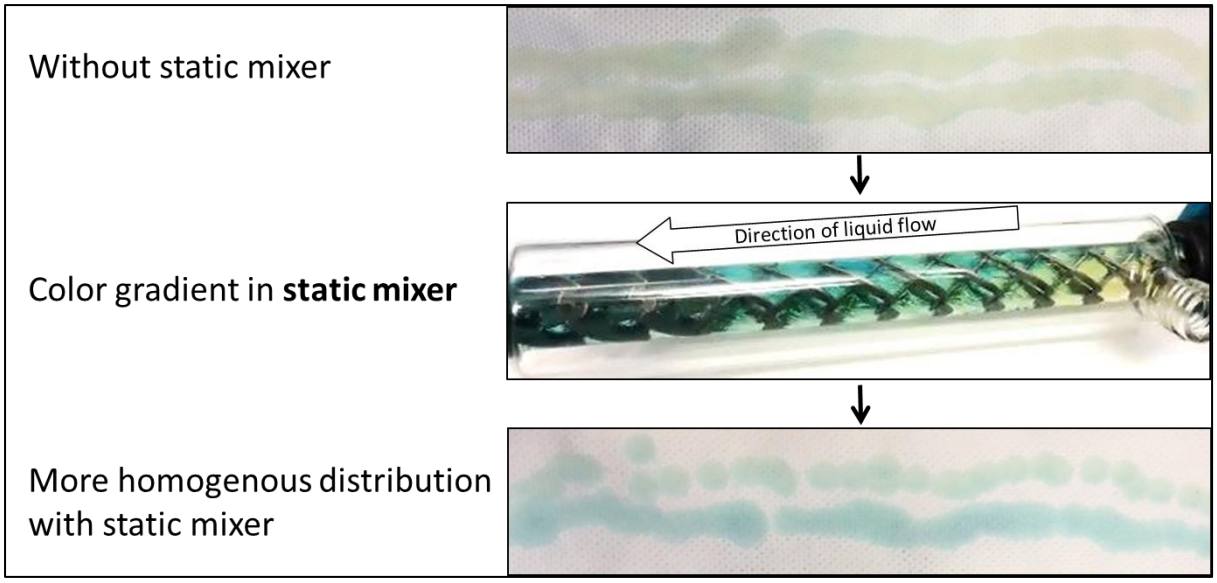

Figure 8. Mixing behaviour with and without static mixer (liquid traces were collected on paper sheets); colour gradient in the static mixer from right to left (binder liquid yellow, water blue)

A limitation of the static mixing tool in view of the conduction of formulation DoEs was that a change of binder liquid type and/or binder concentration in the formulation (i.e. a change of either binder liquid concentration or feed rate) required either dismounting of the liquid feeding system or rinsing the system with large amounts of binder liquid which will be used for the next experiment. Moreover, the static mixer was constructed for these pretrials and is thus a non-GMP (good manufacturing practice) device. The ConsiGma® manufacturing line at Roche, however, was located in a GMP manufacturing area and is dedicated as GMP equipment. Hence, the static mixer (non-GMP) could not be connected with the GMP granulation line for the DoE experiments. Therefore it was decided to not use the static mixer for the DoEs on the ConsiGma© line.

6. Liquid distribution when using two injection ports in the granulation barrel

Using two different liquid injection ports in the granulation barrel was a possible approach which was in alignment with the requirement to adjust the water and binder liquid feed rates independently. The advantage of this set-up was that in view of a DoE with different binder types and binder liquid concentrations, the switch from one to the other binder liquid was facilitated and independent of the water feeding system. However, a homogeneous distribution of the highly viscous binder liquids, which were in scope of the DoE, had to be assured. These pretrials were performed to assess if the mixing behaviour of binder liquid and water in the granulation barrel was sufficient to ensure a homogeneous distribution of binder liquid in the granules when both liquids were added via different injection ports. The binder liquid which had a higher viscosity than water was added via the first injection port to provide a longer granulation time and more mechanic stress to enable the best spread of binder liquid over the filler. Water was added via the second liquid injection port (Figure 9). A dispersion of Kollidon K30 at a concentration of 47% (m/m) was

selected as binder liquid since its high viscosity was expected to be worst case regarding wettability and spread over the dry filler. The binder liquid was coloured with indigo carmine (blue) to enable the detection of potential blue spots in the manufactured granules. Granules were produced with microcrystalline cellulose (Avicel PH105) as filler (fed at 10kg/h). The coloured binder liquid was fed at 18.5g/min and water was fed at 100g/min. A screw configuration of 2x6 kneading elements in an angle of 60° was used, while a block of 6 kneading elements was positioned after each liquid injection port of the granulation barrel (Figure 9).

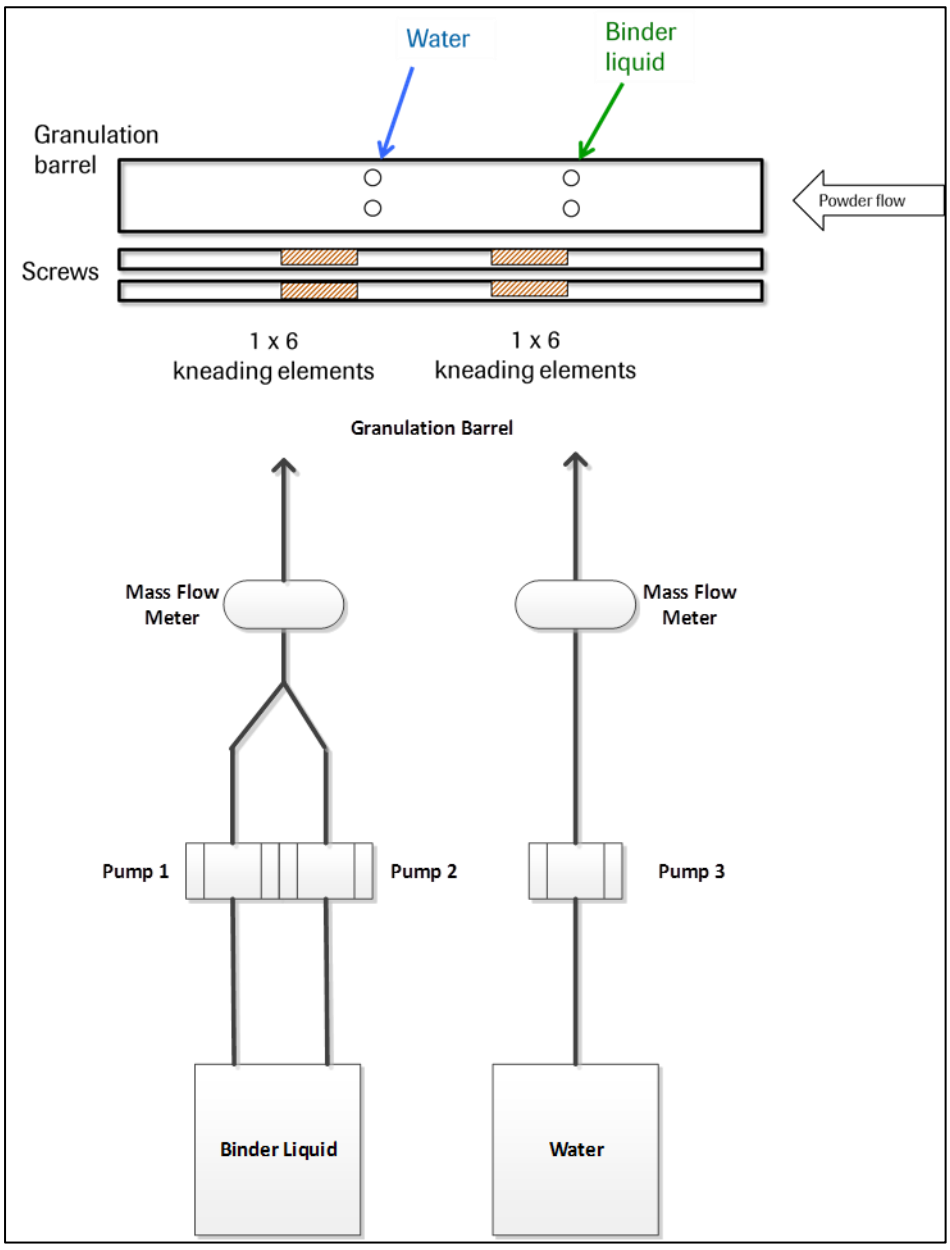

Figure 9. Scheme of experimental set-up for granulation: liquid injection ports, screw configuration and tubing set-up

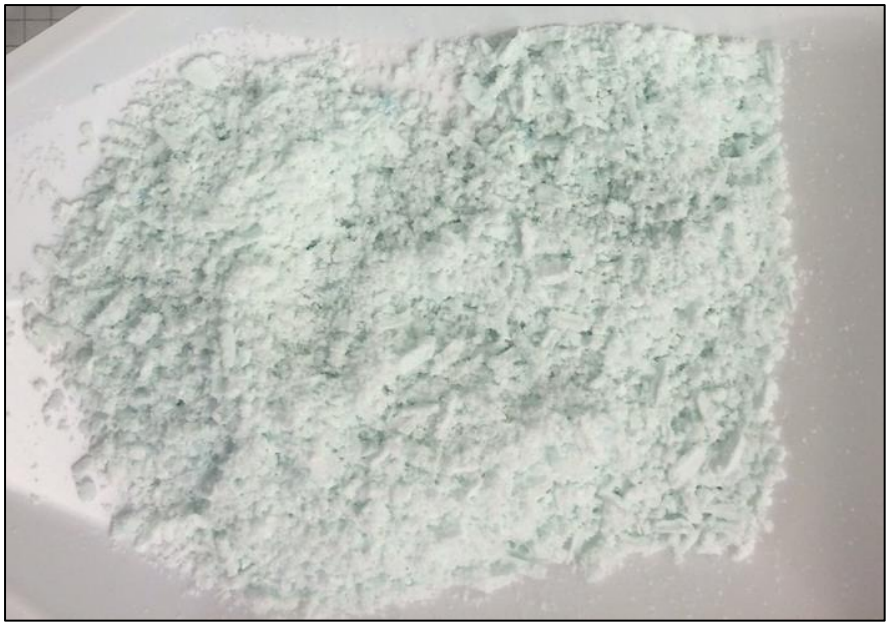

Figure 10. Distribution of coloured binder liquid in wet granules

The overall spread of coloured binder liquid within the granules appeared homogeneous (Figure 10). This visual observation indicates that sufficient mixing of binder liquid and water occurred during wet granulation when feeding them via two different injection ports. Therefore it was decided to use this set-up for the granulation experiments in the DoE study (chapter 4).

7. Conclusions

Kollidon K30 was pumpable in controllable ranges (i.e. the feed rate of the dispersion could be modified in function of pump speed) at higher binder liquid concentrations compared to Pharmacoat 603. Binder liquids from different binder types are different in viscosities and might reveal different shear behaviour. Whenever highly viscous binder liquids are used for granulation, pretests are useful to understand in which concentrations the aqueous solutions of the selected binder types can be prepared and to ensure that the target liquid mass flow falls within a well controllable range (such that the flow rate can be adopted by varying the pump speed). Especially for highly viscous binder liquids, it is recommended to perform pumpability trials in the exact same experimental set-up which will be used for granulation experiments in order to guarantee a smooth conduction of DoE experiments. Results might not be transferable when e.g. longer tubings are used or upon inclusion of a mass flow meter. The gained knowledge from the pretrials can be applied to facilitate the planning of future formulation DoEs by e.g. allowing calculations of feasible binder concentrations in the formulation.

A suggestion for a high level step-wise guidance to evaluate the feasibility of selected binder types and concentrations for a formulation DoE is given below.

1. First, the appropriate water content needed for wet granulation needs to be determined. The formulation that requires the lowest water content will be most critical in view of the selection of the required binder liquid concentration.
2. Based on the lowest water content (see 1.) the targeted binder concentration in the formulation and the resulting binder liquid concentration can be calculated.
3. Depending on the maximum and minimum powder feed rates (targeted in the granulation DoE), the maximum and minimum binder liquid feed rates which are needed to reach the target binder concentration in the formulation can be calculated.
4. For highly concentrated and/or high viscosity binder grades, the binder liquids should be prepared to confirm sufficient solubility.
5. Next, the pumpability of the binder liquids should be tested in the exact same experimental set-up which will be used for granulation experiments. The appropriate combination of parameters (i.e. number of pump heads, pump speed, settings of screws in the pump head, tubing size) to reach a state of consistent liquid flow in controllable ranges (i.e. changes in pump speed must still result in a change of liquid flow rate) should be determined. All previously defined maximum and minimum feed rates should be tested regarding these aspects.

If low viscosity binder grades or binder liquids in low concentrations are applied, pumpability is not expected to be a limiting factor during granulation experiments and thus the given guidance is most certainly not needed.

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CHAPTER 6

BROADER INTERNATIONAL CONTEXT, RELEVANCE AND FUTURE PERSPECTIVES

Broader international context

The ICH Q8 Guidance for Industry of the International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use provides guidance for pharmaceutical development in the industry. The guideline encourages to generate sound process and product understanding in the context of quality-by-design (QbD) principles to support the design of new drug products with the objective to deliver high quality products [1]. Continuous manufacturing is a technology platform that supports the design and manufacturing of high quality products, enhances process understanding in the final scale and provides opportunity for advanced process control when used with process analytical technologies. Also the Food and Drug Administration (FDA) pushes the pharmaceutical industries towards the implementation of continuous manufacturing as one means to ensure a consistent supply of high quality medicines [2]. In the food, petrochemical or polymer industry, continuous manufacturing principles have been established successfully several years ago [3]. Also the pharmaceutical manufacturers are recognizing the benefits associated with continuous manufacturing technology such as the opportunity for rapid and efficient development, the increased flexibility regarding equipment scale and cost effectiveness in development and commercial manufacturing (further details see chapter 1). Besides all advantages, some hurdles exist (e.g. the initially required investments in equipment and resources as well as regulatory uncertainties especially for rest of the world countries; further details see chapter 1) which hinder or decelerate a broad implementation of continuous processes in the pharmaceutical industry [4], [5]. Ultimately, the implementation of continuous manufacturing in the pharmaceutical industry is currently a hot topic being driven by the numerous advantages and slowed down by some relevant hurdles which have to be overcome.

The existence of multiple international partnerships between major pharmaceutical companies, highly rated academic institutions and leading health authorities indicates the high interest in this technology today and suggests that the change towards continuous manufacturing is in the process to happen. The partnership programs aim to share knowledge about continuous manufacturing and to further promote the implementation of continuous processes in the pharmaceutical industry.

Founded in 2007, the *Blue Sky Vision* is a collaboration project between Novartis and the Massachusetts Institute of Technology (MIT) with an investment of 65 million dollar by Novartis. The goal is to develop an integrated approach for fully continuous drug product manufacturing from drug substance starting materials to the final drug product in one facility [4].

Britest was established in 2001 as a not-for-profit and membership-based consortium, with the focus to develop and design innovative techniques, tools and business processes, including continuous manufacturing. As part of their program, Britest supports chemical as

well as pharmaceutical industry with the development of approaches for the transition from batch to continuous manufacturing. Members from pharmaceutical companies like Pfizer, Abbvie and Astra Zeneca as well as members from academia like Purdue University, University of Nottingham and University of Leeds are represented. In 2016, Britest joined the CMAC`s research program for "Continuous Manufacturing and Crystallization" as a member. The CMAC program focuses on accelerating the design and implementation of continuous manufacturing processes for chemical products [4], [6], [7].

The multi-university *C-SOPS consortium* (Center of Structured Organic Particulate Systems) is funded by the National Science Foundation and uses continuous manufacturing methods to develop predictive models for improved process control and process robustness. The objective is to mitigate common batch process problems like segregation or agglomeration. A large number of pharmaceutical companies (e.g. GSK, Pfizer, Vertex, Johnson & Johnson), equipment manufacturers (e.g. Bohle, Thermo Fisher) and universities (e.g. New Jersey Institute of Technology, Purdue University, University of Puerto Rico at Mayaguez) are members of this consortium [4]. Janssen received the FDA approval in 2016 and the EMA approval in 2017 to switch production of their HIV drug product "Prezista™" from batch to a full-scale continuous direct tablet compression process in its manufacturing facility in Puerto Rico. For the development of this integrated continuous manufacturing process, Janssen collaborated with researchers from C-SOPS and Rutgers University [8], [9].

The *European Consortium for Continuous Pharmaceutical Manufacturing (ECCPM)* specifically focuses on the development and implementation of continuous manufacturing for solid oral dosage forms. It is a collaboration between the coordinating Research Centre Pharmaceutical Engineering Graz (RCPE), various pharmaceutical companies (like Astra Zeneca, Bayer Health Care) and academic partners (like Ghent University, University of Eastern Finland, Heinrich Heine University Düsseldorf). One of the goals is to develop a guideline for the set-up of continuous processes in the frame of workshops for expertise exchange among the consortium members. Moreover the consortium supports academic research projects in the context of continuous manufacturing aiming to generate knowledge in areas which are of high relevance for continuous processes (e.g. Process Analytical Technologies) [10].

These collaborations are typically setup by partners from academia and industry, however, it is considered beneficial to also involve health authorities as stakeholders. An example is the collaborations between the FDA and the Biomedical Advanced Research Development Authority (BARDA), that aims to facilitate the implementation of continuous manufacturing strategies in the field of medical countermeasures (i.e. FDA-regulated products like drug, biologics or devices which are intended for use in events of a potential public health emergencies [11]) [2]. Therefore BARDA for example funded a project in collaboration with Janssen for the development of a continuously manufactured influenza antiviral drug. In the future, continuous manufacturing should be transferred from private industry and be

implemented for the production of medical countermeasures. By implementing smaller and multi-product continuous manufacturing facilities, the overall manufacturing capabilities can be increased resulting in improved domestic resilience and national security in view of health emergency issues [12].

In conclusion, the high interest reflected in the partnerships as well as the increasing number of approved products manufactured via continuous manufacturing technology (i.e. Orkambi™ (Vertex, FDA approval in 2015 [13]) and Prezista™ (Johnson & Johnson, FDA/EMA approval in 2016/2017 [8],[9])), and finally the increasing investment in this technology suggest that the change towards continuous manufacturing is happening, tough slow in a highly regulated Industry. Aiming to facilitate the implementation of continuous manufacturing processes across the pharmaceutical industry, the ICH is currently in the process to develop a new guideline (ICH Q12) [13].

Relevance

As previously described, continuous manufacturing is gaining attention in the pharmaceutical industries and the transition from batch to continuous manufacturing is on-going. Hence, the focus is shifting from conventional batch high shear wet or fluid bed granulation towards continuous wet granulation technologies.

This research work was conducted in the field of continuous manufacturing – more precisely on formulation development for continuous twin screw wet granulation. A considerable public knowledge on process understanding for continuous wet granulation was available upon the start of this research project. However, the public knowledge regarding formulation understanding was limited. As this PhD project addresses the topic of formulation design for continuous twin screw wet granulation the results can thus be considered of great interest. In particular two main focus areas of this research project, which are the material sciences (excipient characterization & database) and the application of statistical models to support formulation design, are of high relevance: A detailed understanding of material properties and its impact on drug product performance will a support an efficient formulation design, especially in combination with statistical models which allow to link excipient characteristics with drug product quality attributes.

Material science

The role of material science is becoming more important to support a lean and goal-oriented drug product development which is needed to comply with e.g. accelerated development timelines. One reason for accelerated timelines is for instance the increasing cost pressure in the pharmaceutical industries due to generic competition products. Another driver is the development of medicines with high unmet medical need (e.g. oncology therapies) for which the regulatory agencies accept an acceleration of the clinical development program in order to make these life-saving medicines available to patients as

early as possible. The formulation design is going away from a “trial and error” approach towards the approach where unfavourable API (active pharmaceutical ingredient) properties are identified and suitable excipients are selected to compensate them. A higher level of material understanding enables a “right-first-time” excipient selection which decreases the number of experimental studies needed and thus reduces development time and costs equally.

In this research project, an extensive characterization of the physico-chemical and solid state properties of selected pharmaceutical fillers and binders was performed with the advantage that results are comparable due to equal measurement techniques and conditions. An in-depth understanding of similarities and differences of these excipients was obtained. The gained knowledge and databases are considered as an important basis for a data-driven and rationale-based oral solid dosage form development [13].

The knowledge on material properties which was generated in the context of this research work is not necessarily limited to continuous wet granulation technology. The excipient understanding can serve as starting point to support a lean formulation development irrespective of the applied manufacturing technology (wet and dry granulation technologies, but also direct compression for example).

Application of statistical models for continuous manufacturing

Next to the material science and the excipient database, the methodical approaches (i.e. the application and combination of different statistical models) of this PhD project can be considered to have a high relevance for pharmaceutical research and development. Since the amount of data which is generated during the development of pharmaceutical products is steadily increasing (DoE studies, on-line and real-time process monitoring), statistical methods are required to process the large amount of data accordingly. In this research project, multivariate data analysis (MVDA) was combined with DoE.

MVDA is a useful tool to extract and assess the most important information out of large data sets. MVDA is for example becoming a widely accepted technique in the pharmaceutical sciences, being applied for qualitative work like raw material classification via principle component analysis (PCA). MVDA models are for example used for quantitative in-line analysis like the water determination of materials via near infrared spectroscopy [13].

DoE is a statistical approach for experimental work that allows to generate a high level of process understanding based on a reasonable number of experiments while at the same time the statistical power of the results typically increases compared to univariate experimental design. Especially by combining MVDA with DoE, broad experimental spaces can be investigated with a limited number of experimental trials. This is the experimental approach that was used for this PhD research.

Moreover, the statistical techniques and methods like MVDA and multiple linear regression (MLR) models which were applied in this research project are comparable to the approaches which are used for process analytical technologies (PAT) applications and real-time release testing (RTRT). An example of RTRT in continuous commercial processes was recently presented for tablet dissolution as a critical quality attribute (CQA) underlining the relevance of statistical models for continuous manufacturing: Multivariate analysis tools (like PCA) were therefore applied to detect the factors which influenced the dissolution behaviour. In a next step, statistical models including the identified relevant factors were calculated to develop a suitable dissolution method [14], [15]. This example shows that the application of statistical models as used in this research project is of relevance for the development of robust continuous manufacturing processes.

In conclusion, a combination of statistical tools, like DoE practices, advanced data analysis techniques with risk-based development strategies such as the quality risk assessment (QRA) concept and process models substantially enhance the process and product understanding generated during pharmaceutical research and development. This can support the manufacturing of high quality products with increased safety while contributing to a cost-effective drug product development.

Future Perspectives

Excipient selection based on raw material characteristics for an efficient formulation design

One main achievement in this research project was the compilation of the excipient database consisting of pharmaceutical fillers and binders. The database describes the solid-state and physico-chemical properties of several excipients that are frequently used for the production of solid dosage forms. The measurements of excipient properties were conducted using comparable testing conditions such that the numerical results can be compared. Literature search is usually applied to receive this kind of information about excipient properties. However, results are mainly not directly comparable due to differences in the applied measurement techniques and conditions.

In an advanced stage of a formulation development process, the excipient understanding can be applied for trouble shooting purposes. In case the formulation (API and excipients) reveals unfavourable properties regarding processability or drug product attributes, specific excipients can be selected to compensate these negative effects. If the resulting granules would for example reveal poor flow behaviour and an adversely high fine fraction, the statistical models can be used to replace the filler in the formulation by another filler type which decreases the amount of fines and increases the flowability at the same time.

Overall, the application of this approach reduces the number of formulation experiments that need to be performed, which results in savings of API and resources. Likewise this

efficient formulation design can be helpful when formulations are developed under time constraints, e.g. when the project timelines are accelerated.

Application of material science for other granulation processes and continuous manufacturing

Although the excipients which are included in the database of this research project were selected in view of suitability for a continuous wet granulation process, there is no connection to the granulation technology as such. The knowledge about key differences and similarities between the excipients is independent of continuous wet granulation and thus the gained excipient understanding is valid in general and not limited to wet granulation processes. Hence, the knowledge can be applied as a beneficial source of information to support a rationale-based formulation development irrespective of the applied manufacturing technology.

As valuable results were obtained via the combined PCA/DoE approach for the continuous twin screw wet granulation process, this approach could also be used for other (batch) wet granulation technologies and even be applied in the context of other continuous technologies as well, e.g. for continuous direct compression or continuous dry granulation. The excipient database which served as basis for the DoE is already available. As appropriate, the existing excipient database could therefore be complemented with further excipients (by applying the used measurement techniques) which are for instance dedicated either for direct compression or continuous dry granulation technologies. By adding the measurement results to the PCA model, the model can be updated with new data which is expected to result in an improved model. In a next step experimental trials can be performed to link the excipient properties with the intermediate and drug product quality attributes.

Opportunities for further scientific investigations

In the frame of this research project, areas of interest for further investigations were identified which are summarized in this section.

Further investigations regarding pharmaceutical binders in a twin screw continuous wet granulation process might be of interest. In the experimental studies of this research project, the binders were added to the granulation process as an aqueous dispersion. As previously described, limitations regarding binder pumpability and thus maximum achievable binder concentration in the formulation were observed (chapter 5). Some published studies are available where wet and dry binder addition was compared [17], [18], [19]. However, contradictory results regarding the impact of binder state during addition on granules and tablets were observed. Especially in view of the short granulation time during continuous wet granulation processes (i.e. less than 10 seconds), further experimental studies should be performed to compare the effect when different binder types are added

in dry and wet state on granule and tablet properties and also if higher or lower binder concentration might be needed when comparing wet and dry binder addition.

Moreover investigations are needed to evaluate the impact of binders: Are the commonly used binder types for batch wet granulation equally suitable for continuous wet granulation processes? Or do certain binder types reveal specific effects which make them more/less suitable for continuous wet granulation purposes?

The Application of the used PCA approach for formulations containing filler mixtures or APIs was identified as another potential topic of interest for future investigations. The formulations which were evaluated in this research project were binary systems consisting of one filler type and one binder type. For commercial drug products, however, more complex formulations are typically applied, often including two different filler types to achieve a synergistic effect. For example for tablet compression, a filler with brittle compression behaviour is usually combined with a filler with plastic compression behaviour. Hence, it would be valuable to characterize filler mixtures in the same way as done for pure fillers and include the results in the excipient database. An interesting aspect of filler mixtures would be to investigate which excipient properties behave additive and for which properties interactions are observed.

Since this work focused on placebo formulations, a next step could be to include API in the PCA models. On the one hand, APIs could be considered as “excipients” and simply be an additional part in the formulation composition. In this case characterization of APIs must be performed in the same way as for the fillers. On the other hand, APIs might have additional properties (e.g. polymorphism, melting point, distribution coefficient/log D value) that could potentially influence the process and product performance. Hence, additional material characteristics need to be identified and determined using suitable techniques to include these parameters in an expanded PCA model. Since APIs certainly differ in some of the material characteristics (e.g. APIs often have smaller particle sizes compared to fillers), the addition of APIs would be beneficial in view of a broader model space.

In addition, the interrelation of formulation characteristics and process parameters could be addressed in further experimental studies. To investigate the impact of excipient characteristics on drug product properties, it was desired to reduce the influence of process parameters on the product to a minimum. The process parameters were therefore kept constant wherever possible. A remaining question is to what extent the currently used fixed process settings might be a limitation regarding future model predictions. Evaluations regarding the effect of process parameters together with formulation properties on the drug product are needed. Since the effect of both is usually interrelated it would be valuable to investigate them simultaneously, e.g. in one statistical design. That way, the maximal possible impact through process parameters and formulation composition on product CQAs could be determined. Knowledge about the interrelation of process parameters and formulation characteristics could be valuable for the implementation of feed-forward and

feed back control loops in a continuous wet granulation process: In case raw material variability is detected through real-time process monitoring tools, an appropriate signal would be send to adjust upstream process parameters based on that knowledge.

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GENERAL CONCLUSIONS

This research project investigated the impact of pharmaceutical fillers and binders on granule and tablet attributes manufactured via continuous twin screw wet granulation.

Within Roche, and also in the public domain limited knowledge was available regarding formulation and excipient impact in a continuous twin screw wet granulation process. The objective of this research was therefore to generate fundamental understanding about the influence of excipient characteristics on drug product attributes and process performance of a continuous twin screw wet granulation process. The knowledge gained during this project will support an effective and efficient formulation design for continuous wet granulation technology.

The fillers and binders that were selected within the scope of the project were intensively characterized as a large number of physico-chemical and solid state characteristics were measured. By applying principal component analysis (PCA), the large number of excipient properties was condensed to a few overarching properties. PCA proved to be a useful tool to extract the overarching excipient properties from the large excipient data set. The interpretation of the PCA allowed to identify the meaning of the overarching property which represented several underlying excipient properties. The combination of PCA with design of experiments (DoE) allowed to evaluate excipients covering a broad range of properties in the same experimental design. Moreover, this approach enabled to reduce the number of DoE factors and subsequently also the number of experimental trials. Overall, the manufactured granules and tablets resulted in a substantial variation in their properties, and the statistical model revealed that a considerable number of responses were impacted to a relevant degree by the selected fillers or binders. For the studied excipient and concentration ranges, the filler impact dominated the binder impact on granule and tablet properties.

Another objective was to generate understanding whether commonly used excipients for high shear or fluid bed wet granulation processes are suitable for continuous wet granulation. In general, the excipients for wet granulation which were evaluated in this research project proved to be suitable for continuous wet granulation technology as well. One exception is the filler dicalcium phosphate (DCP), which resulted in granules of poor quality for the majority of manufactured formulation compositions. However, tablets with DCP, had a similar quality compared to tablets manufactured with other fillers. Limitations regarding the binder pumpability were observed. As a result the maximum binder concentration in the formulation is limited. Especially high viscosity binder grades were problematic in view of pumpability. This limitation can however be mitigated if formulations with higher water uptake capacity (e.g. containing microcrystalline cellulose as filler) are manufactured. As these experimental studies were designed to manufacture formulations with a large concentration of highly water soluble lactose, this was basically considered as the root cause for the observed limitations. Another approach to overcome these

limitations would be the addition of dry binder to the powder pre-blend before wet granulation.

The knowledge gained in this research project will be used for formulation optimization and troubleshooting. External model verification was performed which confirmed the validity of the statistical models for new data that was not included in the model. Hence, the model predictive power can be used to support excipient selection in early stage of formulation development as well as for trouble shooting purposes, e.g. aiming to compensate adverse API (active pharmaceutical ingredient) properties.

SUMMARY

For decades, the pharmaceutical industry has relied on batch-wise manufacturing for the production of solid dosage forms. In the recent years, however, continuous manufacturing became of interest due to its potential for efficient development, advanced process control and time-scaling. Continuous wet granulation technologies are now emerging as an alternative wet granulation technology to realize the concept of a fully integrated continuous manufacturing line. The overall objective of this research project was to understand the influence of excipient characteristics on drug product attributes and process performance of a continuous twin screw wet granulation process in order to support a QbD-based formulation design.

The **introduction (chapter 1)** addresses advantages and opportunities of continuous manufacturing (like rapid and efficient development, increased flexibility and improved drug product quality) as well as challenges which have to be overcome for the implementation of continuous processes in the pharmaceutical industries. Different continuous granulation technologies and examples for integrated manufacturing lines with continuous wet granulation are explained. Finally, a high-level overview of current knowledge available is compiled regarding a) process parameters` impact on product properties in a continuous twin screw wet granulation process and b) the impact of raw material properties on process performance and product properties.

Research work regarding raw material characterization of selected fillers and binders for wet granulation is summarized in **chapter 2.** 9 fillers and 9 binders were selected for this study. These fillers and binders were extensively characterized regarding their physico-chemical and solid state properties using a total of 21 material characterization techniques. Subsequently, principal component analysis (PCA) was performed on the data sets of filler and binder characteristics in order to reduce the variety of single characteristics to a limited number of overarching properties. Four principal components (PC) explained 98.4% of the overall variability in the fillers data set, while three principal components explained 93.4% of the overall variability in the data set of binders. Both PCA models allowed in-depth evaluation of similarities and differences in the excipient properties.This knowledge also served as basis to define experimental trials for continuous wet granulation DoE studies (chapter 3 and 4).

The objective of the DoE studies described in **chapter 3** and **chapter 4** was to generate understanding about the impact of excipients on granule and tablet attributes by following a systematic statistical approach. Finally, the knowledge gained in these studies is intended to be used for Quality by Design (QbD)-based formulation design as well as formulation optimization troubleshooting. In both studies, a combination of principle component analysis (described in chapter 2) and design of experiments was applied. The majority of process parameters were kept constant to minimize their influence on the granule and drug product quality. The studies differed regarding the applied statistical design (full factorial design versus d-optimal design), the selection of fillers and binders (by hand selection via

principal components versus selection via the d-optimal design) and the applied binder concentrations (fixed versus varied concentrations). In addition, slightly different ConsiGma© machine set-ups were used for granulation.

In the DoE study which is described in **chapter 3**, the impact of a broad range of filler and binder characteristics on granule and tablet properties was investigated based on a set of 36 experimental trials. A good understanding of formulation impact on drug product critical quality attributes was achieved and the models' predictive power was acceptable. Dicalcium phosphate as an insoluble and abrasive filler might require special granulation conditions compared to other fillers which were manufactured in this study. Based on the results of this experimental study, limitations in the experimental set-up and statistical approach were identified and used to optimize the approach as well as to define areas of interest for further investigations which were addressed in chapter 4.

27 DoE batches consisting of binary filler/binder mixtures were processed via continuous twin screw wet granulation followed by tablet compression which is presented in **chapter 4**. By combining PCA with DoE, the number of design factors and subsequently the number of experimental batches was reduced while a broad experimental space of filler characteristics was investigated in the same statistical design. Moreover, the combined PCA/DoE approach allowed to link the excipient properties with the drug product quality attributes. It was found that the impact of fillers on the granule and tablet responses was more dominant compared to the impact of binder type and concentration. In order to evaluate the DoE models' validity, a verification of the DoE models was performed with new formulations which were initially not included in the dataset used to build the DoE models. The predictive power of the models can be used to select fillers and binders with appropriate properties to improve suboptimal granule or tablet characteristics.

Chapter 5 summarizes the learnings from preliminary trials about processability and mixing behaviour of aqueous binder liquids in view of a continuous wet granulation process. Two binder types (Pharmacoat 603 and Kollidon K30) and different tubing sizes were selected for the pretrials in order to ensure consistant binder liquid flow during DoE granulation experiments. The approach to add binder liquid and water via two different injection ports to the granulation barrel resulted in homogeneous distribution of water and binder liquid in the granules. Pretrials proved to be useful whenever highly viscous binder liquids are used for granulation to ensure that the target liquid mass flow falls within a well controllable range and to facilitate planning of DoE studies.

Chapter 6 compiles information regarding the broader context of continuous manufacturing in the pharmaceutical industries. Multiple international partnerships between major pharmaceutical companies, highly rated academic institutions and leading health authorities exist, which indicates the high interest in this technology today and suggests that the change towards continuous manufacturing is in the process to happen. As this PhD project addresses the topic of formulation design for continuous twin screw wet granulation the

results - in particular the two main focus areas “material sciences” and the “application of statistical models” to support formulation design - can thus be considered of great interest.

SAMENVATTING

Gedurende de voorbije decennia heeft de farmaceutische industrie bijna uitsluitend gebruik gemaakt van batchprocessen voor de productie van vaste doseringsvormen. Tijdens de laatste jaren heeft continue productie echter aan belang gewonnen omwille van de mogelijkheden die dit concept biedt, onder andere een efficiëntere productontwikkeling, het implementeren van geavanceerde procescontrole en een eenvoudige opschaling. Hierdoor worden momenteel verschillende technologieën voor continue vochtige granulatie geëvalueerd, met als doelstelling het ontwikkelen van een volledig geïntegreerde continue productielijn voor vaste doseringsvormen.

De algemene doelstelling van dit onderzoeksproject is het verder uitbouwen van het concept Quality by Design (QbD)-gebaseerde formulatie-ontwikkeling tijdens continue productie van vaste doseringsvormen. Hiervoor ligt de focus op de impact van materiaaleigenschappen van de aangewende grondstoffen op de kwaliteit van granules en tabletten geproduceerd via continu twin-screw granulatieproces.

De **inleiding (hoofdstuk 1)** geeft een overzicht van zowel de voordelen van continue productie (o.a. snelle en efficiënte productontwikkeling, meer flexibiliteit en betere kwaliteit van het eindproduct) als de uitdagingen die moeten overwonnen worden om dit concept te realiseren binnen de farmaceutische industrie. Verschillende continue granulatietechnieken en voorbeelden van geïntegreerde productielijnen voor continue vochtige granulatie worden beschreven. Eveneens wordt een globaal overzicht gegeven van de state-of-the-art in verband met de invloed van procesparameters en materiaalkarakteristieken op de eigenschappen van de granulaten geproduceerd via continue twin-screw granulatie.

Het onderzoek in verband met de karakterisering van de eigenschappen van een aantal geselecteerde vul- en bindmiddelen voor vochtige granulatie wordt voorgesteld in **hoofdstuk 2.** Negen vulmiddelen en 9 bindmiddelen werden geselecteerd voor dit onderzoek, en hun fysico-chemische en vaste-fase eigenschappen worden uitgebreid gekarakteriseerd gebruik makend van 21 technieken. Vervolgens werd principal component analyse (PCA) uitgevoerd op de datasets van de vulmiddel- en bindmiddeleigenschappen om het grote aantal individuele materiaalkarakteristieken te reduceren tot een beperkt aantal overkoepelende eigenschappen. Vier principale componenten (PC) verklaarden 98,4% van de variabiliteit in de vulmiddel-dataset, terwijl 93,4% van de variabiliteit van de bindmiddel-dataset werd omvat via een model met drie PCs. Beide PCA modellen lieten een uitgebreide evaluatie toe van de overeenkomsten en verschillen tussen de eigenschappen van de geselecteerde hulpstoffen. Deze kennis werd aangewend als uitgangspunt voor de design of experiment (DoE) studies van continue vochtige granulatie uitgevoerd in hoofdstukken 3 en 4.

De doelstelling van de design of experiment studies, voorgesteld in **hoofdstukken 3 en 4**, is inzicht te verwerven over de impact van de gebruikte grondstoffen op de granulaat- en de tableteigenschappen door het volgen van een systematische statistische benadering. De informatie die verzameld wordt via deze studies zal worden aangewend voor Quality by

Design (QbD)-gebaseerde formulatie-ontwikkeling en voor het optimaliseren van formulaties. In beide studies wordt een combinatie van principal component analyse (beschreven in hoofdstuk 2) en design of experiments (DoE) toegepast. Tijdens de experimenten werden de meeste procesparameters constant gehouden om hun invloed op de granulaat- en productkwaliteit te beperken.

De studies verschilden wat betreft het aangewende statistische model (full factorial design versus d-optimal design), de selectieprocedure van vul- en bindmiddelen (handmatige selectie via principal component analyse versus d-optimal design) en de concentratie aan bindmiddel (constante versus variabele concentratie). Daarenboven waren er beperkte verschillen in de setup van de ConsiGma©-apparatuur die in beide hoofdstukken voor de granulatie-experimenten werden gebruikt.

In de DoE studie, beschreven in **hoofdstuk 3**, wordt de impact onderzocht van een brede waaier aan karakteristieken van de vul- en bindmiddelen op granulaat- en tableteigenschappen, gebaseerd op 36 experimenten. Dit liet toe inzicht te krijgen over de impact van de formulatie op de kritische parameters van het eindproduct, waarbij de voorspellende kracht van het model aanvaardbaar was. Dicalcium fosfaat als een onoplosbaar vulmiddel vergde specifieke granulatiecondities in vergelijking met de andere vulmiddelen geëvalueerd in deze studie. Gebaseerd op de resultaten van dit experimenteel onderzoek werden de beperkingen in de experimentele opzet en de statistische evaluatie geïdentificeerd. Deze informatie werd aangewend om de benadering te optimaliseren en ook de verdere onderzoekstappen te definiëren die worden aangepakt in hoofdstuk 4.

In **hoofdstuk 4** werden 27 DoE batchen van een binair vul- en bindmiddelmengsel verwerkt via continue twin screw granulatie, gevolgd door compressie tot een tablet. Door PCA te combineren met DoE was het mogelijk het aantal factoren en ook het aantal uitgevoerde experimenten te reduceren, terwijl toch een brede range aan vulmiddeleigenschappen werden geïncludeerd in de studie. Daarenboven liet de gecombineerde PCA/DoE benadering toe om een correlatie te leggen tussen de eigenschappen van de hulpstoffen en de doseringsvormen. Hieruit bleek dat de invloed van de vulmiddelen op het granulaat- en de tableteigenschappen groter was dan de invloed van het bindmiddel en zijn concentratie. Om de validiteit van de DoE modellen te evalueren werd een verificatie uitgevoerd, gebruik makend van formulaties die initieel niet werden geselecteerd voor het opstellen van de DoE modellen. De predictiviteit van de modellen kan aangewend worden om vul- en bindmiddelen met specifieke eigenschappen te selecteren teneinde de eigenschappen van granulaat en tablet te optimaliseren.

In **Hoofdstuk 5** worden de resultaten besproken van de preliminaire testen die werden uitgevoerd op de processeerbaarheid en het mengen van waterige dispersies van de bindmiddelen met het oog op hun gebruik in het continue vochtige granulatieproces. Twee types binders (Pharmacoat 603 en Kollidon K30) en tubings met verschillende interne diameters werden geëvalueerd tijdens deze preliminaire testen om te verzekeren dat een

constante flow van de bindvloeistof mogelijk is gedurende de DoE granulatie experimenten. De benadering om bindvloeistof en water via twee verschillende injectiepoorten in de granulator te pompen resulteerde in een homogene verdeling van water en bindvloeistof in de granulaten. Deze testen waren essentieel indien hoogviskeuze bindvloeistoffen werden aangewend voor granulatie om te verzekeren dat de vereiste flow rate zich in het gebied bevindt waar deze te controleren is zodat de geplande experimenten van de DoE kunnen uitgevoerd worden.

Hoofdstuk 6 bespreekt de bredere context van continue productie binnen de farmaceutische industrie. Diverse internationale samenwerkingen tussen farmaceutische bedrijven, academische instellingen en gezondheidsorganisaties rond deze topic zijn reeds opgestart, wat de hoge interesse in deze technologie benadrukt en wat aangeeft dat de transitie van batch naar continue productie binnen de farmaceutische industrie momenteel in volle gang is. Het belang van dit doctoraatsonderzoek is groot aangezien dit project zich focust op het ontwikkelen van formulaties voor continue twin screw granulatie waarbij in het bijzonder aandacht wordt besteed aan de eigenschappen van de grondstoffen die worden aangewend en aan statistische modellen die het ontwikkelen van nieuwe formulaties ondersteunen.

API	Active pharmaceutical ingredient
BARDA	Biomedical Advanced Research Development Authority
BET	Brunauer, Emmett, Teller
CDC	Continuous direct compression
CMAC	Continuous Manufacturing and Crystallization
conti	Continuous
CQA	Critical quality attribute
C-SOPS	Center of Structured Organic Particulate Systems
D50	Mean particle size
DCP	Dicalcium phosphate
DoE	Design of Experiments
DVS	Dynamic vapor sorption
ECCPM	European Consortium for Continuous Pharmaceutical Manufacturing
EMA	European Medicines Agency
FBR	Focused beam reflection
FDA	Food and Drug Administration
ffc	Flow function coefficient
GCU	Granule conditioning unit
GMP	Good manufacturing practice
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HPC	Hydroxypropyl cellulose
HPMC	Hydroxypropyl methylcellulose
HSWG	High shear wet granulation
ICH	International Conference on Harmonisation
IPC	In-process control
L/S	Liquid-to-solid

LOD	Loss on drying
Log	Logarithmical
MCC	Microcrystalline cellulose
MIT	Massachusetts Institute of Technology
MLR	Multiple linear regression
MODCOS	Integrated modular continuous system
MVDA	Multivariate data analysis
NIR	Near infrared
OOS	Out-of-specification
P/O	Predicted to observed
PAT	Process analytical technology
PC	Principal Component
PCA	Principal Component Analysis
PCMM	Portable, continuous, miniature, and modular
pCQAs	Potential critical product attributes
PLS	Partial least square
PSD	Particle size distribution
PVP	Polyvinylpyrrolidone
QbD	Quality by Design
QRA	Quality risk assessment
QTPP	Quality target product profile
RCPE	Research Centre Pharmaceutical Engineering
ROW	Rest of the world
rpm	Rounds per minute
RTRT	Real time release testing
SSA	Specific surface area

CURRICULUM VITAE

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Professional Experience

Since 02/2017 — Project Manager at F. Hoffmann-La Roche Ltd Kaiseraugst
(Department of Biologics Drug Product Manufacturing)

- Responsibility for strategic and technical transfer projects
- Management of project resources, timelines and stakeholders
- Matrix team leader

11/2013 – 12/2016 — PhD studies at F. Hoffmann-La Roche Ltd Basel
(Department of Small Molecules Drug Product Development)

- Planning, execution and evaluation of Design of Experiments (DoE)
- Manufacturing of DoE batches applying continuous wet granulation technology
- Multivariate data analysis (MVDA) and use of statistical software (SIMCA®, MODDE®)
- Co-supervision of interns
- Extensive literature search

06/2013 – 10/2013 — Temporary employment at F. Hoffmann – La Roche Ltd Basel
(Department of Small Molecules Drug Product Commercial Manufacturing)

- Support for implementation of new quality system: Identification of gaps and definition of corrective actions
- Revision of local GMP documents

07/2012 – 12/2012 Internship at F. Hoffmann – La Roche Ltd Basel
(Department of Small Molecules Drug Product Commercial Manufacturing)

- Working in a GMP environment
- Process validation reviews
- Contribution to risk assessments and implementation of defined actions
- Deviation report trending
- Use of various in-house database systems (Condor, Manufacturing Execution System)

01/2012 – 06/2012 Internship at Mariahilf Apotheke (Pharmacy) in Munich

- Customer consultation and prescription drug sales
- Preparation of custom-made formulations
- Handling of narcotic substances
- Documentation of re-imported drugs

11/2007 – 12/2011 Student job at Coreografía Production GmbH in Munich

- Decoration of event locations and cafés
- Backstage assistant coordinator at fashion shows
- Installation and design of promotion areas
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09/2007 and 03/2008 Internship at Apotheke am Rathaus (Pharmacy) near Munich

Education

11/2013 – 12/2016	PhD in Pharmaceutical Sciences (Joint PhD project of F. Hoffmann-La Roche and Ghent University Belgium) "Formulation design for continuous twin screw wet granulation"
04/2007 – 10/2011	Pharmacy studies at Ludwig-Maximilians University Munich
02/2013	3rd State Examination (final grade: 1.88)
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Language Skills:

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International Publications

- Identifying overarching excipient properties towards an in-depth understanding of process and product performance for continuous twin screw wet granulation
  International Journal of Pharmaceutics, 2017, 522, 234–247

- A novel approach to support formulation design on twin screw wet granulation technology: Understanding the impact of overarching excipient properties on drug product quality attributes
  Submitted to International Journal of Pharmaceutics

Oral Presentations

- Formulation Development for Continuous Wet Granulation
  Science and Innovation Forum, F. Hoffmann – La Roche Ldt, Basel, June 8th-10th, 2015

- Formulation Development for Continuous Wet Granulation
  9th Annual Symposium of Pharmaceutical Solid State Research Cluster, Ghent University, Belgium, September 16th-18th, 2015

- Continuous Drug Product Manufacturing
  Alessio Lo Faro Scientific Symposium, University of Pavia, Pavia, October 9th, 2015

Poster Presentations

- Identifying overarching excipient properties towards an in-depth understanding of process and product performance
  10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology (PBP World Meeting), Glasgow, United Kingdom, April 4th-7th, 2016

- A novel approach towards formulation development for continuous twin screw wet granulation
  MINT Symposium, F. Hoffmann – La Roche Ltd, Basel, Switzerland, September 14th-15th, 2016