Ghent University

Faculty of Pharmaceutical Sciences

TOWARDS CONTINUOUS PHARMACEUTICAL TABLET MANUFACTURING: IMPLEMENTATION OF CONTINUOUS AGGLOMERATION TECHNIQUES

Valérie VANHOORNE

Master of Science in Drug Development

Thesis submitted to obtain the degree of Doctor in Pharmaceutical Sciences

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The promoters

Prof. Dr. C. Vervaet

Prof. Dr. J.P. Remon

The author

Valérie Vanhoorne

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Valérie

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LIST OF ABBREVIATIONS

a_{50}	Median aspect ratio
API	Active pharmaceutical ingredient
C%	Compressibility index
d	Tablet diameter
d_{50}	Mean median particle size
E	Energy
F	Diametral crushing force
FDA	Food and drug administration
EMA	European Medicine Agency
ffc	Flowability index
F_{wt}	Weight of granules retained on a 250 µm sieve after friability testing
GSD	granule size distribution
HPMC	hydroxypropylmethylcellulose
ICH	International Council for Harmonization
IER	In-die elastic recovery
I_{wt}	Weight of granules subjected to friability testing
L/S	Liquid-to-solid
LOD	Loss on drying
MCC	Microcrystalline cellulose
MCP	Main compression pressure
MDSC	Modulated differential scanning calorimetry
MPT	Metoprolol tartrate
PAT	Process analytical technology
PC	Principal component
PCA	Principal component analysis
PCMM	Portable continuous miniature modular
Ph. Eur.	European Pharmacopea
PLC	Plasticity constant
PVP	Polyvinylpyrrolidone
RH	Relative humidity
RMSECV	Root mean square error of cross validation
SEM	Scanning electron microscopy
SME	Screw mixing elements
t	Tablet thickness
T_a	Tablet height immediately after ejection

T_{id}	Tablet height under maximum compression force
To	Outlet temperature
TS	Tensile strength
USP	United States Pharmacopea
V_0	Bulk volume
V_{1250}	Tapped volume
XRD	X-ray diffraction

OUTLINE AND AIMS

Up to now pharmaceutical manufacturing has been synonymous with batch processing and little attention was paid to optimization of the manufacturing processes. However, faced with high pressure on the profit margins by generic competitors, decreasing health care budgets and smaller drug pipelines, the pharmaceutical industry and competent authorities recently recognized the potential of continuous processing to improve the efficiency and productivity of drug manufacturing. Indeed, continuous manufacturing offers numerous economic, environmental and quality-related advantages. The ultimate goal of continuous manufacturing is to continuously produce a high-quality product 24/7 for up to 50 weeks a year with real time product release. Although innovative continuous processes and implementation of process analytical technology were intensively studied by academic institutions and R&D units of brand and generic drug manufacturers over the last decade, more knowledge concerning the process dynamics, control strategies and process-formulation interactions is essential to implement fully continuous manufacturing lines.

Agglomeration processes are often necessary to improve the flowability, homogeneity and tabletability of powders prior to tableting. Spray drying and twin screw granulation are continuous agglomeration processes with high potential for implementation in continuous 'from-powder-to-tablet' lines. Therefore these techniques were studied in this research project.

The first aim of this project was to develop a modified spray drying process to improve the flowability and tabletability of drug formulations with poor tabletability. Although modified spray drying setups with return of fines into the atomization zone and integrated fluid beds in the bottom of the drying chamber are available to improve the flowability of spray dried powders, these setups have limited applicability in the pharmaceutical industry as the residence time of particles is uncontrolled. Therefore in current study a modified setup was developed to introduce solid particles in an atomized spray of droplets during spray drying with the intention to induce agglomeration between droplets and particles and consequently to improve the flowability and tabletability of the coprocessed particles.

Twin screw granulation is an emerging continuous granulation technique. In recent years, studies on twin screw granulation focused on the influence of process parameters on critical quality attributes of granules while formulation development received little attention. Although mannitol is a preferred excipient for the formulation of tablets, most studies on twin screw granulation used lactose or microcrystalline cellulose as fillers. Therefore the second aim of

this project was to evaluate the potential of β- and δ-mannitol as excipient during twin screw granulation. Finally, research on twin screw granulation was almost exclusively limited to immediate release formulations. Therefore, the third aim was to investigate the potential of twin screw granulation with water as granulation liquid, for the production of a controlled release formulation with hydroxypropylmethylcellulose as matrix former. The influence of process parameters (screw speed, throughput, temperature, screw design) and formulation parameters (concentration of HPMC in the formulation, viscosity and substitution degree of HPMC) on critical quality attributes of granules and tablets was evaluated.

1

INTRODUCTION

CONTINUOUS MANUFACTURING OF TABLETS IN THE PHARMACEUTICAL INDUSTRY

TOWARDS CONTINUOUS MANUFACTURING

Driven by strict regulations the pharmaceutical industry has been very conservative and for a long time did not question its traditional batch-wise manufacturing methods while in other industries (e.g. chemical, food, personal care, mining and electronics industry) continuous techniques were introduced decades ago. The first continuous paper machine was developed and patented in 1799 by Louis-Nicolas Robert, and the Haber process for continuous production of ammonia, was fully operational around 1920 [1, 2]. However, under pressure from generic competitors, governments and rising development costs, the pharmaceutical industry recently recognized the potential of continuous manufacturing for more cost-efficient production, delivery of high quality products and lower environmental footprint.

During batch processing raw materials are charged into the system at the beginning of the process and the product is discharged all at once at a later point in time. No ingredients are added or removed from the system between charging of the raw materials and discharge of the product. A common pharmaceutical manufacturing process generally consists of sequential batch processes with storage and off-line quality testing of intermediate products. If the product does not meet the quality specifications the complete batch is discarded [3]. This concept is schematically presented in Figure 1 for the production of tablets which is typically preceded by blending, granulation, drying and milling.

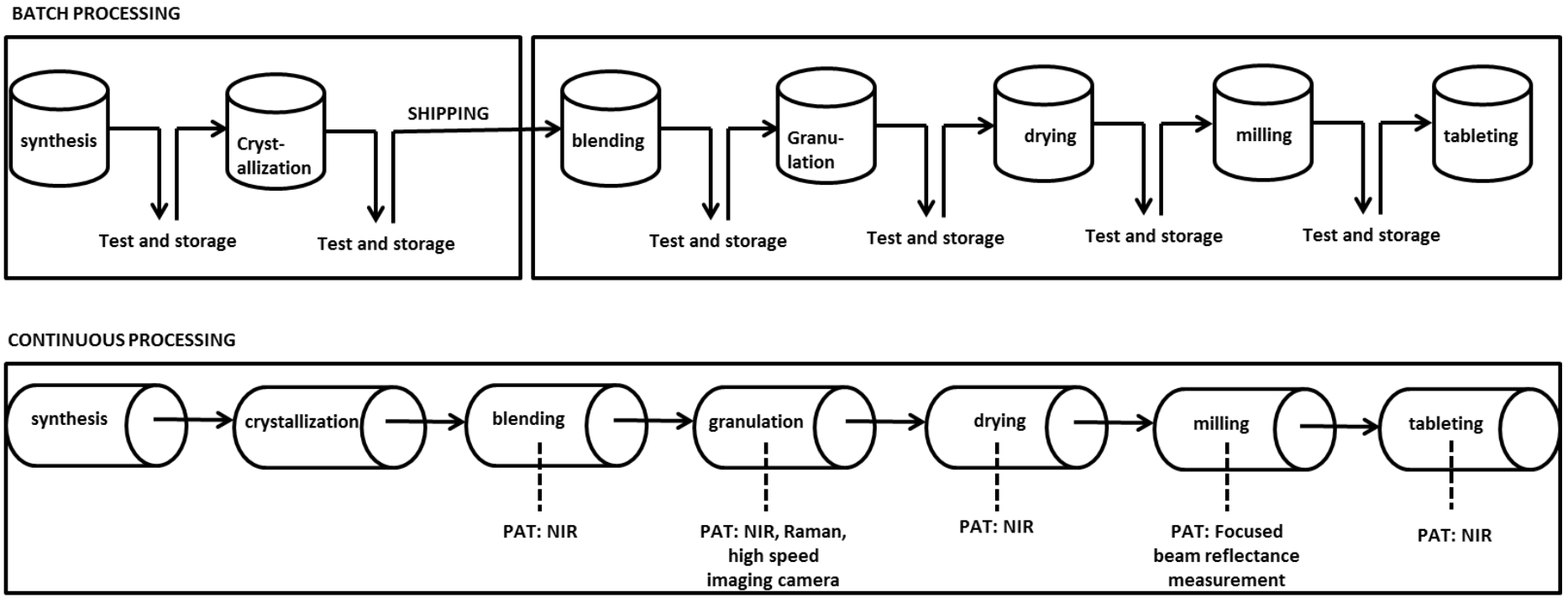

Figure 1. Schematic overview of typical unit operations in batch-wise manufacturing (top) and continuous manufacturing (bottom) including possibilities for monitoring critical quality attributes by PAT.

In a continuous manufacturing process all unit operations are connected and starting materials and end products are continuously charged into and discharged from the process, respectively, following the first-in-first-out principle. Additionally, process analytical technology (PAT) systems integrated in the manufacturing line can provide real-time data for process monitoring and control. This eliminates the need for storage and off-line characterization of intermediates and the final product, making the process more cost-efficient. This concept of fully continuous manufacturing is compared in Figure 1 to traditional batch processing [3]. The ultimate goal of continuous manufacturing is to produce a high-quality product 24/7 for up to 50 weeks a year with two weeks for annual maintenance of the equipment and this from the primary stage of drug production (API synthesis) on.

Definition of a batch is important to trace the final product back to the used raw materials, applied process parameters and quality testing. Whereas batch definition is straightforward during batch processing, it should not be a hurdle after continuous processing as the definition of a batch by the Food and Drug Administration (FDA) is not related to the production method (batch-wise or continuous). Instead the FDA's definition refers to the quantity of manufactured drug, defining a batch as 'a specific quantity of a drug or other material that is intended to have uniform character and quality, within specified acceptance limits, and is produced according to a single manufacturing order during the same cycle of manufacture'. Therefore this definition should not impede the adoption of continuous processing from a regulatory point of view. The batch size of a continuous process could be defined either by a fixed quantity of product or by the amount produced in a fixed time interval [4].

Over the last decade individual companies have invested over a billion dollars in total in the development of continuous manufacturing technologies as they recognized the numerous benefits offered by this emerging manufacturing concept. Whereas initially there was limited collaboration across the industry, more recently a broader forum was initialized by the FDA as it is convinced of the enormous potential of continuous manufacturing. This platform aims to promote collaborations and exchange of knowledge between pharmaceutical companies and subsequently to facilitate the implementation of continuous manufacturing. With this initiative the discussion has shifted from whether continuous manufacturing should be implemented to how it is best implemented [5]. The numerous benefits of continuous manufacturing listed in Table 1 will be discussed in the following paragraphs. These benefits are related to improved product quality, cost-efficiency and reduced environmental impact.

Table 1 Benefits of continuous manufacturing within the pharmaceutical industry

Improved product quality
Higher level of process robustness and control
Implementation of PAT
Elimination of batch-to-batch variability
Compliance with Quality-by-design principle
Prevention of drug shortages
Faster market access of new drugs
Improved cost-efficiency
Flexibility
Elimination of scaling-up
Faster market access
Accelerated capacity response in case of changing market needs
Faster supply chain
Reduced footprint
Possibility for transportable manufacturing lines
Reduction of API consumption during product development
Less time needed for product development
Lower investment in containment of highly potent drugs
Reduced environmental impact
Reduced solvent use
Reduced resource consumption

I**mproved product quality**

During continuous manufacturing intermediates are continuously transferred throughout the entire process, whereas in batch manufacturing a unit operation (e.g. drying, blending) can be prolonged to obtain an intermediate or product with the desired specifications. Therefore a *higher level of process robustness and control* should be implemented during continuous manufacturing to ensure improved product quality. This is achieved by processing under strictly controlled steady state conditions in combination with continuous *evaluation of critical quality attributes via PAT*. As intermediates are not isolated from the process flow during continuous manufacturing real-time monitoring of process parameters and quality attributes of in-process material by PAT is crucial to establish an effective control strategy with feedback and feedforward control loops. Linking critical quality attributes of the final drug product to process controls and intermediate attributes measurable by PAT probes should result in lower product variability. This concept is schematically presented in Figure 2. This is opposed to batch manufacturing where a batch is only transferred to the next unit operation when the quality of a batch is approved by analysis of isolated samples. *Batch-to-batch variability can be eliminated* by continuous manufacturing as the material is operated in plug flow, whereas during batch processing temperature, mass transfer and momentum vary with the position within the equipment, resulting in batch-to-batch variability and eventually rejection of complete batches [6]. Therefore continuous manufacturing is highly suited to

comply with the quality-by-design principle of the ICH Q8 guideline on pharmaceutical development. This guideline states that quality should be built into a product through process and product understanding and to use this understanding for implementation of effective quality control strategies to deliver high-quality products [7].

Drug shortages are a significant public health issue affecting the treatment of patients with life-threatening diseases such as cancer and infections. In 2011 the FDA reported 251 drug shortages in the USA [8]. Improved agility, flexibility and robustness of continuous manufacturing could be key in the prevention of these shortages as they mostly start with quality manufacturing problems [8]. The suitability of continuous processes for implementation of PAT and feedback and feedforward control should ensure a more consistent product quality. Additionally continuous manufacturing techniques allow faster response to changing market needs in case of epidemics or emergencies as the time to market is significantly reduced by real time release testing of the product, elimination of scale-up and faster installation of the typically smaller plants. *Faster market access* can be particularly important for breakthrough therapies (therapies for serious and life-threatening diseases that demonstrated substantial improvement over existing therapies in preliminary clinical trials).

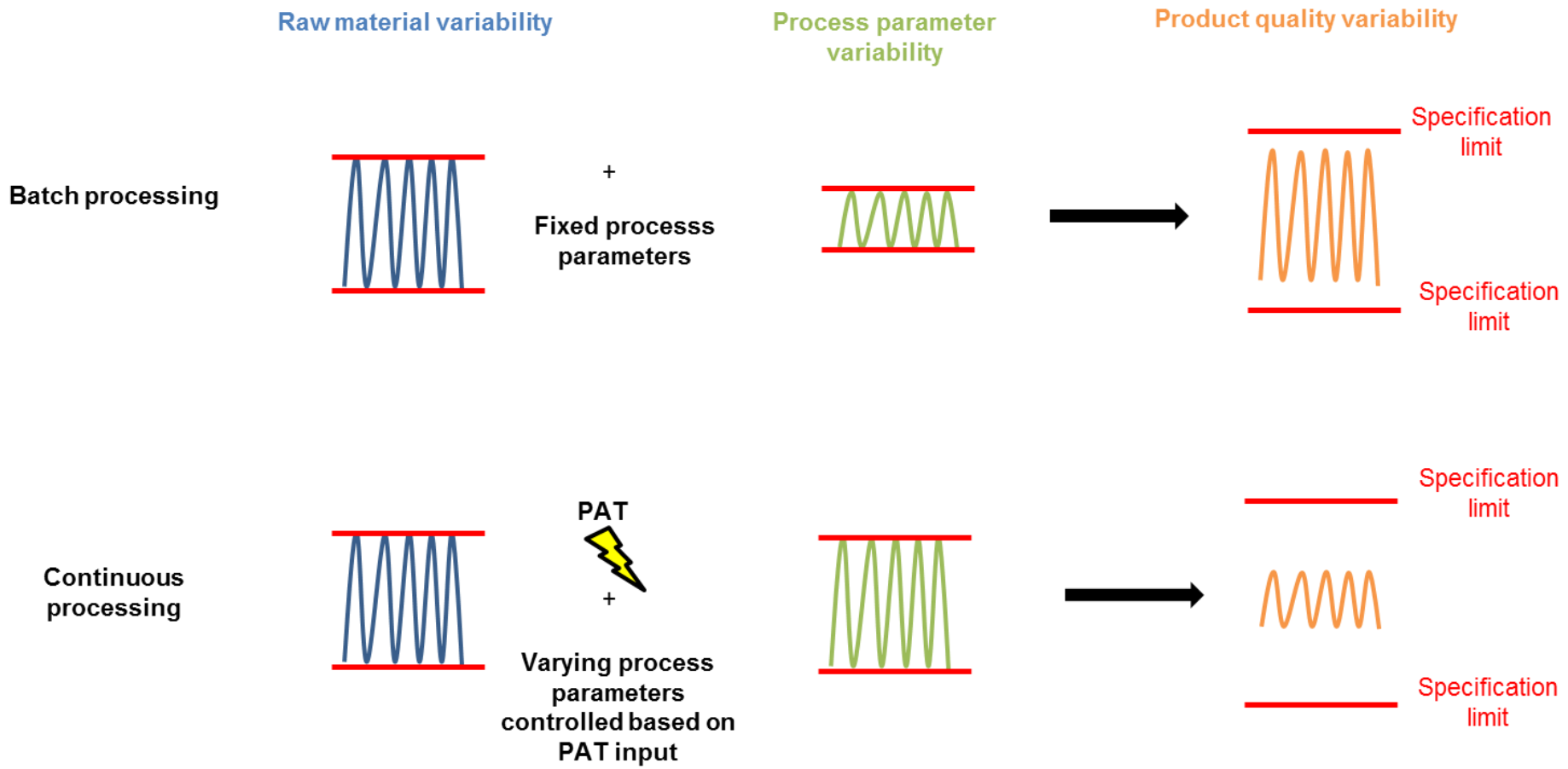

Figure 2. Concept of linking critical quality attributes of the final drug product to process controls and intermediate attributes measurable by PAT probes to improve the drug quality [adopted from 64].

Improved cost-efficiency

Continuous processes offer more *flexibility* as the production can be increased by prolonging the process time. Hence the same equipment can be used for production of small batches intended for clinical trials as for production after product approval by the competent authorities. In contrast scale-up of batch processes is necessary to transfer a process from the development to production stage and to respond to changing market needs. The scale factor between different scales is mostly limited to 10 which signifies that 3-5 scale-up steps are necessary to transfer a batch process to production scale [6, 9]. Scale-up steps are costly and time-consuming as they require different equipment scales and validation must be performed at all scales. Therefore *elimination of the scale-up bottleneck* facilitates *market access* for new drugs and *accelerates the capacity response* in case of changing market needs. In case of increasing demand the process time of continuous processes can easily be prolonged while there is no risk of overstock in case of decreasing market needs.

Currently the supply chains of pharmaceutical products require months as chemical and drug-product manufacturing occur at different facilities around the world [10, 11]. Continuous manufacturing from API synthesis up to tablet production in one manufacturing site would significantly *shorten the supply chain*. In this regard Vertex expects to produce 100 000 tablets of Kalydeco®, a new cystic fibrosis drug, in an hour by continuous processing rather than in four to six weeks which would be needed at a traditional batch plant, and Novartis aims to reduce the total process time of drug manufacturing (raw chemicals to finished drug product) from 300 to 10 days through adoption of continuous processing [11, 12].

Continuous manufacturing plants typically have a drastically *reduced footprint* as intermediate storage, stockpiling, material handling and off-line quality control are reduced. This offers opportunities to setup a continuously operating plant in portable containers which can be shipped around the world by boat, helicopter or truck in function of the manufacturing needs. This potential was recognized by Pfizer which invested several million dollars on its portable continuous miniature and modular (PCMM) line which is a prototype of an *autonomous and transportable manufacturing line* for oral solid dosage development and production. The PCMM line has a 60 – 70% lower footprint than a traditional batch manufacturing facility [13].

A significant decrease of API expenses can be achieved in process development studies through adoption of continuous processing. A design of experiments (DOE) is often used to explore the process space of a new product. A data point of the process space can be determined with 1 - 10 kg of product (considering a machine running at 25 kg/h) for a

continuous process, depending on the time necessary to reach steady state and the residence time distributions of the unit operations. In contrast, 500 – 2000 kg of product is required to produce a data point at commercial scale using batch processing [14]. Moreover, running full-scale batch processes in the drug development stage is highly time-consuming. Thus *reducing the amount of API and time needed during drug development* is of great economic importance, particularly with highly dosed and expensive API's.

Containment of potent drugs requires higher equipment investments and safety precautions during batch processing as operators handle the material multiple times between each unit operations. In contrast, material handling is limited when production is organized in a continuous way.

From the above it is clear that significant economical savings can be realized when switching from batch to continuous processing. In this context vice-president of Pfizer claimed as 'a general rule of thumb that a well-designed continuous plant should cost about 40% less than a comparable batch plant'. An in-depth economic comparison between an optimized and commercially run (by Novartis) batch process and two continuous process (direct compression and roller compaction) for the same drug product was made by Schaber et al. [15]. The comparison started at the level of an intermediate molecule three steps before final synthesis of the API and ended with the product of tablets. Savings of 9 – 40% on the total budget for drug production were realized (depending on the price of the API intermediate and API loading) when switching from batch to continuous manufacturing [15].

Reduced environmental footprint

During primary manufacturing continuous drug synthesis and crystallization could significantly *reduce solvent use,* but also during secondary manufacturing there are opportunities to reduce the ecological impact of drug production via continuous manufacturing [16, 17]. Recently the *resource consumption reduction* (chemicals, heating, electromechanical power, cleaning agents, waste disposal, compressed air) was calculated to be 10.2% when switching Tramacet®, an analgetic drug product commercialized by Johnson & Johnson, from fluid bed batch granulation to continuous granulation. However, excluding the use of API and excipients (as more or less the same amount of API and excipients is needed for both manufacturing modes) a resource consumption reduction of 34.0% was recorded [18].

Challenges

Despite the many advantages of continuous manufacturing, there are still some challenges related to its implementation. Initial investment in the construction of facilities, generation of process knowledge and possibly development of new equipment are necessary as batch manufacturing is still the prevailing production mode. Therefore a convincing business case is necessary to justify the replacement of existing batch technology by continuous manufacturing lines, and initially continuous manufacturing will most likely be implemented for new API's rather than for existing drug products. However, the initial investments can be compensated during drug development by API savings and the elimination of scaling-up.

PAT probes were successfully implemented in-line (a PAT probe is directly inserted in the product stream), at-line (a sample is removed from the product stream but analyzed in the process area) and on-line (automatic sampling and return of the sample to the product stream) for e.g. mixing performance after blending (by near infrared (NIR) spectroscopy), solid state analysis after wet granulation (by NIR or Raman spectroscopy), particle size analysis after wet granulation (by high speed camera or spatial filter velocimetry), moisture content after drying (by NIR spectroscopy), particle size distribution during spray drying (by laser diffraction), particle size analysis after milling (by focused beam reflectance measurement) and content uniformity of tablets (by NIR spectroscopy) [19]. Nevertheless interfaces between PAT probes and process remain challenging. Determination of the location of the sensor to achieve representative sampling and minimization of the influence of the probe on the process are important issues. Systems with purging gases or mechanical removal of material disturbing the measurements to solve probe fouling were therefore developed.

There are also some other technical challenges and issues that require further development and investigation such as the development of in-line tests for friability, disintegration and dissolution, minimization of the start-up and shut-down phases and build-up of material during long runs (e.g. along the granulator barrel).

Regulatory uncertainty was long perceived as a major hurdle to implement continuous manufacturing, but over the past few years the regulatory authorities (especially the FDA) expressed their preference for switching to continuous manufacturing. Early and frequent discussions with the FDA are encouraged before implementation to avoid that the choice for continuous manufacturing would delay the regulatory approval [4, 20]. Although the FDA and European Medicine Agency (EMA) are open for implementation of continuous processes, regulatory acceptance of continuous processes by other competent authorities is unclear.

Additionally, the pharmaceutical industry itself is a risk-aversed and conservative industry that is sceptic towards novel continuous processing as there is limited experience with long-term routine manufacturing.

Although few challenges remain they appear surmountable and are clearly outweighed by the advantages continuous manufacturing offers. This was recognized by several big pharmaceutical companies with e.g. Johnson and Johnson aiming to manufacture 70% of its highest-volume products continuously within 7 years from now [12].

CONTINUOUS MANUFACTURING TECHNIQUES FOR PRODUCTION OF TABLETS

The full potential of continuous manufacturing will only be realized by coupling the primary (API production) and secondary (production of final dosage form) manufacturing steps in a continuous manufacturing train. Concerning primary manufacturing, several research groups studied continuous API synthesis and crystallization [16, 17, 21, 22, 23, 24, 25]. However, the discussion in this thesis is focused on secondary manufacturing of tablets. Tablets are the most popular dosage form for patients as well as manufacturers because of the convenience of administration, accurate dosing, ease of manufacturing and low costs. Additionally, they exhibit improved product stability in comparison to liquids, tamper-proofness in comparison to capsules and safety in comparison to parenterals [26].

The preferred tablet manufacturing method is direct compression where tablets are compressed directly from a powder blend of API and suitable excipients without prior granulation steps. The simplicity of this method and absence of water during processing is attractive to manufacturers [26]. Moreover, it is an inherently continuous process and the blending and feeding steps preceding tableting can also be operated in a continuous way [27, 28, 29]. These steps were incorporated in the ConsiGma^{TM} Continuous Direct Compression line (GEA Pharma Systems) which is an integrated continuous manufacturing platform for direct compression of tablets. However, it is estimated that only 20% of pharmaceutical ingredients are suited for direct compression [26]. The other materials exhibit insufficient flowability, tabletability and homogeneity for the production of tablets by direct compression [26, 30]. Excellent flowability is required to ensure uniform die filling during high-speed tableting. Homogeneity of the powder mix to be tableted is essential to avoid content uniformity issues. Finally, powders need to exhibit sufficient binding potential, by plastic deformation or fragmentation, for successful tableting. Powder agglomeration techniques such as granulation and spray drying can overcome issues related to flowability, tabletability and homogeneity, and can deliver agglomerates suitable for tableting.

Granulation

Granulation can be performed by wet or dry granulation techniques. During roller compaction a powder mixture is compacted between the compactor's rolls into ribbon-shaped compacts that are finally milled to obtain granules suitable for tableting. A schematic of the roller compaction process is shown in Figure 3 [31].

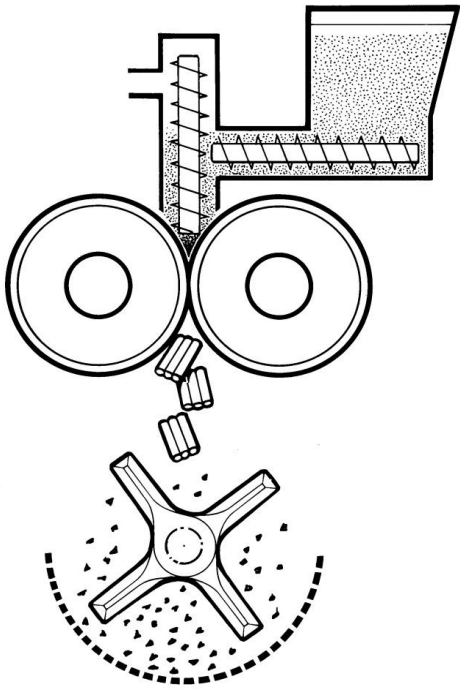

Figure 3. Schematic of the roller compaction process [adopted from 31].

This technique is inherently continuous and is therefore ultimately suited for implementation in a fully continuous tablet manufacturing line. Additionally, roller compaction is attractive for granulation of moisture and heat sensitive API's. However, absence of water also causes the main limitation of the process; lack of binding potential. After all, bonding between particles during roller compaction exclusively depends on the compression properties of the material, whereas during wet granulation capillary forces and formation of solid bridges after crystallization also contribute to the granule formation. Additionally roller compaction was linked to inferior tablet hardness after tableting [32, 33, 34]. Thus the potential of dry granulation is limited to powders with excellent tabletability and formulators often need to resort to wet granulation techniques.

Wet granulation has mostly been applied in batch-wise manner using fluid bed or high shear granulators. During fluid bed granulation granules are formed by spraying a binder solution on top of a powder bed that is fluidized by conditioned air (Figure 4).

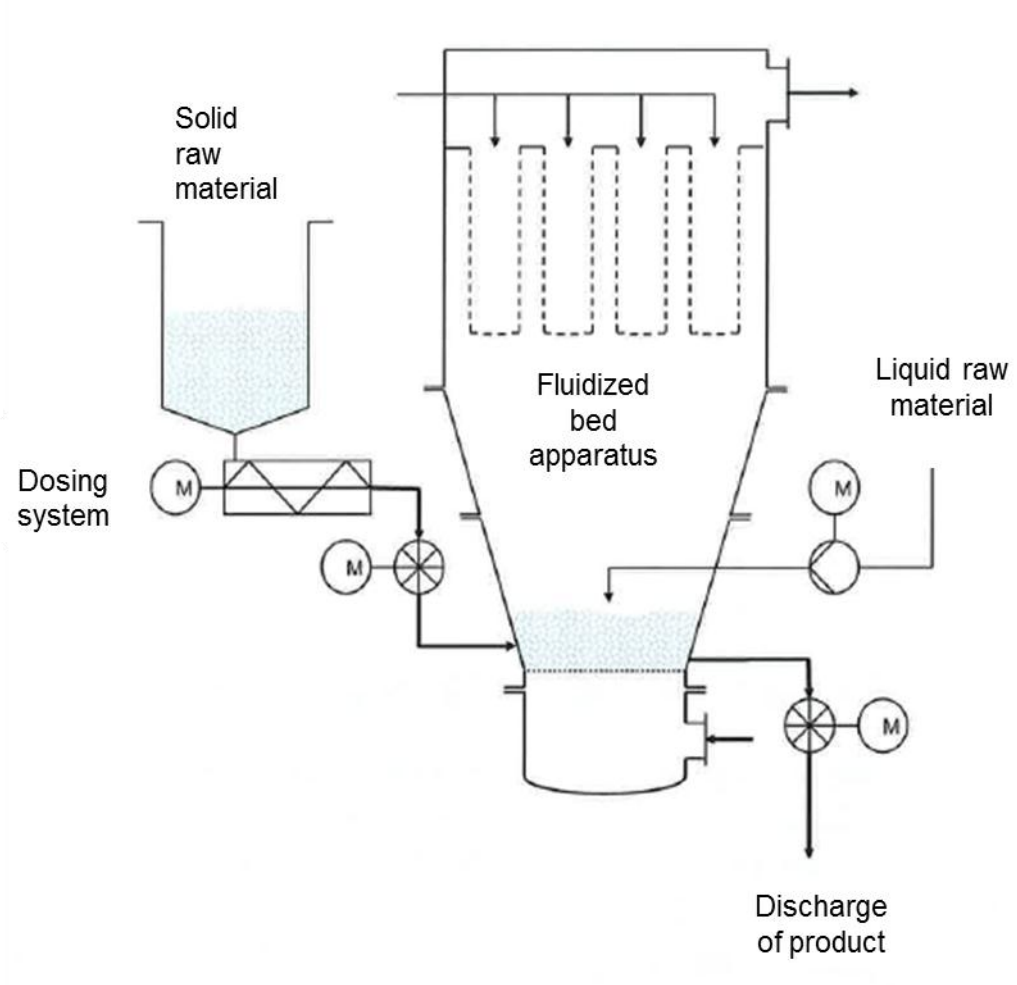

Figure 4. Schematic of fluid bed granulation [adopted from 40].

High shear granulators consist of a jacketed mixing bowl, an impeller and a chopper (Figure 5). The process starts with mixing of the dry powder ingredients by an impeller. After several minutes the granulation liquid is added, and the dry powder and granulation liquid are mixed by the impeller, while the chopper breaks down the wet mass to produce granules. Finally the wet granules are transferred from the granulator bowl and dried via fluid bed drying or tray drying. The desired granule density and friability can determine the choice of granulation process as granules produced via high shear granulation are denser but less friable than granules produced via fluid bed granulation [35]. As discussed in the first part of this chapter, batch manufacturing is not cost-efficient in comparison to continuous granulation and batch-to-batch variability is often high. Therefore traditional batch high shear and fluid bed processes were modified for continuous operation.

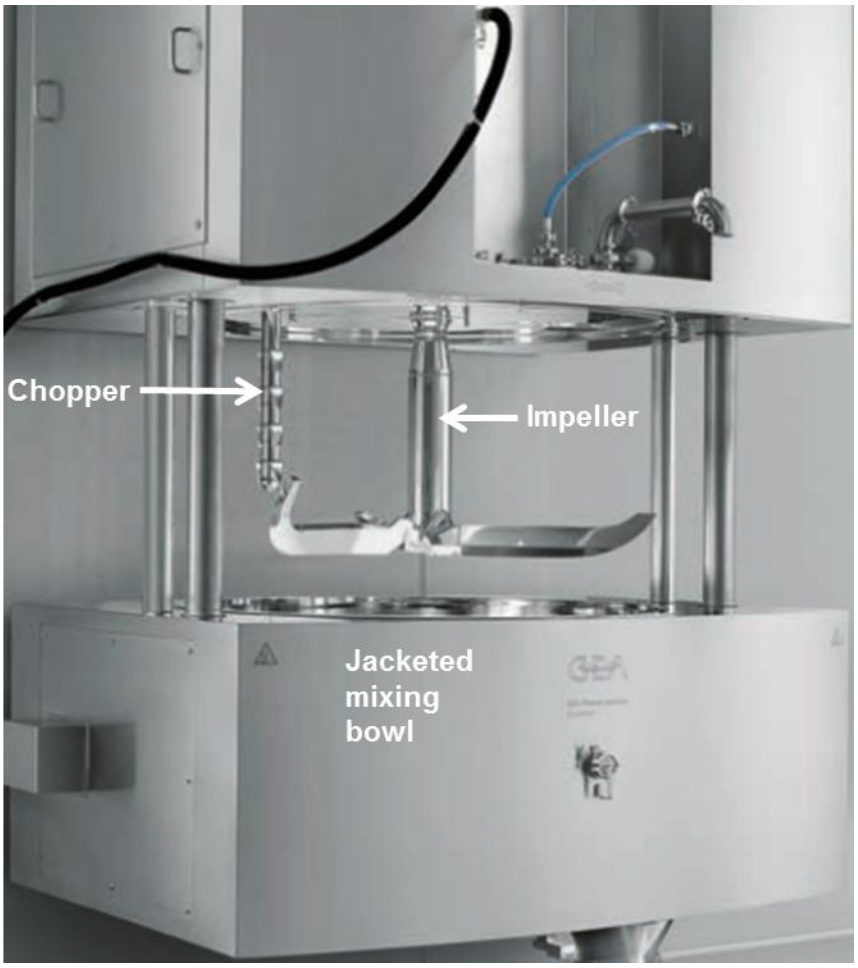

Figure 5. Batch high shear granulator [Courtesy GEA Pharma Systems].

Horizontal fluid beds (e.g. Glatt GF series, Niro Contipharm granulator, Heinen drying technologies) consist of different functional zones where feeding, mixing, spraying, drying, cooling and discharging are performed (Figure 6). The air inlet temperature and air flow in these zones are independently regulated. Although popular in the food industry for manufacturing of instant products (e.g. instant coffee, milk powder, soup), horizontal fluid beds are generally not applicable in the pharmaceutical industry due to the long residence time of material and lack of plug-flow in the granulator [36, 37, 38]. Short and controllable residence times are of utmost importance during granulation of pharmaceutical products to avoid product degradation.

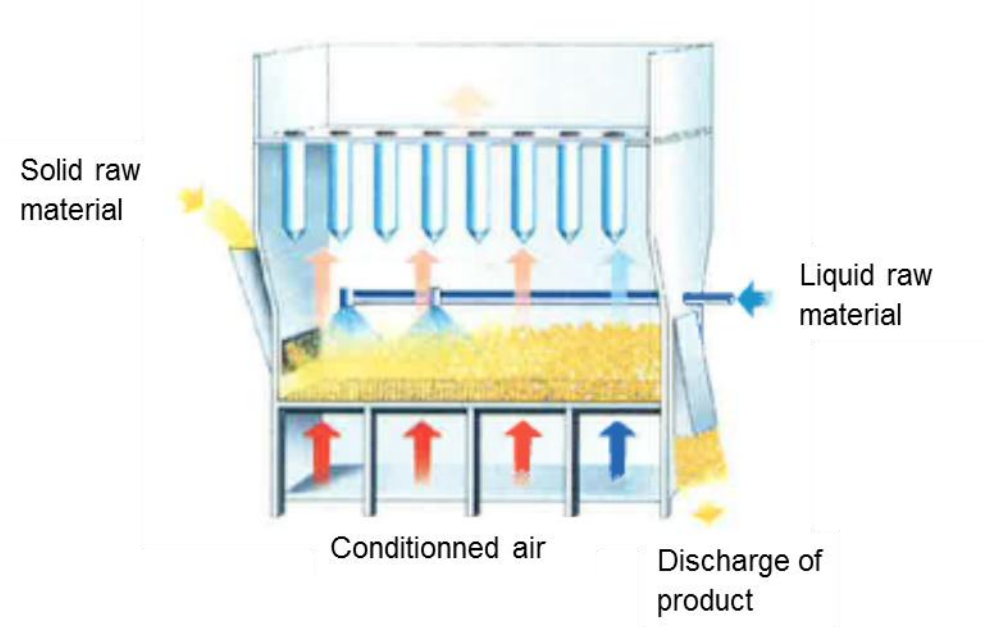

Figure 6. Horizontal continuous fluid bed granulator [adopted from 40].

In spouted bed granulators (Figure 7) fluidizing air enters the granulation chamber at high velocity through two longitudinal slots and spraying nozzles are positioned between these slots. Forward particle movement is obtained by applying an angled air flow. This design results in homogeneous wetting, fluidization of difficult-to-fluidize materials, elimination of lump formation and a short residence time, according to the manufacturer [39, 40].

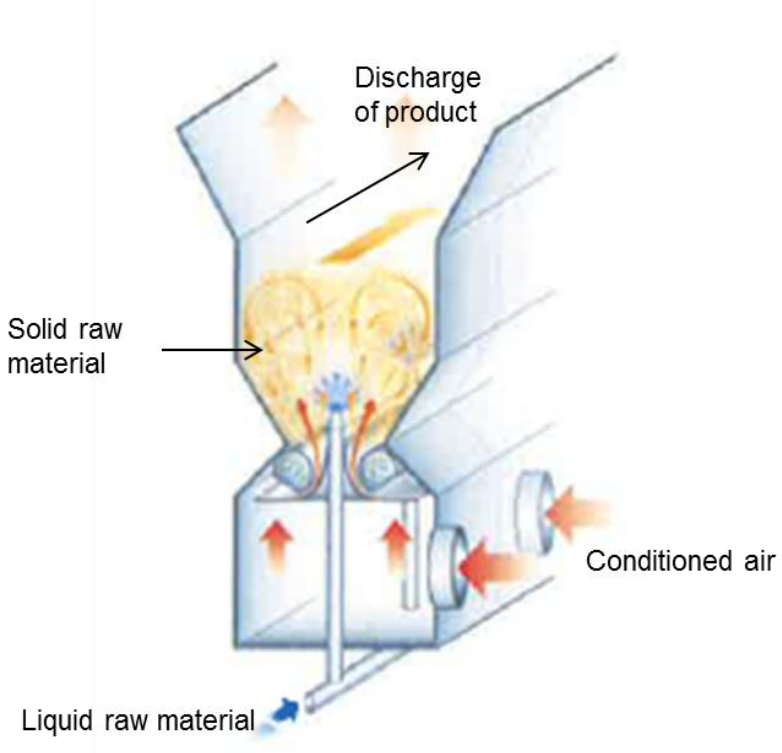

Figure 7. Spouted bed granulator [adopted from 40].

Glatt also developed another continuous fluid bed granulator based on the traditional batch granulator design. In the AGT system (Figure 8) granules exit the system via an outlet tube positioned in the middle of the bottom screen while starting material is fluidized and wetted in the granulation chamber. A classifying air stream through the outlet tube ensures that only larger particles can be discharged and that fine particles are returned to the granulation chamber. A major drawback of this system is again the long and uncontrollable residence time of granules as the concept is not based on plug-flow [37, 40]. Additionally, strict control of the powder feeding system is required as the amount of starting material added to the granulation chamber must match the amount of discharged granules to avoid varying powder/liquid ratios as this would result in varying granule characteristics [37].

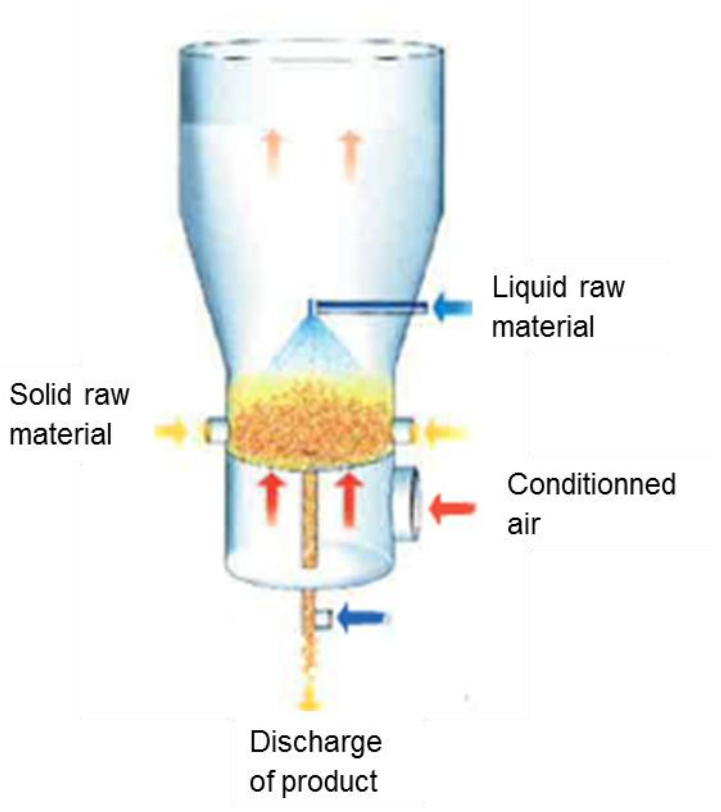

Figure 8. AGT system for continuous fluid bed granulation [adopted from 40].

Traditional batch high shear granulators were also modified for continuous operation (e.g. Böhle Easy Flow™ system) by continuous addition of powder and granulation liquid to the granulation chamber while granules are simultaneously discharged by a chopper [37, 38]. This principle is illustrated in Figure 9 [41].

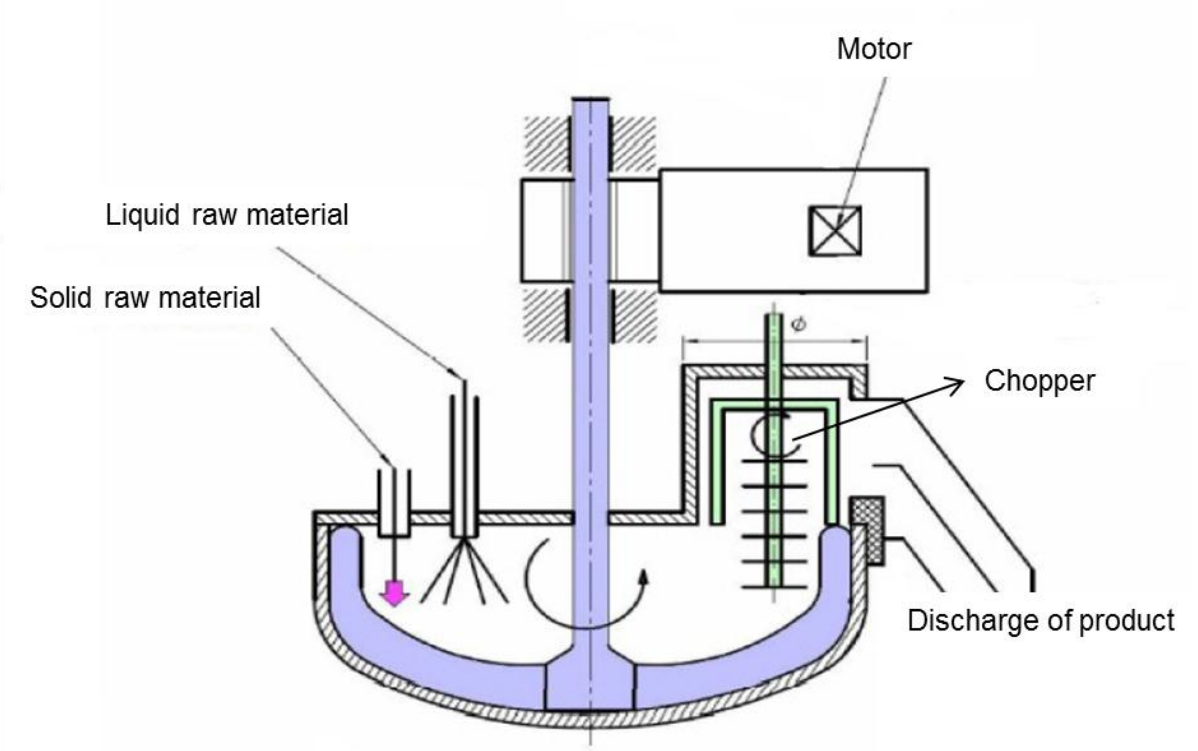

Figure 9. Traditional high shear granulator modified for continuous operation [adopted from 41].

Next the granules are continuously fed into a rotating cylindrical dryer [37]. Although the concept is promising, it was only described in one research paper [41]. Another technique for continuous high shear granulation, ring layer granulation, was launched by Lödige (CoriMix^{TM}). In the process chamber of the ring layer unit mixer blades are rotating on a central axis (Figure 10). High speed rotation of the blades results in formation of a concentric annular layer of product in the process chamber. The granulation liquid is sprayed via one or multiple nozzles onto the annular layer. According to the manufacturer, the design ensures plug-flow and the residence time can be influenced by the number of revolutions, geometry and adjustment of the mixing tools.

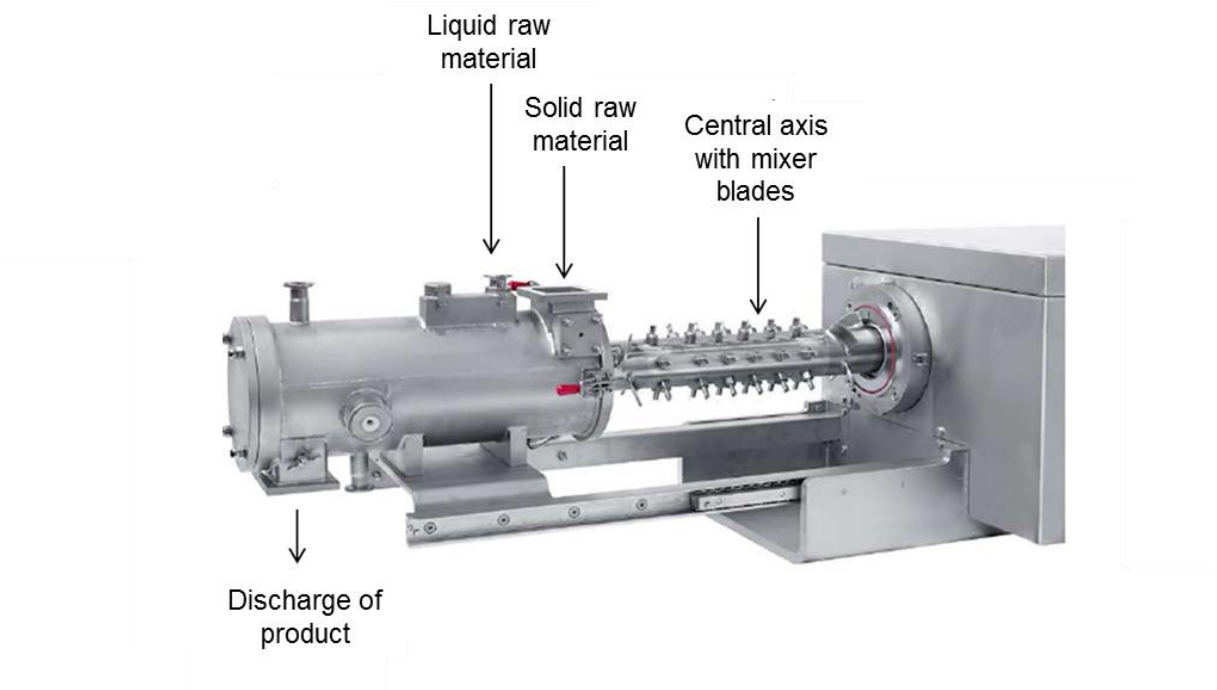

Figure 10. Ring layer unit for continuous high shear granulation [adopted from Loedige.de].

A quasi-continuous granulation unit, combining high shear and fluid bed technology, was developed by Glatt (Glatt Multicell^{TM}) in co-operation with Roche and the University of Basel (Figure 11). In this quasi-continuous approach, discrete amounts of materials (mini-batches) pass sequentially through units of blending, granulation, drying and conditioning [37, 42, 43]. The production line consists of a high shear granulator connected to a series of fluid bed dryers. After granulation the first mini-batch is transferred to the first fluid bed dryer for the initial drying phase at high temperature, then to a second fluid bed dryer for further drying at low temperature and finally to a third fluid bed dryer for conditioning. After transport of the first mini-batch to the first fluid bed dryer, a second mini-batch is loaded into the granulator chamber and this mini-batch is then transferred to the first fluid bed dryer after transfer of the first mini-batch to the second fluid bed dryer. Mini-batches are granulated and transferred to a series of the fluid bed dryers until the required amount of material is produced. This process is not fully continuous as there is no constant output of material in function of time. However, it exhibits some advantages associated with continuous manufacturing such as elimination of scale-up, small footprint, less labor-intensive, improved output and suitability for implementation of PAT [42]. However the full potential of continuous manufacturing can only be achieved by implementation of fully continuous ‘from-powder-to-tablet’ production lines.

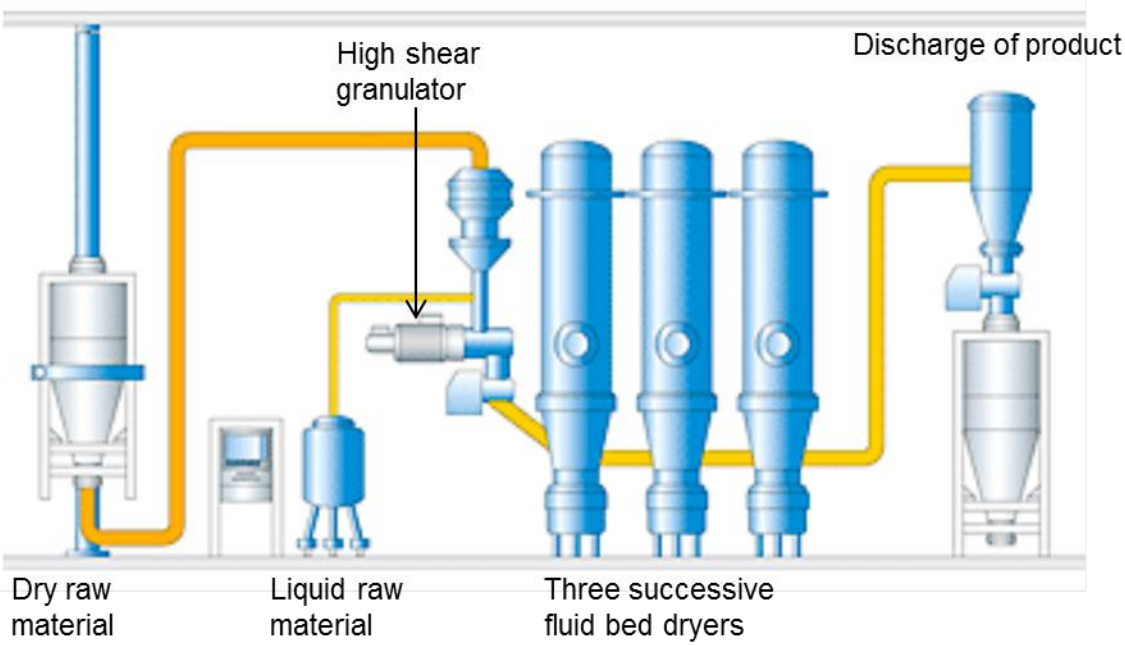

Figure 11. Glatt Multicell™ for quasi-continuous granulation [adopted from 65].

Twin screw granulation is a novel and promising granulation technique as it ensures plug-flow during processing, whereas the continuous granulation techniques discussed earlier often suffered from long and uncontrollable residence times. This technique is based on the extrusion technology, and was first described by Gamlen and Eardley (1986) and Lindberg et al. (1988) for the production of paracetamol and effervescent granules, respectively [37]. Modifications to this setup were made by Kleinebudde and Lindner (1993) and Keleb et al. (2004) through installation of a perforated die and removal of the die, respectively [44, 45]. Removal of the die block dramatically reduced the pressure build up at the end of the granulator barrel and avoided compression of the granules [45]. This resulted in less dense granules, in a higher process yield (as no lumps were produced) and in a higher granulation capacity (as a higher total input rate was possible) [45]. Over recent years multiple research groups studied the influence of process parameters (e.g. screw speed, barrel temperature, throughput, screw configuration) and formulation parameters (e.g. liquid-to-solid ratio, binder addition, particle size of the starting material, hydrophilicity of the excipients) on critical quality attributes of granules [46, 47]. Additionally, PAT probes were successfully implemented to monitor the moisture content, particle size and API content of granules exiting the granulator [19]. Continuous melt granulation using a modified twin-screw granulator is also possible and eliminates drying of the wet granules but requires cooling before further processing of the granules [48].

Integrated 'from-powder-to-tablet' manufacturing lines including continuous granulation technology

Recognizing the potential of continuous manufacturing for pharmaceuticals, equipment suppliers (e.g. GEA Pharma Systems, Glatt, Lödige, Böhle) have developed integrated 'from-powder-to-tablet' continuous production lines. GEA Pharma Systems was one of the first equipment manufacturers to commercialize such an integrated production line, the ConsiGma™ Continuous Tableting Line (Figure 12).

Figure 12. Consigma™ continuous tableting line with: 1. Liquid and powder dosing via loss-in-weight-feeders; 2. Twin screw granulation unit, 3. Segmented fluid bed dryer, 4. Granule evaluation unit, 5. Blender for external phase, 6. Tablet press [Courtesy GEA Pharma Systems].

Following unit operations can be distinguished in the ConsiGma™-25 Continuous Tableting Line: liquid and powder dosing via loss-in-weight feeders, twin screw granulation unit, segmented fluid bed dryer, granule evaluation unit, blender for external phase and tablet press (Figure 12). These units will be discussed below.

- *Liquid and powder dosing via loss-in-weight feeders*: Up to 4 loss-in-weight feeders can be installed in connection with an in-line blender, dosing the powder mixture to the granulator barrel. The granulation liquid is added by two peristaltic pumps via two tubes with nozzles mounted in the granulator barrel. The liquid feed rate is also monitored by the loss-in-weight principle.

- *Twin screw granulation unit*: The granulation unit comprises a jacketed granulator barrel with two co-rotating screws. The granulator barrel consists of three zones: (1) a feed zone where powder is fed by one or multiple feeders and transported by conveying elements, (2) a working zone where granulation liquid is added to the barrel and mixed with the powder by kneading elements and (3) a discharge zone where the granules exit the barrel and are transported to the fluid bed dryer (Figure 13).

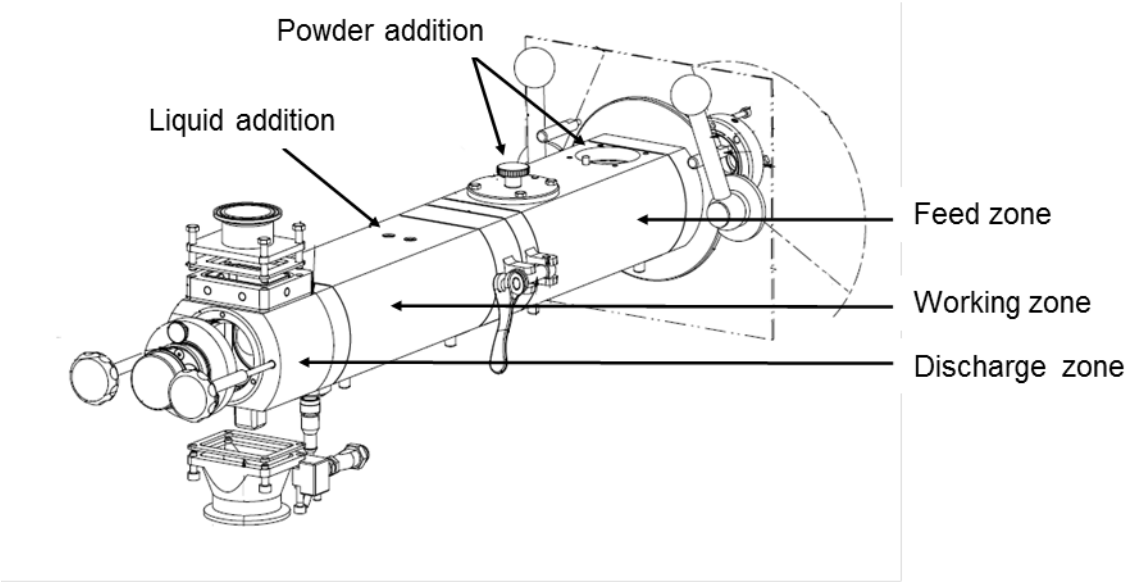

Figure 13. Granulator barrel of a ConsiGma™ Continuous Tableting Line [courtesy GEA Pharma Systems].

A temperature sensor is integrated in the working zone of the barrel and linked to a feedback control system which regulates the temperature in the barrel jacket and compensates for temperature increase during the process due to friction. A torque-gauge is built in for measurement of the torque during processing. The granulator screws are modular and typically consist of conveying elements, one or two blocks of kneading elements in the working zone, followed by a conveying zone and finally two small kneading elements at the end of the screw (Figure 14).

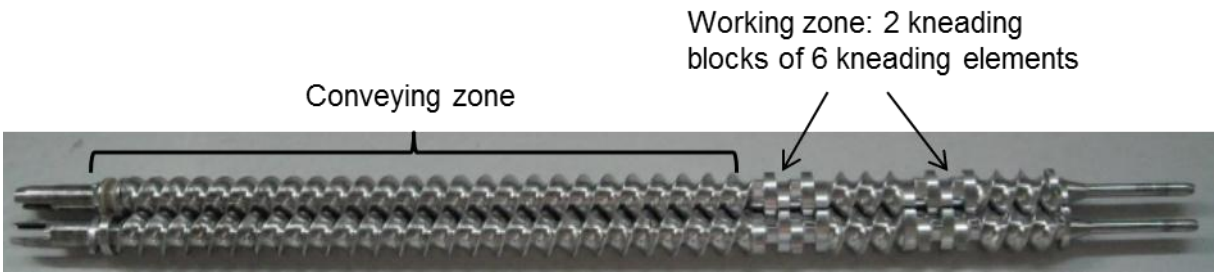

Figure 14. Granulator screws of a ConsiGma™ continuous tableting line, with 2 kneading blocks of 6 kneading elements in the working zone [courtesy GEA Pharma Systems].

Van Melkebeke et al. demonstrated that this standard screw configuration resulted in high process yields [49]. However, alternative screw elements for improvement of the process yield were recently introduced [50, 51]. Granule characteristics such as size distribution, density, friability and shape are affected by the granulation parameters (screw speed, barrel temperature, liquid feed rate, throughput, screw configuration). After granulation the granules are transported gravimetrically or pneumatically to a fluid bed dryer.

- *Six-segmented fluid bed dryer* (Figure 15): Drying is based on traditional fluid bed technology. However to limit the residence time distribution, the fluid bed dryer is divided in 6 identical drying cells. After a first cell is filled for a set filling time, wet granules are filled into the next cell while the granules in the first cell are drying. The dry granules are discharged from the drying cell after a set drying time. This drying approach is quasi-continuous, signifying that plug flow is not maintained during drying, as mini-batches are discharged from the fluid bed dryer. However, quasi-continuous drying can also be advantageous in case of a disturbance in the process since individual mini-batch(es) containing the affected material can be discarded.

- *Granule evaluation unit*: The granules can be milled by an integrated Comil™ (Quadro) system when elimination of oversized granules is required. Additionally, PAT probes for particle size analysis, residual moisture content or content uniformity can be implemented in this unit.

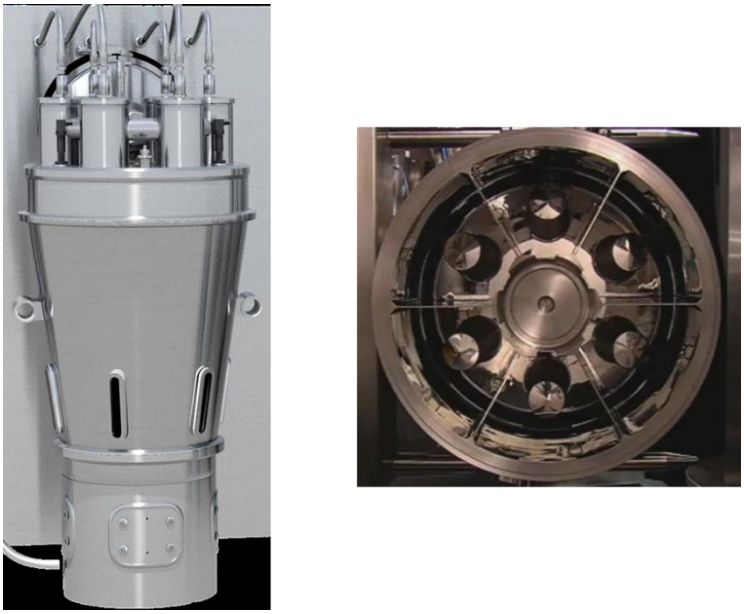

Figure 15. Six-segmented fluid bed dryer of the ConsiGma™-25 line (left: side view, right: bottom view) [courtesy GEA Pharma Systems].

- *Blender for external phase*: The granules are loaded into a continuous blender and mixed with lubricant using a ribbon blender.

- *Tablet press*: The final blend of granules is gravimetrically added to the hopper of the tablet press and compressed to tablets. Optionally, a continuous tablet coater can be implemented as final unit operation in the continuous manufacturing line.

The stability and repeatability of the ConsiGma™-25 continuous tableting line was evaluated by Vercruysse et al. during three consecutive runs of 5h using the entire line [52]. Although steady-state level of torque, barrel temperature, mill screen temperature and differential pressure over the filters was only reached after a stabilization period, the critical quality attributes of granules and tablets were within the specifications during the entire run. Additionally, the three runs were highly repeatable. Therefore the ConsiGma™-25 Continuous Tableting Line can be considered as a stable and repeatable system for the continuous production of granules and tablets [52]. Nevertheless, even longer runs are necessary to validate the process stability over a period of days and weeks.

For research and development purposes a ConsiGma™-1, a mobile and smaller version of the ConsiGma™-25 line, was developed. The ConsiGma™-1 consists of an identical granulator barrel as the ConsiGma™-25 line and one segment of the 6-segmented fluid bed dryer incorporated in the ConsiGma™-25 line (Figure 16). As the fluid bed dryer of the ConsiGma™-1 consists of only one dryer cell, drying is performed batch wise. Nevertheless, this equipment allows performing short granulation experiments during early phases of research and development.

Figure 16. ConsiGma™-1 with: 1. Powder dosing, 2. Granulator barrel, 3. Fluid bed dryer [courtesy GEA Pharma Systems].

Similar lines (consisting of a twin screw granulation unit, fluid bed dryer and tablet press) for continuous production of tablets (MODCOS™ by Glatt in collaboration with Thermo Fisher Scientific and Fette and Böhle Conti Granulator BCG by Böhle in collaboration with Korsch) were recently introduced by Glatt and Böhle.

Lödige designed a continuous line for manufacturing of granules (Granucon™) including a ringlayer mixer and a horizontal fluid bed dryer (the integrated setup is shown in Figure 17). Recognizing the wide retention times continuous fluid bed dryers suffer from, Lödige implemented a screw in the dryer to obtain forced conveyance of granules and consequently to narrow down the residence time distribution of granules in the dryer.

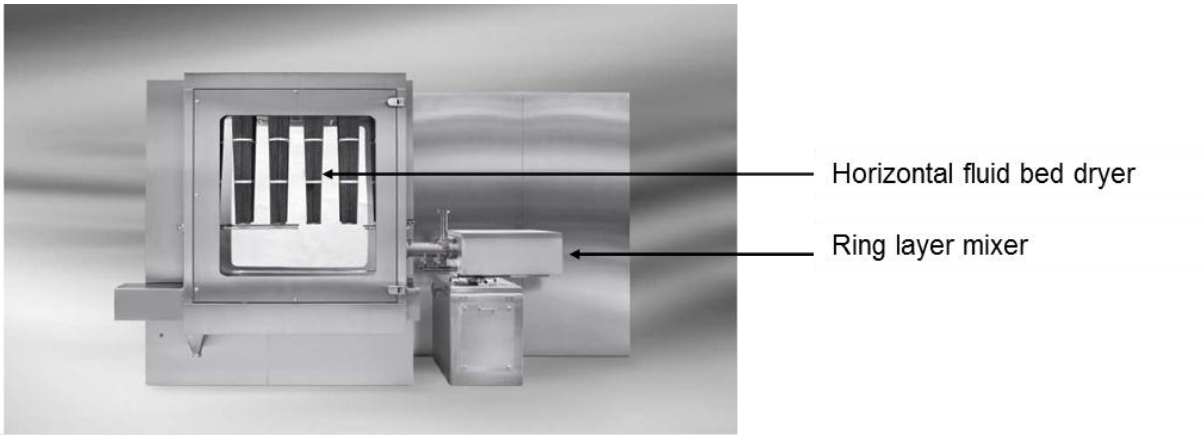

Figure 17. Granucon™ continuous manufacturing line by Lödige [adopted from Loedige.de].

Spray drying

Spray drying is a continuous process which involves spraying of a liquid feed (solutions, suspensions or emulsions) in a hot drying medium to convert it into a dry product. It is widely applied across the food (e.g. production of baby food, milk, instant coffee, soup), chemical (e.g. production of catalysts, detergents, pigments) and pharmaceutical industry [53, 54].

A schematic overview of the spray drying process is shown in Figure 18. A liquid feed is pumped to a drying chamber and atomized in a constant flow of hot air. Consequently the liquid phase of the droplets evaporates, yielding dry powder particles. After exit from the drying chamber, the powder is gravimetrically separated from the air in a cyclone where the particles sediment in a container.

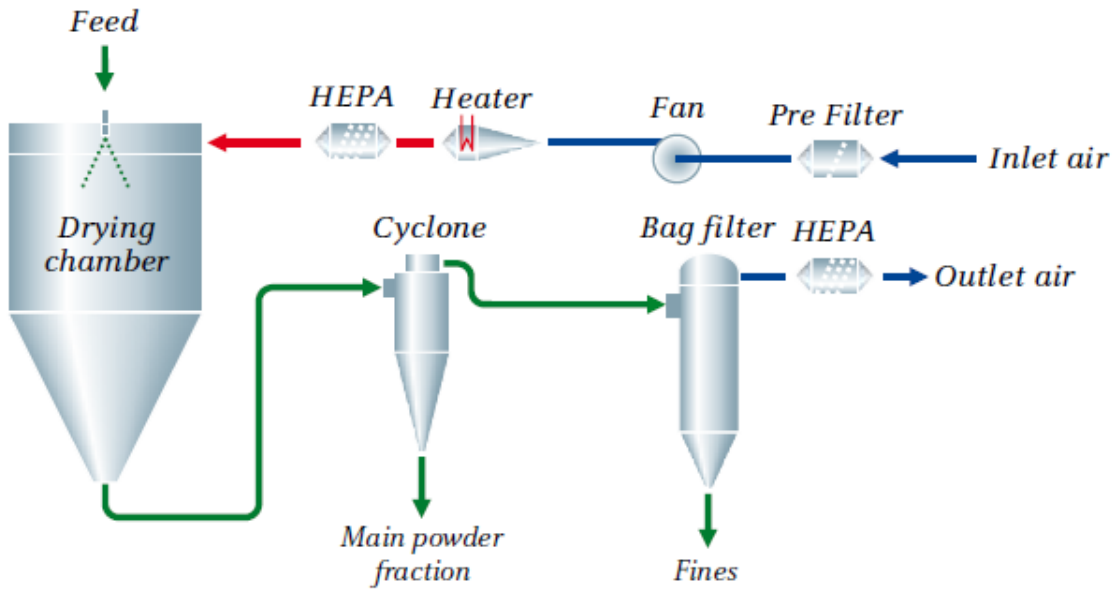

Figure 18. Schematic overview of the spray drying process [courtesy GEA Pharma Systems].

Different spray drying setups can be distinguished depending on the atomization mode, on the direction of the air and droplet/particle flow and on the exhaust of the solvent. Firstly, different atomization designs are available, differing in the energy (centrifugal, kinetic, pressure or sonic energy) used for creation of droplets. The droplet and particle size generated depend on the atomizer type with a pressure and sonic nozzle generating the largest and smallest particles, respectively [54, 55]. However, with all atomizer types the particle size can be reduced by adding more atomization energy [55]. Secondly, depending on the flow direction of drying air and atomized droplets, co-current, counter-current and

mixed flow setups are distinguished. In a co-current flow setup the atomized drops and drying air pass in the same direction through the drying chamber. This way the largest drops are exposed to the hottest air while dry particles are exposed to cooler air at the bottom of the drying chamber. Therefore this setup is ideally suited for spray drying of heat sensitive components. In a counter-current flow setup the atomized drops and drying air move in the opposite direction through the drying chamber. This setup induces particle agglomeration, resulting in larger and better flowing particles, but is not applicable for heat sensitive components as dry particles are exposed to the hottest air in the bottom of the drying chamber. In a mixed flow setup co- and counter-current flows are combined. Free flowing particles can be produced with this setup but it is not suited for heat sensitive components. Thirdly, spray drying systems can operate in open and closed loop. In open loop spray dryers the drying air is drawn from the atmosphere and exhausted back into the atmosphere after extensive filtering. This setup is used for spray drying of aqueous solutions. In closed loop spray dryers an inert drying gas (e.g. nitrogen) is used to allow processing of oxidizable products and flammable solvents. A solvent vapor condenser is implemented in this setup to recycle the solvent and inert gas.

The particle size and flowability of spray dried particles are affected by the spray drying setup. Use of a pressure nozzle and a counter-current setup, for example, results in large and good flowing particles as large droplets are created and agglomeration is favored, respectively. However, spray dried particles are typically smaller than 200 µm [55]. If larger and better flowing particles are required, spray dryers can be equipped with multiple spraying nozzles, a fines return system, an integrated fluid bed dryer or combinations thereof to induce agglomeration of particles (Figure 19). These agglomerated particles exhibit a better flowability and have a porous structure with instant properties (good wettability, dispersibility, solubility) which is desirable for uniform dosing and use as instant product. Use of multiple nozzles induces forced primary agglomeration as the nozzles are positioned to create overlapping spray zones and collisions between droplets. Alternatively, fines collected after a cyclone or bag filter can be recycled to the atomization zone to induce forced secondary agglomeration. Agglomerated particles consisting of many particles are created through collisions between the returned fines and wet atomized drops. Finally, integration of a fluid bed dryer in the bottom of the spray dryer also promotes agglomeration as small fluidized particles are returned into the drying chamber and collide with partially dry particles. Although fines recycling and integration of a fluid bed are often applied in the food industry, these approaches for particle agglomeration are not applicable in pharmaceutical processing as dry particles are exposed to high temperatures in the atomization zone and their residence time is prolonged [56].

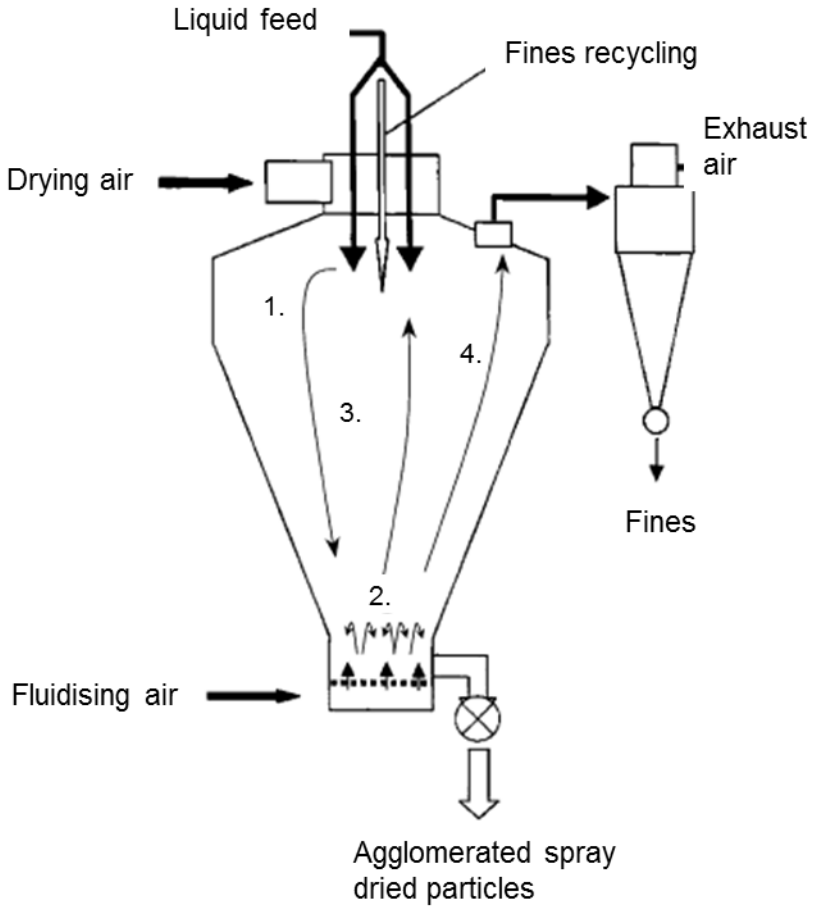

Figure 19. Schematic overview of a spray dryer setup with modifications for particle agglomeration (multiple atomization nozzles, fines recycling, integrated fluid bed) with: 1. Atomization and drying of droplets, 2. Fluidization provoking collisions between mois and dry particles, 3. Collisions of fines and partially dry particles, 4. Exhaust of non-agglomerated material from the drying chamber [adopted from 54].

Spray drying is an inherently continuous, fast and robust process that can be run for months without interruption [55]. It is used during primary and secondary drug manufacturing. After API synthesis and crystallization, spray drying can be applied to obtain an API in powder form for further processing into a solid dosage form. During secondary manufacturing spray drying is applied to improve the tabletability of powders, to increase the bioavailability of an API, for encapsulation and for production of dry powder aerosols [53, 54].

Improved tabletability of excipients as well as API's can be achieved via spray drying. Spray dried lactose is a popular excipient for direct compression as it exhibits excellent flowability and tabletability. It is produced through spray drying of a suspension of lactose crystals and consists of a mixture of α-lactose monohydrate and amorphous lactose exhibiting brittle fracture and plastic deformation upon compaction, respectively. The combination of amorphous and crystalline lactose with different compaction mechanisms results in better tabletability and flowability of spray dried lactose in comparison to α-lactose monohydrate

[26, 57]. Microcrystalline cellulose is another frequently used direct compression excipient that is spray dried during to yield porous microcrystals with good tabletability [26]. However, different materials are often coprocessed via spray drying to obtain a product with improved properties compared to a physical mixture of the individual components. During coprocessing the physical properties of the product are modified without altering the chemical structure [26]. Several spray dried coprocessed excipients for direct compression are available: e.g. Cellactose® (α-lactose monohydrate and powdered cellulose), Starlac® (α-lactose monohydrate and native maize starch), Combilac® (α-lactose monohydrate, microcrystalline cellulose and native corn starch), Ludipress® (lactose monohydrate, polyvinylpyrrolidone K30, crospovidone) and Prosolv® SMCC (microcrystalline cellulose and silicon dioxide). Coprocessing of excipients and a poorly compressible API (e.g. paracetamol, ibuprofen, cimetidine) via spray drying can also improve the tabletability of the formulation [58, 59].

The physical properties of spray dried particles, e.g. size, shape, moisture content, density, can be controlled through selection of the spray drying setup and process parameters [55]. These particle properties are important for clinical efficacy of pulmonary and nasally administered dry powder aerosols as they affect the site of drug deposition in the airways or lungs. Therefore spray drying is ideally suited for the production of dry powder aerosols. Examples of dry powder aerosols produced by spray drying include a vaccine for mass vaccination of poultry and antibiotics for treatment of cystic fibrosis, chronic obstructive pulmonary disease and tuberculosis [60, 61, 62, 63]. The solid state of spray dried particles can also be controlled by the process parameters. Amorphous products are often formed during fast dehydration during the spray drying process [53]. The sticky nature of amorphous particles present during spray drying can favor agglomeration by acting as a binder between particles and result in good flowing, highly wettable particles. Turchiuli et al. and Williams et al. reported on agglomeration of maltodextrin due to the sticky nature of amorphous maltodextrin and lactose, respectively [56, 66]. However, amorphization during the spray drying process is not always desired as it can result in stability issues.

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2

CRYSTAL COATING VIA SPRAY DRYING TO IMPROVE POWDER TABLETABILITY

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Abstract

A continuous crystal coating method was developed to improve both flowability and tabletability of powders. The method includes the introduction of solid, dry particles into an atomized spray during spray drying in order to coat and agglomerate individual particles. Paracetamol was used as a model drug as it exhibits poor flowability and high capping tendency upon compaction. The particle size enlargement and flowability was evaluated by the mean median particle size and flow index of the resulting powders. The crystal coating coprocessing method was successful for the production of powders containing 75% paracetamol with excellent tableting properties. However, the extent of agglomeration achieved during coprocessing was limited. Tablets compressed on a rotary tablet press in manual mode showed excellent compression properties without capping tendency. A formulation with 75% paracetamol, 5% PVP and 20% amorphous lactose yielded a tensile strength of 1.9 MPa at a compression pressure of 288 MPa. The friability of tablets compressed at 188 MPa was only 0.6%. The excellent tabletability of this formulation was attributed to the coating of paracetamol crystals with amorphous lactose and PVP through coprocessing and the presence of brittle and plastic components in the formulation. The coprocessing method was also successfully applied for the production of directly compressible lactose showing improved tensile strength and friability in comparison to a spray dried direct compression lactose grade.

KEYWORDS: Spray drying, Coprocessing, Particle coating, Direct compression, Amorphous lactose, Paracetamol, Tabletability, Continuous production.

INTRODUCTION

Tablets are the most popular dosage form for patients as well as manufacturers because of the convenience of administration, accurate dosing, ease of manufacturing, product stability in comparison to liquids and tamper-proofness in comparison to capsules [1]. Direct compression is the preferred manufacturing method for tablets because of its simplicity, continuous nature and related financial benefits. However, it is estimated that less than 20% of pharmaceutical powders can be directly compressed into tablets as powders must have appropriate flowability, compressibility and homogeneity to be suited for direct compression [1, 2].

To improve these properties coprocessing of materials is widely applied for the preparation of powder mixtures enabling direct compression of a drug substance. During coprocessing two or more components are combined by a specific process, yielding a material with superior properties compared to physical mixtures of their components, without modification of the chemical structure of the ingredients [1, 3].

In this work we aimed to improve both flowability and tabletability of powders by the development of a continuous crystal coating method. The manufacturing method is based on the introduction of dry powder particles into an atomized spray during spray drying. The resulting powders were microscopically evaluated and characterized through particle size analysis, flowability testing and tableting experiments. It was first investigated if the method allowed to produce paracetamol tablets without capping tendency via coating of paracetamol particles with spray dried lactose and polyvinylpyrrolidone (PVP). The flowability and tabletability of the resulting powders was assessed and compared to the characteristics of the corresponding physical mixtures. In a second part, it was investigated if the method is also applicable for the production of direct compression lactose.

MATERIALS AND METHODS

Materials

Paracetamol (semi fine) was received from Mallinckrodt Chemical (Hazelwood, USA). Milled α-lactose monohydrate (Pharmatose® 200M) was purchased from Caldic (Hemiksem, Belgium). A direct compression grade of spray dried lactose (DCL 11) was purchased from DFE Pharma (Goch, Germany). Silicon dioxide and magnesium stearate (Fagron, Waregem, Belgium) were used as glidant and lubricant, respectively. PVP and Crospovidone® were used as binder and desintegrant, respectively and were received from BASF (Burgbernheim,

Germany). Miglyol (Cremer Oleo, Witten, Germany) with 0.2% polysorbate 80 (Fagron, Waregem, Belgium) was used as dispersant for laser diffraction measurements.

Preparation of the coprocessed powders

In a first set of experiments, aqueous solutions of lactose and PVP (16% and 8% w/w lactose with lactose/PVP ratio 4/1) and of pure PVP (3% w/w) were prepared. These solutions were fed to the fountain two-fluid nozzle (nozzle orifice 2.6 mm) of a production-scale spray dryer (type 6.3-SD, GEA Niro, Copenhagen, Denmark) by a peristaltic pump (type 520U, Watson Marlow, Cornwall, UK) and marprene tubing (inside diameter 4.8 mm). The spray dryer operated in counter-current mode. The dimensions of the spray dryer were 2.0 m cylindrical height with a diameter of 3.5 m and 60° conical base. The main powder fraction was collected in a reservoir under the drying chamber and fines were collected in a reservoir attached to a cyclone. The solutions were spray dried according to the following parameters: feed rate: 100 g/min, inlet drying air temperature: 240 °C, outlet drying air temperature: 112 °C, drying gas rate: 210 kg/h, atomizing air pressure: 0.5 bar. Paracetamol was preblended with 0.05% silicon dioxide and introduced during the spray drying process into the cone of the drying chamber via an in-house designed setup shown in Figure 1. This setup consists of a vibratory feeder (DR 100, Retsch, Haan, Germany) presenting the powder to a Venturi-based system that introduces the powder through two small tubes (internal diameter 7 mm) into the dryer. The tubes were positioned close to the nozzle and were oriented to directly inject the solid particles in the spray pattern of the atomized drops.

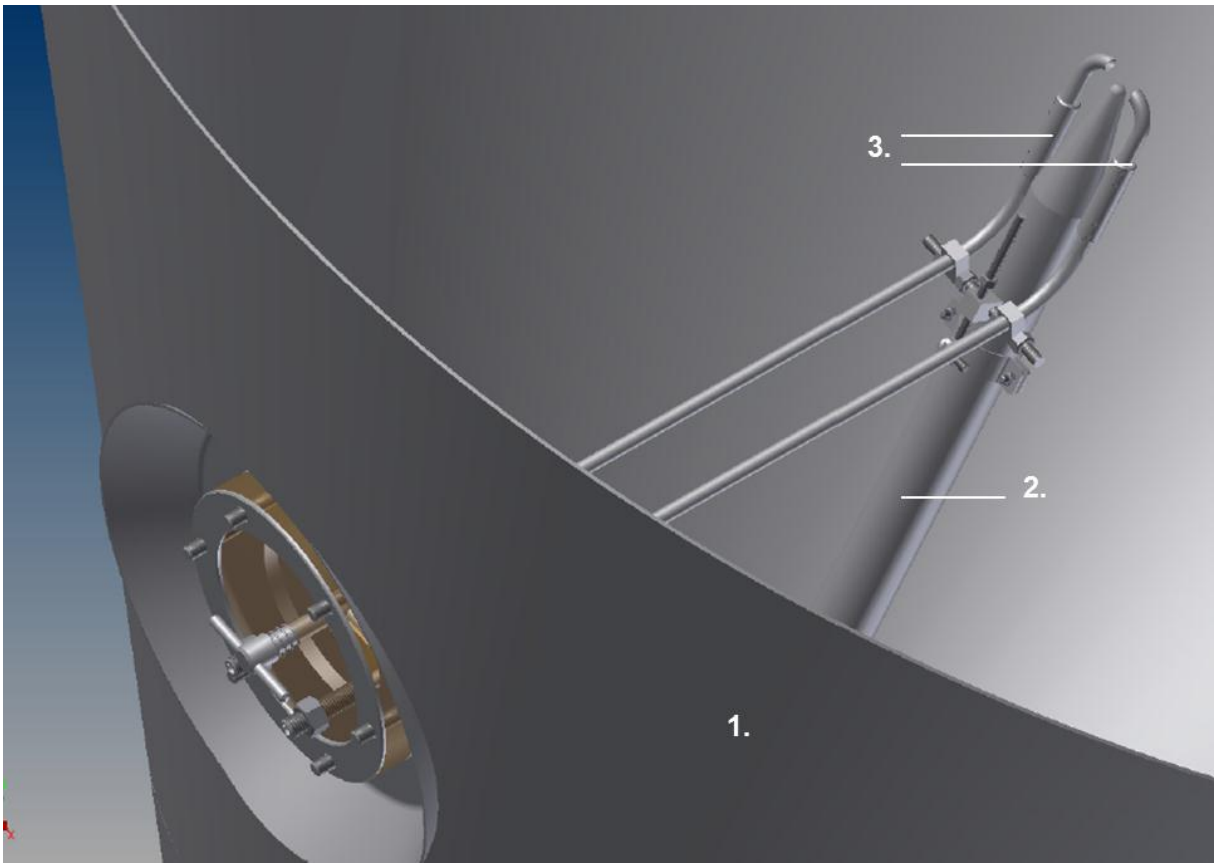

Figure 1. Schematic of the setup that allows to directly inject solid particles into the atomization zone of a two-fluid nozzle positioned in the drying chamber of a spray dryer. 1. Wall of the drying chamber, 2. Two-fluid nozzle, 3. Tubes for dry powder injection into the spray zone.

The composition of the spray dried solutions, the feed rate of solid particle introduction and the final composition of the coprocessed powders (fraction spray dried lactose, fraction dry inserted paracetamol, content PVP) is given in Table 1.

Formulation	Composition of the spray dried solution		Feed rate solid particles (g/min)	Final composition of the coprocessed powders (%)		
	Lactose (%w/w)	PVP (%w/w)		Lactose	PVP	Para-cetamol
Lac/PVP/par(1)	16	4	60	20	5	75
Lac/PVP/par(2)	8	2	30	20	5	75
PVP/par	-	3	49	-	5	95

Table 1. Composition of the spray dried solution, feed rate of the solid particles introduced into the spray drying chamber and final composition of the coprocessed paracetamol powders.

In a second set of experiments, aqueous solutions of lactose (2.5%, 5%, 10% and 16% w/w) and PVP (0.85%, 1%, 1.25%, 0.8% w/w, respectively) and of pure PVP (0.8% w/w) were spray dried, while lactose crystals were introduced via the same procedure as described above. The composition of the solutions, feed rate of solid particle introduction and the final composition of these coprocessed powders are listed in Table 2.

Formulation	Composition of spray dried solution		Feed rate solid particle introduction (g/min)	Final composition of the coprocessed powders (%)		
	PVP (%w/w)	Lactose (%w/w)		Spray dried lactose	Dry introduced lactose	PVP
1	0.8	0	14	0	95	5
2	0.85	2.5	14	14	81	5
3	1	5	14	25	70	5
4	1.25	10	14	40	55	5
5	0.8	16	-	95	-	5

Table 2. Composition of the spray dried solution, feed rate of the solid particles introduced in the spray drying chamber (g/min) and final composition of the coprocessed lactose powders.

Tableting

The coprocessed powders, physical mixtures and reference lactose (spray dried α-lactose monohydrate for direct compression) were blended (Turbula mixer type T2F, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) with 5% Crospovidon® and 0.5% magnesium stearate.

Tablets (500 ± 5 mg) of the coprocessed powders with paracetamol and of the corresponding physical mixtures were compressed on a rotary tablet press (MODUL™ P, GEA Pharma Systems, Courtoy, Halle, Belgium) equipped with a single round concave Euro B punch of 12 mm diameter at a tableting speed of 5 rpm. The tablets were compressed at 7 different main compression pressures: 31, 61, 104, 146, 188, 237 and 288 MPa after precompression at 18 MPa. The friability was tested on tablets compressed at 188 MPa.

The coprocessed powders consisting of lactose and PVP and the lactose reference were compressed (1g ± 10 mg) on an excentric tablet press (Type EKO, Korsch, Berlin, Germany) equipped with 16.0 mm edged punches at a compression pressure of 132 MPa.

Material characterization

Morphology

The powders were examined by scanning electron microscopy (SEM) (JEOL JSM-5600-LV, JEOL Ltd., Zaventem, Belgium) after sputtering with a platinum coating using the JEOL JFC 1300 Autofine Coater (JEOL Ltd., Zaventem, Belgium) to improve the electron conductivity of the samples.

Loss-on-drying (LOD)

The residual moisture content of the coprocessed powders was determined via LOD using a moisture analyzer (Mettler LP16, Mettler-Toledo, Zaventem, Belgium) including an infrared dryer and a balance. A sample of 5 g was dried at 105 °C until the weight was constant for 30 s.

Particle size analysis

The particle size distribution of the paracetamol starting material and coprocessed powders was measured in triplicate by laser diffraction (Mastersizer S long bench, Malvern Instruments, Worcestershire, UK). The wet dispersion technique was applied using the 300RF lens (Malvern Instruments, Worcestershire, UK). The powders were dispersed in a solution of 0.2% Tween 80 in Miglyol 812 and subsequently vortexed and sonicated in order to eliminate agglomerates. The results are expressed as volume diameters.

Ring shear testing

The flowability expressed as the flowability index (ffc) of the powders was measured in triplicate by ring shear testing (Type RST-XS, Dietmar Schulze Schüttgutmesstechnik, Wolfenbuttel, Germany). The powders were tested using three consolidation stresses, 400, 600 and 800 Pa, and a preshear of 1000 Pa.

Solid state characterization

Crystallinity was analyzed using X-ray diffraction (XRD) and modulated differential scanning calorimetry (MDSC) on the pure compounds, physical mixtures and coprocessed samples. XRD was performed on a CuKα diffractor (ARL^{TM} X'TRA, Thermo Fischer Scientific, Waltham, United States) with a voltage of 40mV in the angular range of $8° < 2\theta < 60°$ using a step scan mode with step size of 0.02° and counting time of 1s/step.

MDSC was performed using a Q2000 differential scanning calorimeter (TA Instruments, Zellik, Belgium) equipped with a refrigerated cooling system. Samples (5-10 mg) were accurately weighed and run in Tzero pans (TA Instruments, Zellik, Belgium). They were cooled to -20 °C and subsequently heated up to 220 °C with a heating rate of 2 °C/min. The modulation time and amplitude were set at 60 s and 0.318 °C, respectively. Dry nitrogen was used as a purge gas through the cell at a flow rate of 50 ml/min. The results were analyzed using TA Instruments Universal Analysis software.

Tablet characterization

The hardness, thickness and diameter of the tablets (n=10) were determined using a hardness tester (Type HT 10, Sotax, Basel, Switzerland) and the tensile strength (T) of the tablets was calculated according to the formula of Fell and Newton [4]:

$$T = 2F/\pi dt$$

Where F, d and t denote the diametral crushing force, tablet diameter and tablet thickness, respectively.

The tablet friability was determined using a friabilator (PTFE, Pharma Test, Hainburg, Germany) as described in the European Pharmacopea at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

RESULTS AND DISCUSSION

Lack of flowability and tabletability often constitutes a problem for the production of tablets. Turchiuli et al. reported particle size enlargement due to forced secondary agglomeration when part of the spray dried powder was reintroduced into a spray of droplets [5]. They attributed the achieved agglomeration to the sticky nature of spray dried maltodextrin acting as an amorphous binder between reintroduced particles and drops. Similarly, Williams et al. studied the effect of fines recycling on agglomeration of milk powder during spray drying aiming to produce a free-flowing, non-dusty and easily dispersable powder [6]. It is known that fast evaporation during spray drying can yield amorphous particles and a high content of low molecular sugars reduces the glass transition temperature of the spray dried material below its product temperature. At this stage a liquid-like state of amorphous material exists, which is responsible for cohesion between particles [7]. As uncontrolled recycling of particles is not applicable in pharmaceutical industry, we investigated if particle size enlargement and as a consequence also improvement of flowability through formation of agglomerates of

discrete particles was achievable via injection of solid particles in the atomization zone of a spray dryer.

In a first set of experiments it was investigated if the proposed coprocessing method could overcome the poor tableting properties of paracetamol by coating paracetamol crystals with spray dried lactose and PVP. PVP was included in the formulation as it is reported to increase the physical stability of amorphous lactose [8]. Paracetamol was used as a poorly compactable model drug as it has a low flowability and high capping tendency during tableting. Moreover, high doses (300 to 1000 mg) are needed for its analgesic and antipyretic actions, indicating that a minimal amount of excipients should be added to the formulation to minimize the weight of the final dosage form. Approaches to overcome the high capping tendency of monoclinic paracetamol include the preparation of a different crystal structure [9, 10], special crystal habits [11-16], production of partially amorphous particles [17, 18], formation of cocrystals [19], granulation with different binder types [20, 21] and coprocessing via spray drying and extrusion [22, 23]. As most of these approaches address only the tableting issues associated with paracetamol, it was our aim to improve both tabletability and flowability of paracetamol through application of the proposed coprocessing method. Aqueous solutions of lactose and PVP and pure PVP were spray dried while introducing paracetamol crystals in the atomized spray.

The mean median particle size (d_{50}) of the samples was measured (Table 3) in order to evaluate the extent of agglomeration taking place during coprocessing. The d_{50} of samples Lac/PVP/par(1) and (2) were 226.0 and 165.0 µm, respectively, exceeding highly the d_{50} of paracetamol starting material. The composition of these powders is identical but they were processed under different conditions. A higher d_{50} value was obtained by spray drying an almost saturated lactose solution (16% w/w) and introducing paracetamol crystals at a higher feed rate. Under these conditions the collision probability between particles and droplets is higher which induces more agglomeration. Therefore, it appears that forced secondary agglomeration is achievable via the proposed coprocessing method as the density of particles inside the drying chamber is sufficient to allow interaction between the solid particles and the liquid droplets. Despite the differences in d_{50}, all powders were classified as cohesive powders based on their ffc value. This is attributed to the short residence time of particles in the dryer. In contrast to the food industry where the agglomeration efficiency is increased by recycling fines to the process, this way of extending product residence time is not desirable in pharmaceutical processing. It is however expected that the extent of agglomeration will increase when the process is scaled-up to a production spray dryer. Especially when using tall spray drying towers, the residence time of the product will be

prolonged [24]. Although in preliminary tests the position of the tubes to inject solid particles in the atomization zone was evaluated, the setup is probably also susceptible for improvement. Addition of more tubes for particle injection around the spraying nozzle could favor the mixing between particles and atomized drops and therefore also the agglomeration efficiency.

	d_{50} (µm) ± SD	ffc ± SD	Friability (%)	
			Coprocessed powder	Physical mixture
Lac/PVP/par(1)	226.0 ± 4.2	2.9 ± 0.1	0.6	21.8
Lac/PVP/par(2)	165.0 ± 4.0	2.9 ± 0.2	0.6	21.8
PVP/par	167.4 ± 2.6	2.6 ± 0.2	4.7	- (*)
Paracetamol starting material	66.5 ± 0.8	1.3 ± 0.1	- (*)	- (*)

(*) Tablets could not be compressed at 188 MPa due to extensive capping

Table 3. Mean median particle size (µm) and flowability index (mean ± SD) of coprocessed paracetamol powders and paracetamol starting material, and friability (%) of tablets compressed at 188 MPa from the coprocessed paracetamol powders and corresponding physical mixtures.

The crystallinity of the powders was investigated by XRD and MDSC. It was clear from XRD that lactose in all samples was amorphous after coprocessing as no characteristic reflections from the lactose crystals were detected in the spectral region specific for lactose between 19.2 and 20.1° (Figure 2).

The assessment of the crystallinity of lactose by MDSC was complicated by the predominant presence of paracetamol in the samples. However, a weak T_g was detected for the Lac/PVP/par(1) sample at 53.0 °C, confirming the presence of amorphous lactose. The morphology of the coprocessed particles was examined via SEM. While the paracetamol starting material consisted of needle-like particles, the sharp edges were rounded during coprocessing with spray dried lactose and PVP, due to the presence of an amorphous coating of lactose and PVP on the paracetamol crystals (Figure 3).

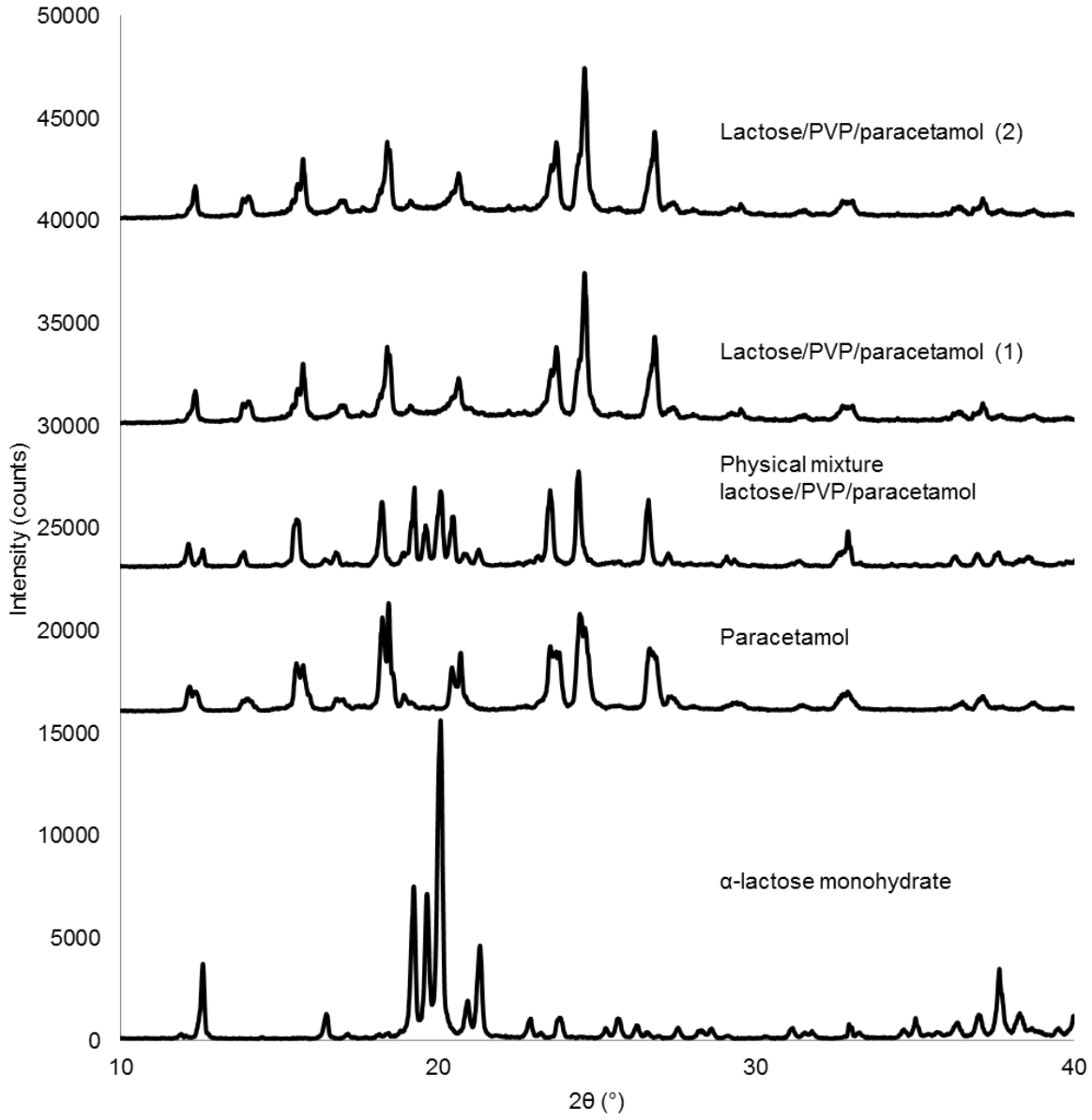

Figure 2. XRD patterns of coprocessed Lac/PVP/par(1), Lac/PVP/par(2) mixtures and their corresponding physical mixtures and starting materials.

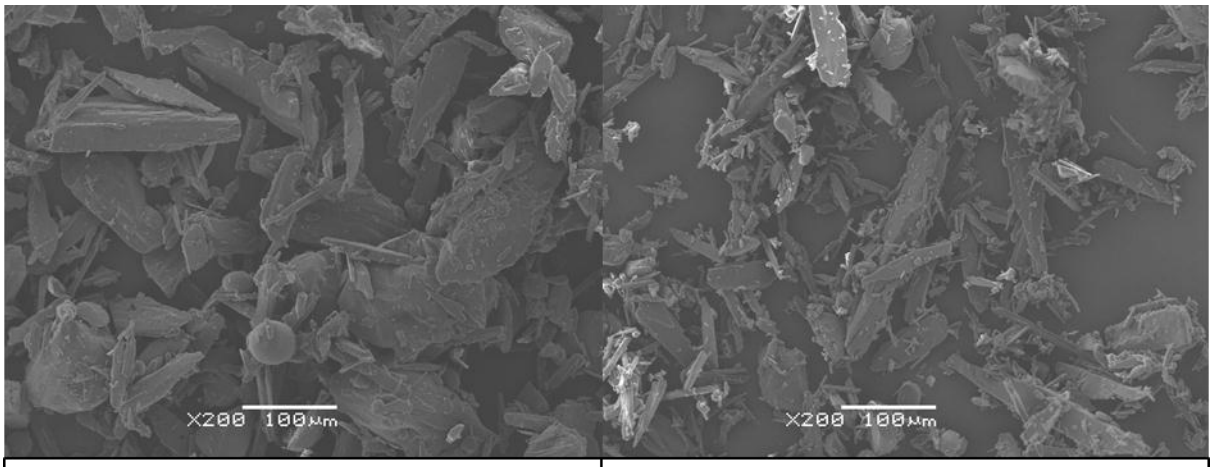

Figure 3. SEM photographs of the coprocessed Lac/PVP/par(1) mixture and paracetamol starting material consisting of needle-like particles.

The compression profiles of the coprocessed powders and their corresponding physical mixtures were compared in order to evaluate their tableting behavior (Figure 4). The Lac/PVP/par(1) and (2) powders exhibited similar tabletability with an almost linear relationship between the applied compaction pressure and tensile strength. The composition of these powders was identical but they were produced under different conditions resulting in a slightly different particle size distribution. Thus, the process conditions did not influence the tabletability of the formulation.

Paracetamol coprocessed with lactose and PVP clearly exhibited superior tabletability in comparison to the corresponding physical mixture that in addition to low tensile strength suffered from capping and lamination during tableting (Figure 4). The excellent tabletability of the coprocessed powders can be attributed to the coating of monoclinic paracetamol crystals, exhibiting fragmentation and elastic recovery upon compaction, with a layer of amorphous lactose and PVP, displaying plastic behavior. In contrast to the coprocessed powders, the lactose present in the physical mixtures is crystalline α-lactose monohydrate which is brittle. It is well recognized that if a brittle and plastic material are combined in an optimal ratio, tabletability can be improved as during compaction of the fragmenting material a large number of interparticulate contacts are created while stronger bonds are formed during compaction of a ductile material [3, 25, 26]. The amorphous coating of lactose and PVP on the paracetamol crystals induces more binder-binder interactions during compression which also contributes to the excellent tabletability. The binding action of this coating is sufficient to allow some elastic recovery of paracetamol without breakage of the interparticulate bonds in the compacts.

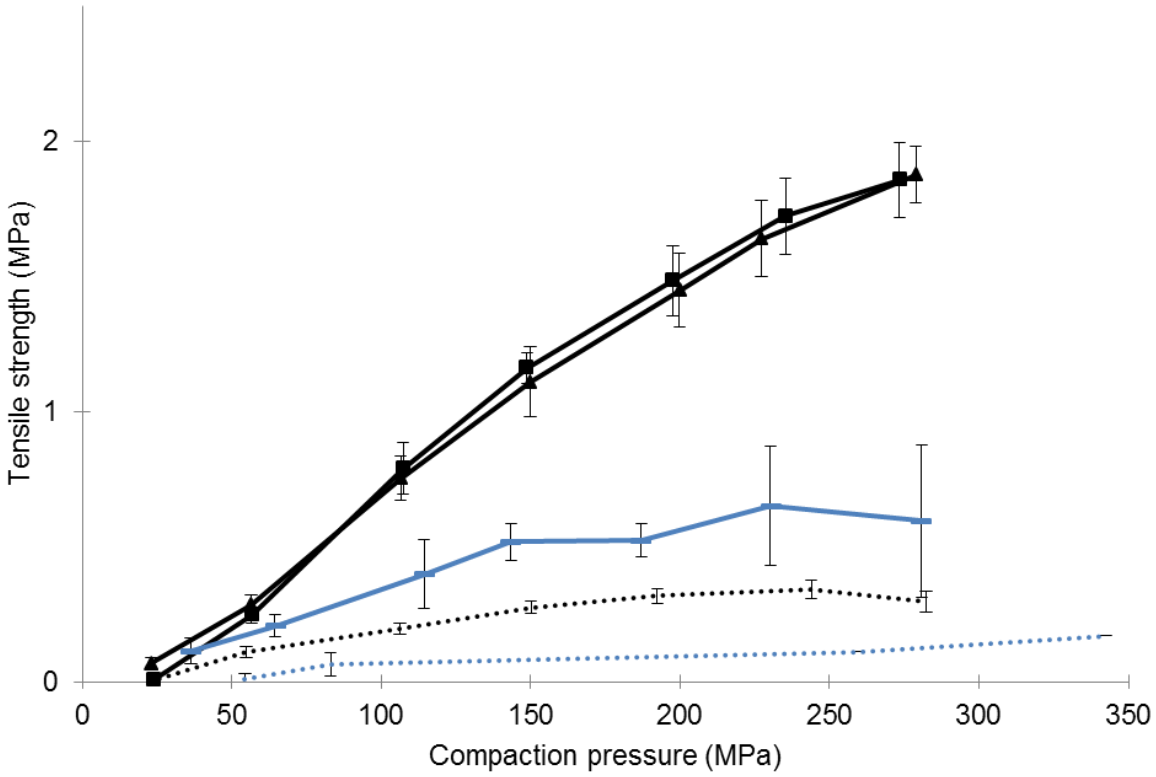

Figure 4. Tabletability of the coprocessed powders with lactose and/or PVP: Lac/PVP/par (1) (full black line ▪) and Lac/PVP/par (2) (full black line▲) and their physical mixture (dotted black line), PVP/par (full blue line) and its physical mixture (dotted blue line).

In order to assess the impact of solely PVP in the coprocessed powders, a solution of PVP was sprayed over paracetamol crystals (formulation PVP/par). The tensile strength of the resulting powder was inferior to the tensile strength of the coprocessed powders containing lactose, PVP and paracetamol (Figure 4). This indicates that the presence of amorphous lactose in the coprocessed powders is essential for the production of coprocessed powders with improved tableting properties. However, the tabletability of the coprocessed formulation PVP/par was clearly superior to its corresponding physical mixture, demonstrating the added value of the proposed coprocessing method.

The excellent tabletability of the coprocessed Lac/PVP/par powders is also reflected in the friability of the resulting tablets, respectively 0.6 and 0.6%, whereas the friability of their physical mixture was 21.8%. The PVP/par formulation also suffered from a too high friability (4.7%).

As the proposed coprocessing method was successfully applied to improve the tabletability of paracetamol, it was investigated in a second set of experiments if the method is also applicable for the production of direct compression lactose. Therefore lactose crystals were coated with spray dried lactose and PVP via the proposed coprocessing method. The

percentage of spray dried lactose in the coprocessed powders varied between 0 and 40% w/w (formulation 1 to 4 in Table 2). The d_{50}, flowability, morphology and tabletability of these powders was assessed.

The d_{50} of the coprocessed powders ranged between 80 and 134.5 µm, and all powders were classified as cohesive based on their ffc values. From microscopic evaluation, the edges of the particles appeared to be rounder and smoother when more spray dried lactose was present in the coprocessed powders. These coprocessed powders consisted of a mixture of amorphous and crystalline lactose (as indicated by XRD), whereas a spray dried solution of lactose and PVP was completely amorphous. It could therefore be assumed that by coprocessing a lactose solution in combination with solid lactose crystals an amorphous lactose coating was formed on the lactose crystals, smoothening the edges of the solid particles.

As it is known that lactose powders consisting of an amorphous fraction (which displays plastic deformation) and a crystalline fraction (which exhibits brittle fragmentation upon compaction) have excellent tableting properties [1, 27, 28], the tensile strength of tablets manufactured using the coprocessed powders was compared to that of tablets formulated with a commercially available direct compression spray dried lactose grade (15% amorphous content) (Table 4). The coprocessed powders showed improved tensile strength when compared to a direct compression spray dried lactose grade. This was linked to the presence of PVP in the formulations as it was seen that the coprocessed powder consisting of solely crystalline lactose and PVP (formulation 1) also showed excellent tableting properties. It was reported by Schmidt et al. that PVP is present in Ludipress®, a commercially available direct compression lactose grade produced by spray agglomeration and consisting of both amorphous and crystalline lactose, in order to increase the compactibility of lactose [29]. The friability of the tablets consisting of coprocessed powders was acceptable as it ranged between 0.0 and 1.2%. In contrast, tablets made from the commercially available direct compression spray dried lactose grade suffered from a too high friability (Table 4).

Thus, although the extent of agglomeration achieved by application of the coprocessing method was limited, it allowed producing powders with excellent tableting properties which were attributed to coating of lactose or paracetamol crystals with a layer of amorphous lactose and PVP.

Formulation	D_{50} (µm)	Ffc	Tensile strength (MPa)	Friability (%)
1	134.5 ± 3.5	3.9 ± 0.1	8.2 ± 2.0	0.1
2	93.3 ± 4.8	3.2 ± 0.3	8.5 ± 1.3	0.0
3	80.9 ± 3.4	3.2 ± 0.1	8.3 ± 1.71	1.0
4	85.3 ± 4.7	3.1 ± 0,1	8.3 ± 2.0	1.2
5	117.3 ± 4.1	2.8 ± 0.4	6.9 ± 1.0	0.2
reference	93.0 ± 3.6	3.9 ± 0.5	4.9 ± 0.9	3.9

Table 4. Powder (mean median particle size, flowability index, n:3, mean ± SD) and tablet (tensile strength, n:10, mean ± SD, friability) properties of the coprocessed lactose samples and reference (direct compression spray dried lactose grade, DCL 11).

CONCLUSIONS

Paracetamol crystals, used as a poorly compactable model drug, were successfully coated with amorphous lactose and PVP in a continuous way via the simultaneous introduction of paracetamol crystals during spray drying of a lactose/ PVP solution. These particles did not exhibit capping during compaction. The excellent tableting properties are credited to the combination of a ductile (amorphous lactose, PVP) and brittle component (paracetamol) and to the coating of amorphous lactose and PVP on the paracetamol crystals ensuring extensive binder-binder contact. The proposed method was also suitable for the production of direct compression lactose and can therefore be considered as a promising platform technology for the single-step production of coprocessed drug substances or excipients with improved tableting properties.

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3

CONTINUOUS MANUFACTURING OF DELTA-MANNITOL BY COSPRAY DRYING WITH PVP

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V. Vanhoorne, P. J. Van Bockstal, B. Van Snick, E. Peeters, T. Monteyne, P. Gomes, T. De Beer, J. P. Remon, C. Vervaet, Continuous manufacturing of delta mannitol by cospray drying with PVP, Int. J. Pharm. 501 (2016) 139-147.

Abstract

Mannitol is a frequently used diluent in the production of tablets due to its non-hygroscopic character and low drug interaction potential. Although the δ-polymorph of mannitol exhibits superior tabletability in comparison to α- and β-mannitol, the latter are most commonly used because large-scale production of δ-mannitol is difficult. Therefore, a continuous method for production of δ-mannitol was developed in the current study. Spray drying an aqueous solution of mannitol and PVP in a ratio of 4:1 resulted in formation of δ-mannitol. The tabletability of a physical mixture of spray dried δ-mannitol with PVP (5%) and paracetamol (75%) was clearly superior to the tabletability of physical mixtures consisting of spray dried α- and β-mannitol with PVP (5%) and paracetamol (75%) which confirmed the excellent tableting properties of the δ-polymorph. In addition, a coprocessing method was applied to coat paracetamol crystals with δ-mannitol and PVP. The tabletability of the resulting coprocessed particles consisting of 5% PVP, 20% δ-mannitol and 75% paracetamol reached a maximal tensile strength of 2.1 MPa at a main compression pressure of 260 MPa. Moreover the friability of tablets compressed at 184 MPa was only 0.5%. This was attributed to the excellent compression properties of δ-mannitol and the coating of paracetamol crystals with δ-mannitol and PVP during coprocessing.

KEYWORDS: Delta mannitol, Spray drying, Coprocessing, Particle coating, Direct compression, Paracetamol, Tabletability, Continuous production

INTRODUCTION

Tablets are the most commonly used dosage form, accounting for 70 - 80% of all pharmaceutical preparations, due to their ease of manufacturing, accurate dosing and high patient compliance [1, 2].

Mannitol is an acyclic sugar often used as tablet diluent in the nutraceutical and pharmaceutical industry [3]. The major advantages of mannitol over other excipients are its non-hygroscopic character, which makes it an excipient of choice for moisture sensitive drugs, and its low drug interaction potential [4, 5, 6]. Mannitol is also frequently used in chewable and orodispersible tablets due to its sweetness, cooling mouth sensation, high solubility and fast disintegration in water [3, 4, 6]. Especially with pediatric and geriatric patients, rapidly disintegrating and dispersing tablets can add to the patients' compliance as it overcomes swallowing problems. Additionally, mannitol is used as a bulking agent in lyophilizates due to its ability to form solid, elegant cakes in the vials [4, 7].

Three polymorphs, α-, β- and δ-mannitol, and mannitol hemi-hydrate, a pseudo-polymorphic form formed during freeze-drying, have been described in literature [8]. Burger et al. evaluated the compaction properties of these three polymorphs since the crystallographic and thermodynamic properties of polymorphs vary which can affect their compaction behavior [8]. They reported on superior compressibility and tabletability of the δ-polymorph in comparison to the α- and β-polymorphs of mannitol. More recently, Wagner et al. confirmed this result as they found an improved tabletability of δ-mannitol granules after roller compaction [3].

Several crystallization reactions are reported for the production of δ-mannitol [8, 9, 10, 11]. However, reproducible and scalable production of δ-mannitol by crystallization is difficult [8]. δ-mannitol was also obtained during cospray drying of aqueous solutions of mannitol and trypsin in different ratios [12]. However, a coprocessed excipient including a protease is not preferred. As a result, commercially available mannitol grades consist almost exclusively of α- or β-mannitol or a mixture thereof. Therefore, it was the first aim to develop a continuous manufacturing method for the production of δ-mannitol via spray drying. Aqueous solutions of mannitol and polyvinylpyrrolidone (PVP) were spray dried at two outlet drying temperatures and the polymorphic content and tabletability of these spray dried samples were evaluated.

The second part of the study evaluated if coprocessing of paracetamol with δ-mannitol and PVP could overcome the poor tabletability of paracetamol in a single processing step. Coprocessing of excipients is widely practiced for the production of directly compressible excipients: e.g. Cellactose® (microcrystalline cellulose and lactose), Ludipress® (lactose, PVP

and crospovidone), StarLac® (lactose and maize starch), Avicel® CE (microcrystalline cellulose and guar gum) [1]. Cospray drying of excipients and active pharmaceutical ingredients has also been successfully applied to generate agglomerates with a unique particle size and shape and physicochemical properties [13]. In the current study, a coprocessing method recently described by Vanhoorne et al. was applied for the production of a coprocessed mixture consisting of 5% PVP, 20% δ-mannitol, and 75% paracetamol [14]. The morphology, solid state and particle size distribution of the coprocessed sample was evaluated and its compression properties were compared to a physical mixture.

MATERIALS AND METHODS

Materials

β-mannitol (C*PharmMannidex) and δ-mannitol (Parteck Delta) were kindly donated by Cargill (Vilvoorde, Belgium) and Merck (Darmstadt, Germany), respectively. β-mannitol was used for the preparation of the spray dried solutions. Paracetamol (semi-fine) was received from Mallinckrodt Chemical (Hazelwood, USA). Magnesium stearate and silicon dioxide (Fagron, Waregem, Belgium) were used as lubricant and glidant, respectively. PVP (Kollidon 30) and crospovidon (Kollidon CR) were received from BASF (Burgbernheim, Germany). Miglyol 812 (Cremer Oleo, Witten, Germany) with 0.2% polysorbate 80 (Fagron, Waregem, Belgium) was used as dispersant for laser diffraction measurements.

Spray drying and coprocessing

In preliminary spray drying experiments, an 18% w/w aqueous solution of mannitol and PVP (ratio mannitol:PVP: 4:1) and an 18% w/w aqueous solution of pure mannitol were spray dried (F1 and F2, respectively) on a lab-scale spray dryer (B290, Büchi Labortechnik, Flawil, Switzerland) equipped with a two-fluid nozzle (nozzle orifice 1.4 mm). The spray dried samples were collected after the cyclone. The solutions were spray dried at a constant feed rate of 16 g/min and an atomization pressure of 50%. The inlet and outlet drying air temperature were 220 and 80 °C, respectively.

In the main spray drying experiments, 18% w/w aqueous solutions of mannitol and PVP (mannitol:PVP ratios of 9:1 and 4:1) and an 18% w/w aqueous solution of pure mannitol were spray dried on a pilot-scale spray dryer (Mobile Minor, GEA Niro, Copenhagen, Denmark) equipped with a two-fluid nozzle (nozzle orifice 2.0 mm). The solutions were transferred to the spray dryer by a peristaltic pump (520U, Watson Marlow, Cornwall, UK) with marprene tubing (inside diameter 4.8 mm). The spray dryer was operated in co-current mode. The dimensions of the drying chamber were 0.84 m cylindrical height with a diameter of 0.80 m

and 60° conical base. The solutions were spray dried at a constant feed rate of 45 g/min and an atomizing air pressure of 1 bar. The inlet drying air temperature was varied between 170 and 220 °C, resulting in outlet temperatures of 60 and 80 °C, respectively.

An overview of the spray dried solutions (F1-3) on the lab-scale and pilot-scale spray dryers and the composition of the resulting solid samples is given in Table 1. The yield (%) of the spray drying process was defined as the weight fraction of the material recovered from the collecting reservoir after spray drying in relation to the amount of mannitol and PVP originally contained in the atomized liquid feed.

In a second part of the study, paracetamol crystals were coated with mannitol and with mannitol and PVP via a coprocessing method proposed by Vanhoorne et al. in order to improve the tabletability of paracetamol crystals [14]. A detailed description of the method and schematic setup was given by Vanhoorne et al. [14]. Hence, 18% w/w aqueous solutions of pure mannitol and of mannitol and PVP (mannitol:PVP ratio: 4:1) were fed to the fountain two-fluid nozzle (nozzle orifice 2.6 mm) of a production-scale spray dryer (type 6.3-SD, GEA Niro, Copenhagen, Denmark) by a peristaltic pump (520U, Watson Marlow, Cornwall, UK) and marprene tubing (inside diameter 4.8 mm). The spray dryer operated in counter-current mode. The dimensions of the spray dryer were 2.0 m cylindrical height with a diameter of 3.5 m and 60° conical base. The spray dried powder was collected in a reservoir under the drying chamber. The solutions were spray dried according to the following parameters: feed rate: 100 g/min, inlet drying air temperature: 240 °C, outlet drying air temperature: 112 °C, atomizing air pressure 0.5 bar. Paracetamol crystals were preblended with 0.05% silicon dioxide and introduced during the spray drying process at a feed rate of 48 g/min into the cone of the spray dryer via an in-house designed setup described by Vanhoorne et al. [14]. Using this setup, the paracetamol crystals were directly injected into the spray of atomized drops in the drying chamber of the spray dryer. The composition of the spray dried solutions and final composition of the coprocessed powders (F4 and F5) is included in Table 1.

	Composition of spray dried solutions (% w/w)		Feed rate solid particle introduction (g/min)	Final composition of spray dried sample (% w/w)			Spray dryer
	PVP	mannitol		PVP	mannitol	paracetamol	
F1	0	18.0	-	0	100	-	lab-scale + pilot-plant
F2	1.8	16.2	-	10	90	-	pilot-plant
F3	3.6	14.4	-	20	80	-	lab-scale + pilot-plant
F4	0	16.0	48	0	25	75	production-scale
F5	3.2	12.8	48	5	20	75	production-scale

Table 1. Overview of the spray dried solutions and composition of the final spray dried and coprocessed samples.

Preparation of physical mixtures

Physical mixtures (PM1-4) were prepared in a tumbling blender (Turbula mixer type T2F, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) for 10 min at 49 rpm to evaluate the influence of PVP and the added value of coprocessing via spray drying on tabletability. An overview of the prepared physical mixtures is listed in Table 2.

	SD sample (% w/w)	**Paracetamol (% w/w)**	**PVP (% w/w)**
PM1	20.0 (F1)	75.0	5.0
PM2	22.5 (F2)	75.0	2.5
PM3	25.0 (F3)	75.0	-
PM4	25.0 (F1)	75.0	-

Table 2. Overview of the prepared physical mixtures.

Tableting

The spray dried and coprocessed powders and physical mixtures were blended (Turbula mixer type T2F, W.A. Bachofen Maschinenfabrik, Basel, Switzerland) for 5 min at 49 rpm with 5% crospovidon® and 0.5% magnesium stearate prior tableting.

Tablets (500 mg ± 10 mg) of the spray dried and coprocessed powders (F1-5) and physical mixtures (PM1-4) were compressed on a rotary tablet press (Modul™ P, GEA Courtoy, Halle,

Belgium) equipped with a single round concave Euro B punch of 12 mm diameter at a tableting speed of 5 rpm. The tablets were compressed at 6 different compaction pressures: 34, 61, 100, 143, 184 and 229 MPa.

Material characterization

Morphology

The powders were examined by scanning electron microscopy (SEM) (JEOL JSM-5600-LV, JEOL Ltd., Zaventem, Belgium) after sputtering with a platinum coating using the JEOL JFC 1300 Autofine Coater (JEOL, Zaventem, Belgium) to improve the electron conductivity of the samples.

Karl Fischer titration

To determine the residual moisture content, Karl Fischer titrations (Mettler DL35, Mettler Toledo, Zaventem, Belgium) were performed (n=3) on the powder samples immediately after production. Powder (100 – 200 mg) was added to an airtight beaker containing absolute dry methanol (Biosolve, Valkenswaard, the Netherlands). Titration of the samples was performed using Karl Fischer reagent (Hydranal_Composite 2, Sigma–Aldrich, Munich, Germany). The mixture was stirred for 5 min before actual titration.

Particle size analysis

The particle size distribution of the paracetamol starting material, spray dried and coprocessed powders was measured in triplicate by laser diffraction (Mastersizer S long bench, Malvern Instruments, Worcestershire, UK) and the average particle size distribution was calculated via the Mastersizer 2000 software. The wet dispersion technique was applied using the 300RF lens (Malvern Instruments, Worcestershire, UK). The powders were dispersed in a solution of 0.2% Tween 80 in Miglyol 812 and subsequently vortexed and sonicated in order to eliminate agglomerates. The results are expressed as volume diameters.

Ring shear testing

The flowability expressed as the flowability index (ffc) of the powders was measured in duplicate by ring shear testing (Type RST-XS, Dietmar Schulze Schüttgutmesstechnik, Wolfenbuttel, Germany) and the mean values were reported. The powders were tested using a preshear of 1000 Pa at three consolidation stresses, 400, 600 and 800 Pa.

Solid state characterization

The polymorphic mannitol composition in the spray dried and coprocessed samples was analyzed using Raman spectroscopy, X-ray diffraction (XRD) and modulated differential scanning calorimetry (MDSC).

Raman spectra (Raman Rxn1, Kaiser Optical Systems, Ann Arbor, United States) of the samples were recorded (n=8) using exposure times of 10 s with 3 accumulations. All spectra were recorded with a resolution of 4 cm^{-1}. The spectral region between 1000 and 1200 cm^{-1} was selected for evaluation of mannitol polymorphism. Spectra were centered and SNV-correction was applied to correct for the physical variation between measurements. The spectra were used for identification of the polymorphic forms present in the formulation and therefore the spectra were compared with the spectra of reference material of α-, β- and δ-mannitol. Additionally, principal component analysis (PCA) was executed on the spectra of the pilot-scale spray dried samples with Simca 13.0.3 software (Umetrics, Umeå, Sweden). To investigate the stability of the pilot-scale spray dried samples, they were stored 6 months at 60% relative humidity and 25 °C in open cups and reanalyzed by Raman spectroscopy as described above. Raman spectra of reference materials of α-, β- and δ-mannitol were adopted from De Beer et al. [7].

XRD analysis of the samples and mannitol references was performed on a CuKα diffractor (ARL^{TM} X'TRA, Thermo Fischer Scientific, Waltham, United States) with a voltage of 40 mV in the angular range of $5°<2\theta<60°$ using a step scan mode with step size of 0.02° and counting time of 1s/step.

MDSC was performed using a Q2000 differential scanning calorimeter (TA Instruments, Zellik, Belgium) equipped with a refrigerated cooling system. Samples (5 – 10 mg) were accurately weighed and run in Tzero pans (TA Instruments, Zellik, Belgium). They were cooled to -20 °C and subsequently heated up to 220 °C with a heating rate of 2 °C/min. The modulation time and amplitude were set at 60 s and 0.318 °C, respectively. Dry nitrogen was used as a purge gas through the cell at a flow rate of 50 ml/min. The results were analyzed using TA Instruments Universal Analysis software.

Tablet characterization

The hardness, thickness and diameter of the tablets (n=10) were determined using a hardness tester (Type HT 10, Sotax, Basel, Switzerland) and the tensile strength (TS) of the tablets was calculated according to the formula of Fell and Newton [15]:

$$TS = 2F/\pi dt$$

Where F, d and t denote the diametral crushing force, tablet diameter and tablet thickness, respectively. The friability of tablets compressed at 184 (±5) MPa was determined using a friabilator (PTFE, Pharma Test, Hainburg, Germany) as described in the European Pharmacopea at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

RESULTS AND DISCUSSION

Influence of PVP inclusion and outlet temperature on the formation of δ-mannitol

In preliminary experiments spray dried mannitol samples without PVP (F1) and with 20% PVP (F3) were prepared on a lab-scale spray dryer. Identification of the mannitol polymorphs in the samples was performed by Raman spectroscopy, XRD and MDSC through comparison with reference material of α-, β- and δ-mannitol. Raman spectroscopy (Figure 1) and XRD (Figure 2) identified a mixture of α- and β-mannitol in the sample without PVP and δ-mannitol the sample with 20% PVP, respectively.

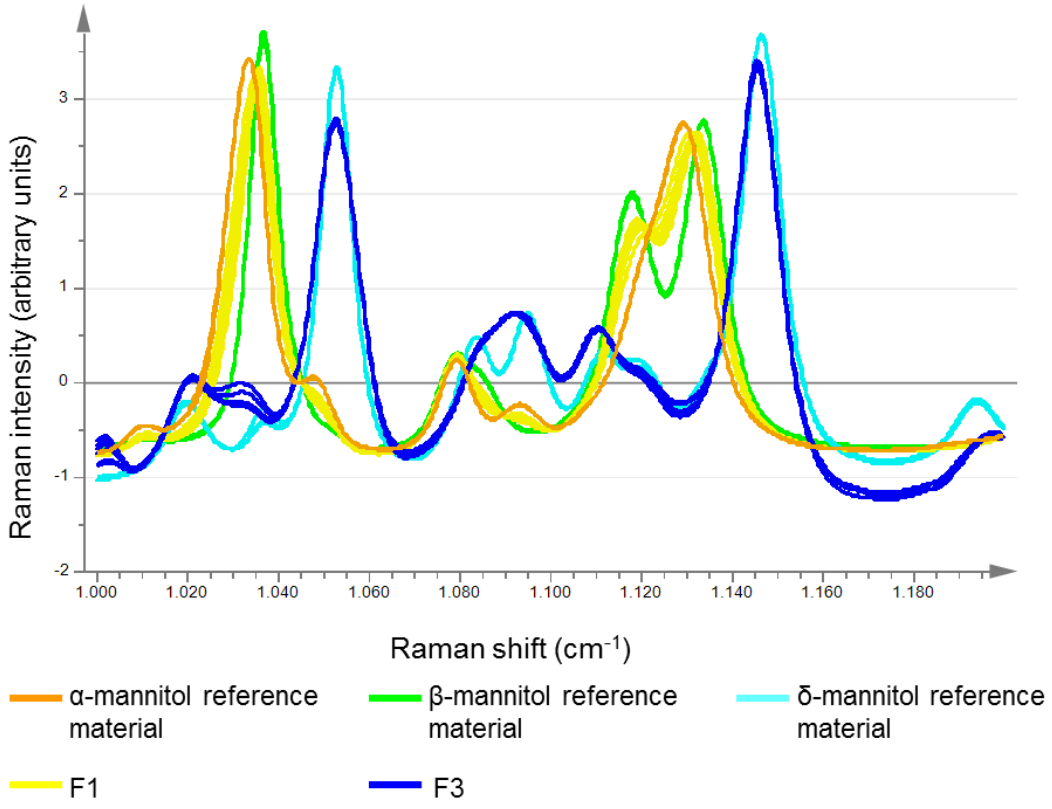

Figure 1. Raman spectra of α-, β- and δ-mannitol reference material and samples F1 and F3 spray dried on a lab-scale spray dryer.

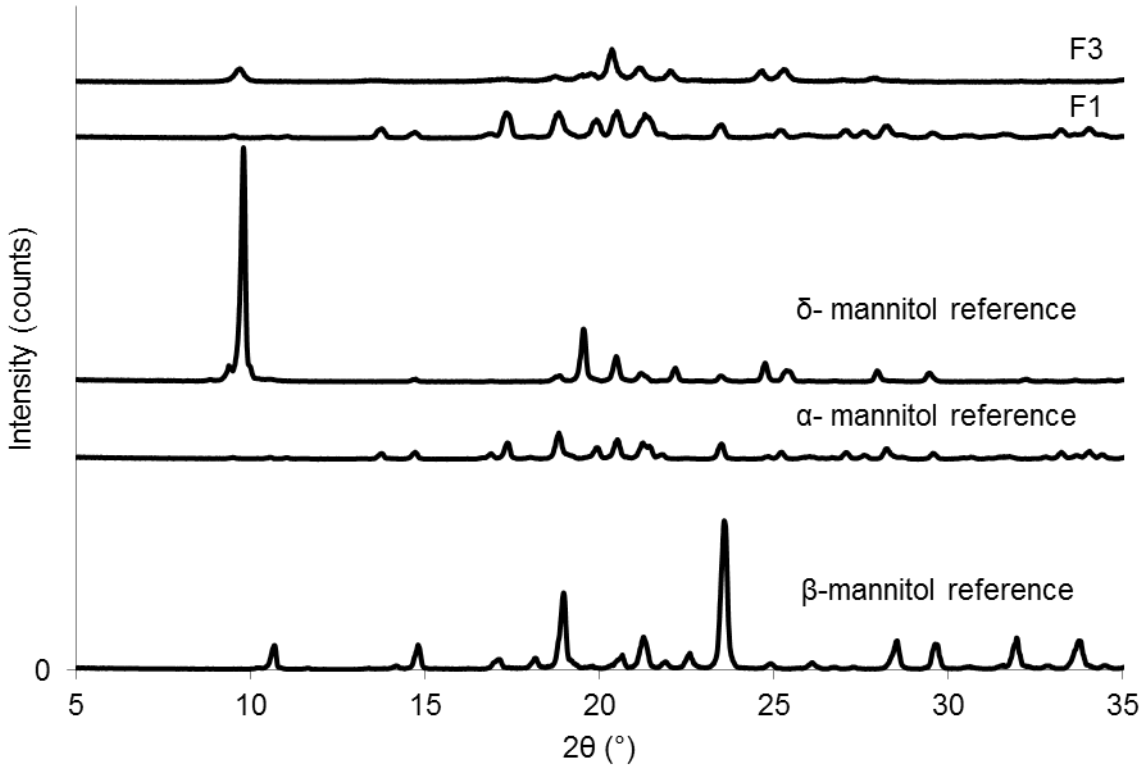

Figure 2. XRD spectra of α-, β- and δ-mannitol reference material and samples F1 and F3 spray dried on a lab-scale spray dryer.

MDSC analysis of the samples proved not to be helpful for the identification of different mannitol polymorphs since a melting peak at 166 – 167 °C with identical melting enthalpy was detected for reference material of α-, β- and δ-mannitol. Not uniform melting of δ-mannitol at 155 °C followed by crystallisation to α- or β-mannitol and melting of the respective crystal form or mixture is nevertheless reported in literature [8, 16].

Formulations F1-3 (Table 1), containing different PVP concentrations in the final spray dried powder, were spray dried on a pilot-scale spray dryer at 2 different outlet temperatures (To): 60 and 80 °C. The influence of the PVP content and the outlet temperature on the mannitol polymorph formed during spray drying was qualitatively evaluated by Raman spectroscopy. The results of the Raman analysis were summarized in a PC1 versus PC2 scores plot of the first and second principal component (PC), explaining 83% and 15% of the variation in the dataset, respectively (Figure 3).

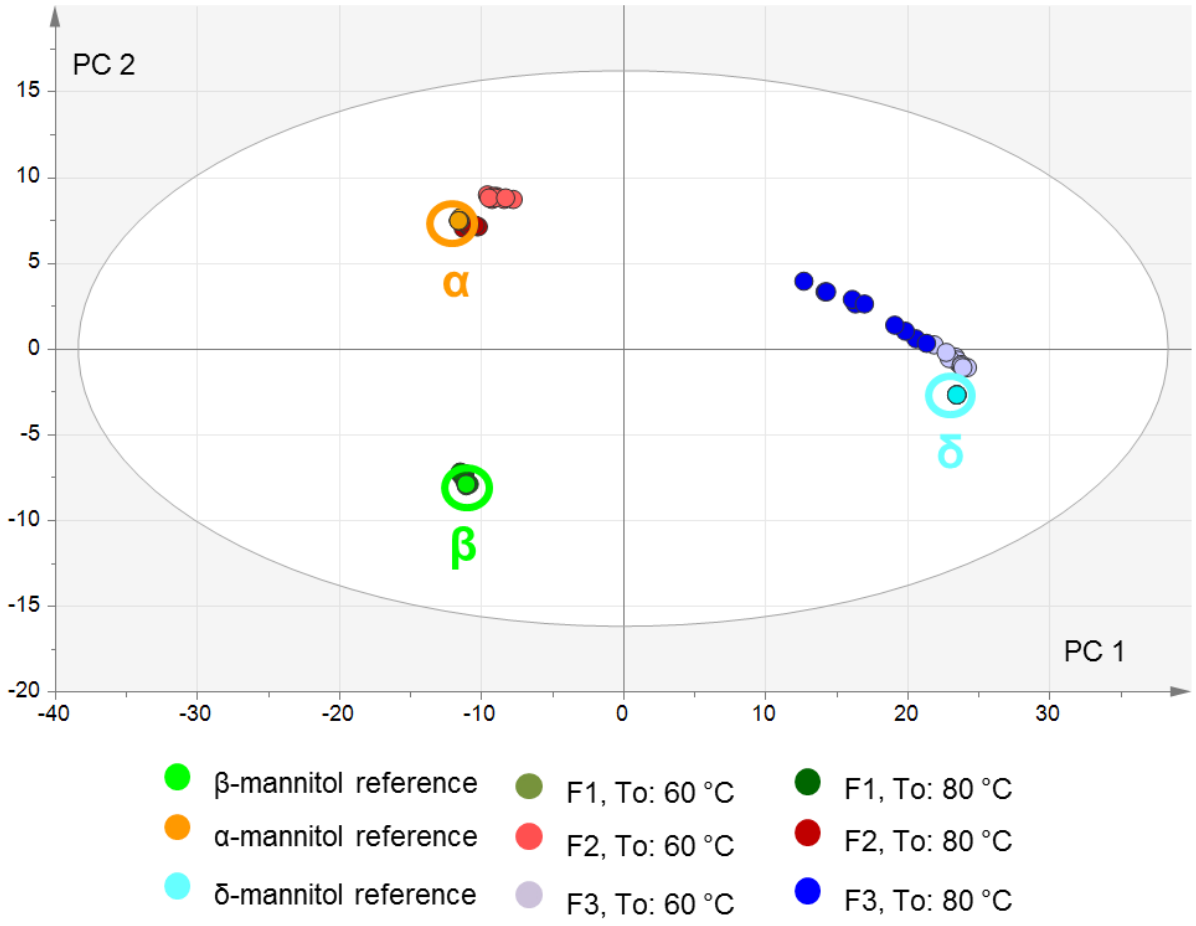

Figure 3. PC1 versus PC2 scores plot obtained after PCA of all pilot-scale spray dried samples (To 60 °C and 80 °C) and reference material of α-, β- and δ-mannitol.

Analysis of the loading plots (Figure 4) of the PC learned that the first PC was selective for the presence of δ-mannitol whereas the second PC could differentiate between α- and β-mannitol. Three clusters of samples around the data points of the α-, β- and δ-mannitol reference materials could be differentiated on the PC1 versus PC2 scores plot. Independently of the applied outlet temperature, the spray dried samples containing 0% and 10% PVP consisted of exclusively β- and α-mannitol, respectively. Inclusion of 20% PVP in the formulation (F3) yielded powders consisting of mainly δ-mannitol but traces of α-mannitol were also detected. The polymorphic content in these samples was dependent on the outlet temperature used. Applying an outlet temperature of 60 °C resulted in a spray dried sample with exclusively δ-mannitol next to PVP whereas traces of α-mannitol were still present in the sample spray dried at an outlet temperature of 80 °C.

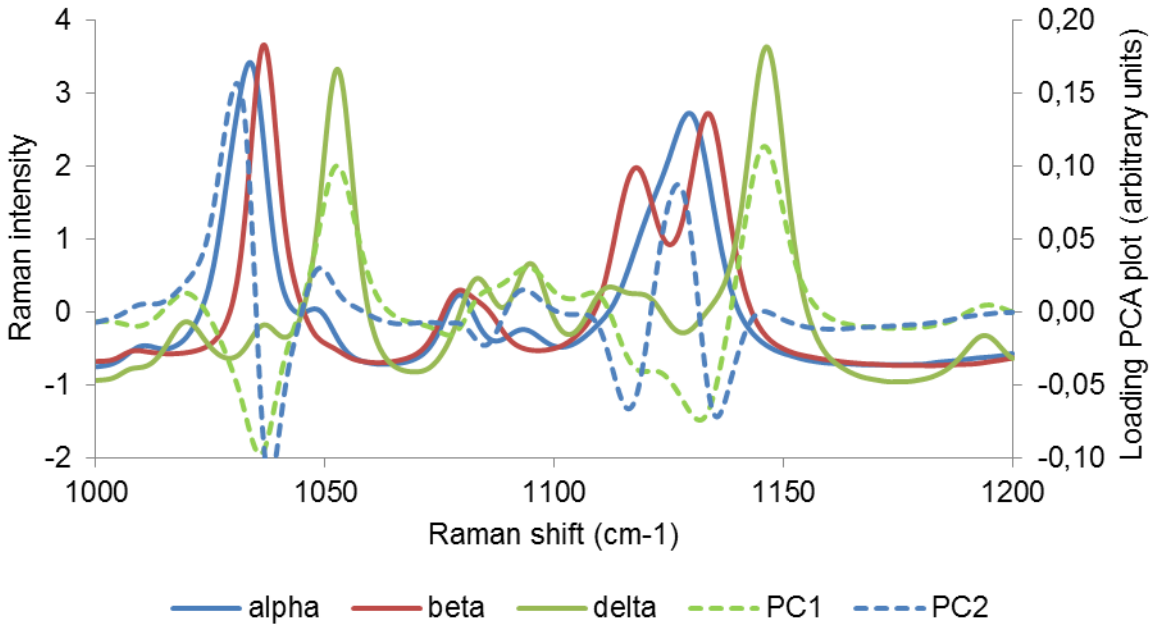

Figure 4. Raman spectra of α-, β- and δ-mannitol reference material and loadings of PC1 and PC2 obtained after PCA analysis.

These results were confirmed by XRD (Figure 5) as characteristic peaks of β-mannitol (10.56°, 14.71°), α-mannitol (13.79°) and δ-mannitol (9.57°) were detected in samples F1, F2 and F3, respectively. [5, 6, 7, 8, 17, 18].

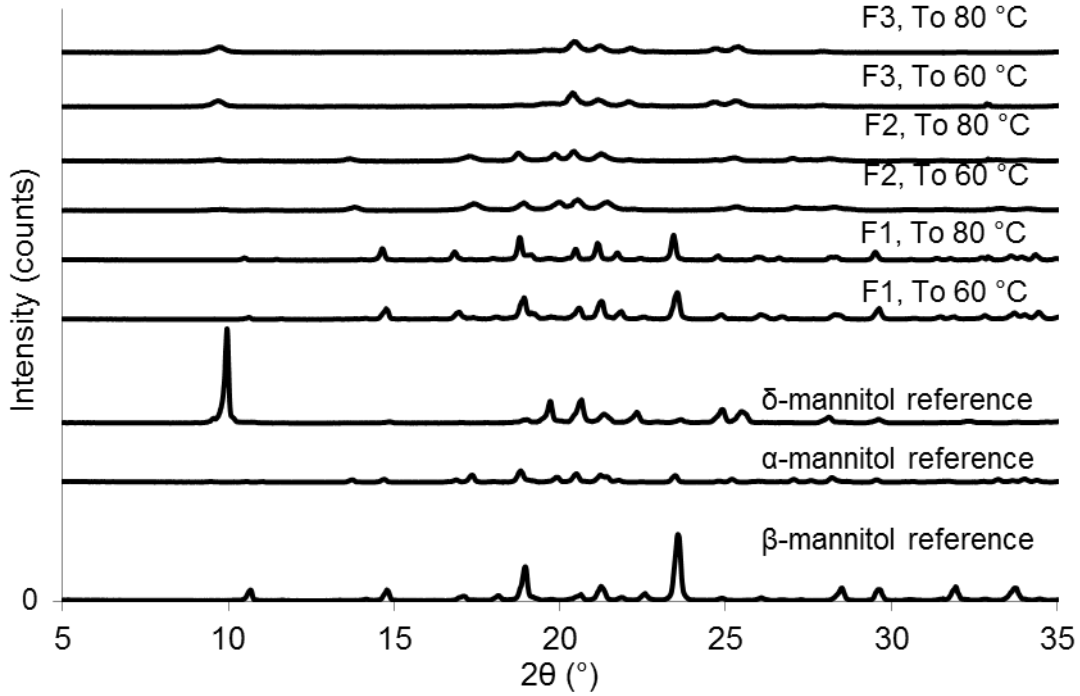

Figure 5. XRD patterns of α-, β- and δ-mannitol reference material and samples F1-3 spray dried at To 80 °C and 60 °C.

The yields of the spray drying experiments and residual moisture content of the resulting samples are listed in Table 3. The process yield varied between 23 and 89%, depending on the percentage of PVP in the formulation and the outlet temperature used. Inclusion of PVP decreased the process yield due to the sticky nature of PVP and its high hygroscopicity which is also reflected in the high residual moisture content of the samples with 20% PVP [4]. Increasing the outlet temperature positively influenced the yield as the particles were drier and therefore less sticky before they hit the dryer wall.

Outlet temperature (°C)	Formulation	Yield (%)	Moisture content (%)	ffc
60	F1	70	0.16 (± 0.05)	-(*)
	F2	54	3.10 (± 0.10)	-(*)
	F3	23	5.50 (± 0.10)	-(*)
80	F1	89	0.63 (± 0.07)	1.68
	F2	66	2.56 (± 0.09)	4.00
	F3	59	5.19 (± 0.10)	5.55

(*) No data collected

Table 3. Overview of the yield and residual moisture (±SD) content of the spray drying experiments performed on the pilot-scale spray dryer.

Spray drying of a pure mannitol solution resulted in small agglomerates composed of spherical particles (Figure 6). Addition of PVP to the spray dried mannitol solution yielded larger coalesced particles where individual particles were more difficult to distinguish.

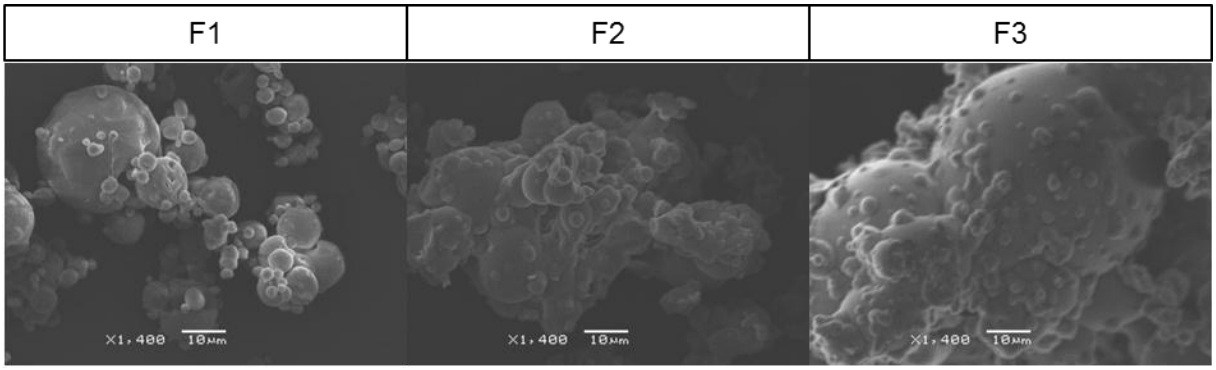

Figure 6. SEM images of spray dried samples F1-3.

The particle size distribution and median particle size (d_{50}) of spray dried samples F1-3 is shown in Figure 7. Inclusion of PVP in the formulation resulted in particles with a higher d_{50} value since PVP acted as a binder favoring agglomeration during the spray drying process. However, increasing the PVP content from 10 to 20% in the final spray dried samples had no effect on d_{50}. The larger d_{50} of F2 and F3 was reflected in their flowability as they were classified as easy-flowing (despite the higher moisture content of these samples), whereas

F1 was classified as very cohesive based on the ffc values. Thus, inclusion of PVP in the formulation to form δ-mannitol during spray drying also proved to be an asset with regard to flowability.

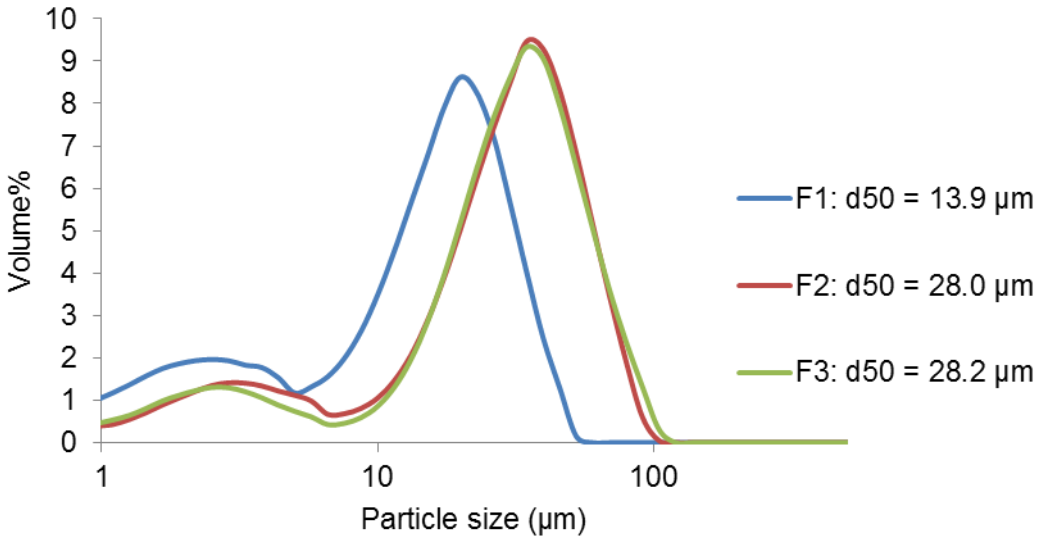

Figure 7. Particle size distribution of samples F1, F2 and F3 spray dried at an outlet temperature of 80 °C.

Compression profiles of the spray dried samples were constructed for evaluation of the tabletability of the different mannitol polymorphs (Figure 8, full lines). The spray dried sample with δ-mannitol (F3) clearly exhibited superior tabletability in comparison to the samples with the α- and β-polymorphs (F1, F2), reaching a maximum TS of 6.2 (±0.3) MPa at a main compression pressure (MCP) of 184 (±5) MPa. Note that the PVP content of these samples was different. To exclude this effect (a plastically deforming binder under compression) paracetamol formulations containing the different spray dried mannitol samples with a constant (5%) PVP content (PM1-3 in Table 2) were processed into tablets (depending on the formulation part of PVP was included in the spray dried material and/or added as such to the physical mixture). Their tabletability is also included in Figure 8 (dotted lines). Obviously the tabletability of these formulations is lower compared to the spray dried samples due to the high load (75%) of paracetamol, a model drug known for its poor tabletability. However, the tabletability of the formulation containing δ-mannitol (PM3) was significantly higher than of the physical mixtures with α- and β-mannitol (PM1 and PM2), which was linked to the superior tabletability of δ-mannitol. This confirmed the findings of Burger et al. and Wagner et al. [3, 8].

The excellent tabletability of spray dried δ-mannitol and PVP was also reflected in the friability of the tablets. While the friability of tablets composed of spray dried samples was below 0.1% (independently of their polymorphic content or the percentage PVP), the

inclusion of paracetamol in the physical mixtures resulted in a friability of 6.4%, 6.4% and 3.0% for PM1, 2 and 3, respectively.

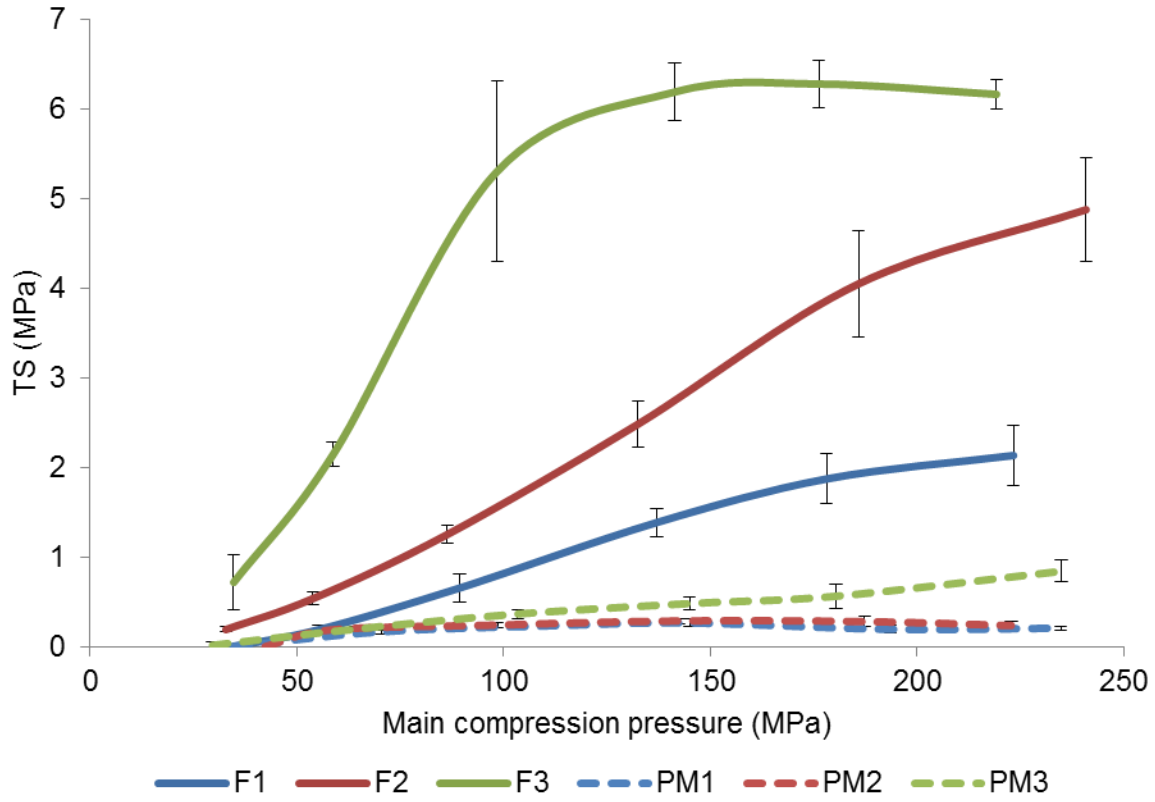

Figure 8. Tabletability of the spray dried powders (F1-3) and physical mixtures (PM1-3).

Tabletability of the coprocessed samples

Since production of δ-mannitol in a continuous way via spray drying was possible, it was next investigated whether paracetamol and δ-mannitol could be coprocessed in a single step, using the method proposed by Vanhoorne et al. [14]. Paracetamol crystals were injected into a spray of atomized drops during the spray drying process. An aqueous solution of 18.0% w/w mannitol (F4) and an aqueous solution of mannitol and PVP (F5) were spray dried (Table 2). The ratio of mannitol to PVP in F5 was 4:1 which is equal to the ratio used in the spray drying experiments (F3) yielding δ-mannitol.

The polymorphic state of mannitol in the coprocessed samples was investigated by XRD and Raman spectroscopy. Identification of the mannitol polymorphs by XRD was not possible due to the presence of 75% paracetamol, dominating the spectrum. Raman analysis revealed the presence of β-mannitol in coprocessed sample F4. However, δ-mannitol could not be detected in coprocessed sample F5 via Raman spectroscopy due to the dominant influence

of paracetamol on the spectrum. Since it was proven in the first part of the study that spray drying mannitol and PVP in a ratio of 4:1 yielded δ-mannitol on both a lab scale and pilot scale spray dryer irrespectively of the applied outlet temperature, the presence of δ-mannitol in sample F5 was assumed.

The morphology of the coprocessed samples was evaluated by SEM and is shown in Figure 9. In this case no spherical particles were obtained since irregular-shaped paracetamol crystals were introduced in the spray of atomized drops, and their shape dominated in the collected spray dried powder. More agglomerated particles were observed in sample F5 which was attributed to PVP acting as a binder.

This was confirmed by laser diffraction analysis of the samples (Figure 10): the d_{50} of samples F4 and F5 were 108.2 µm and 230.9 µm, respectively, exceeding the d_{50} of paracetamol starting material (44.4 µm). Thus in both experiments agglomeration occurred, however, inclusion of PVP in F5 favored agglomeration. Despite the significant difference in particle size of the coprocessed samples, both were classified as cohesive based on their ffc value (which is linked to their irregular shape).

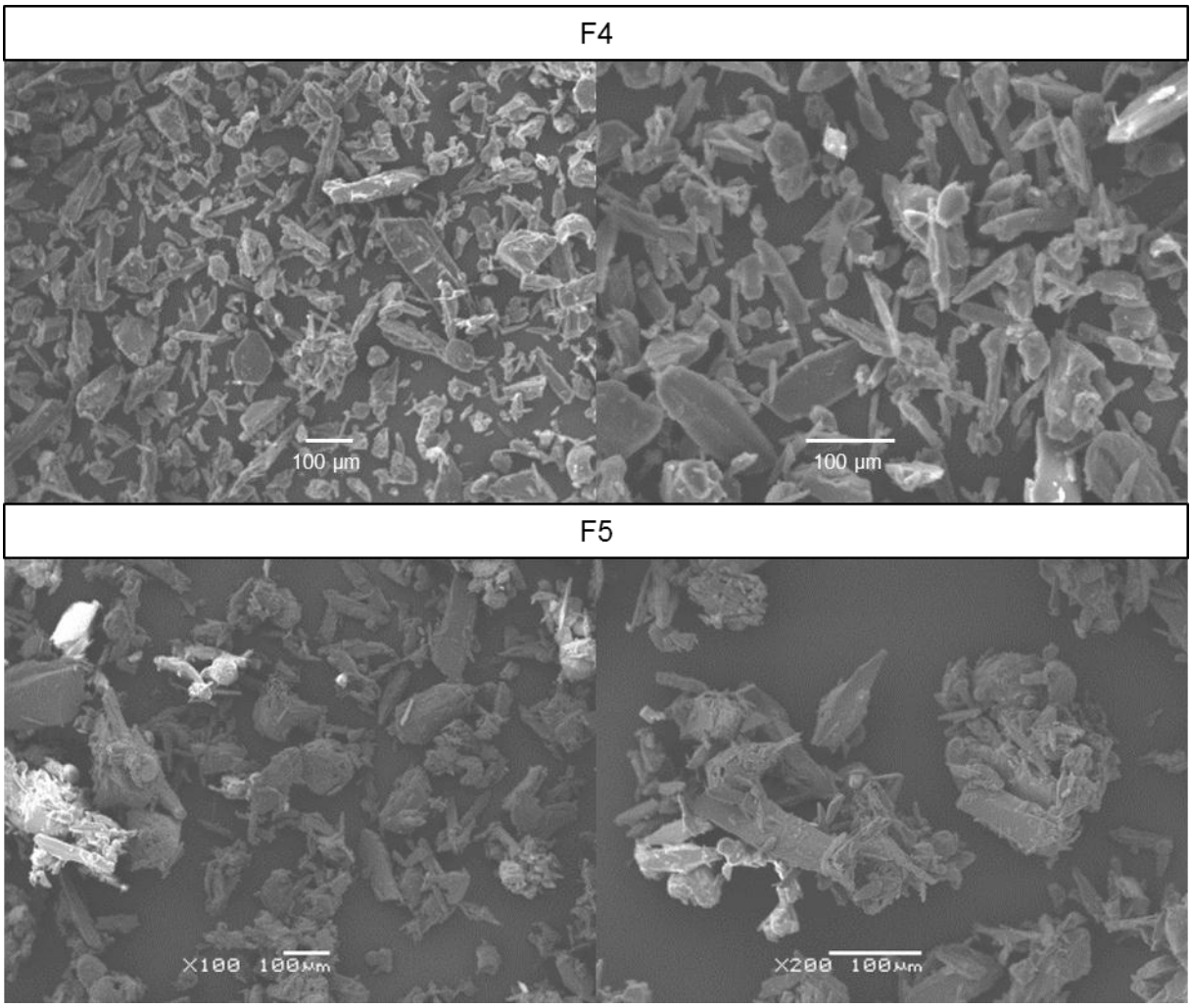

Figure 9. SEM images of coprocessed samples F4 and F5.

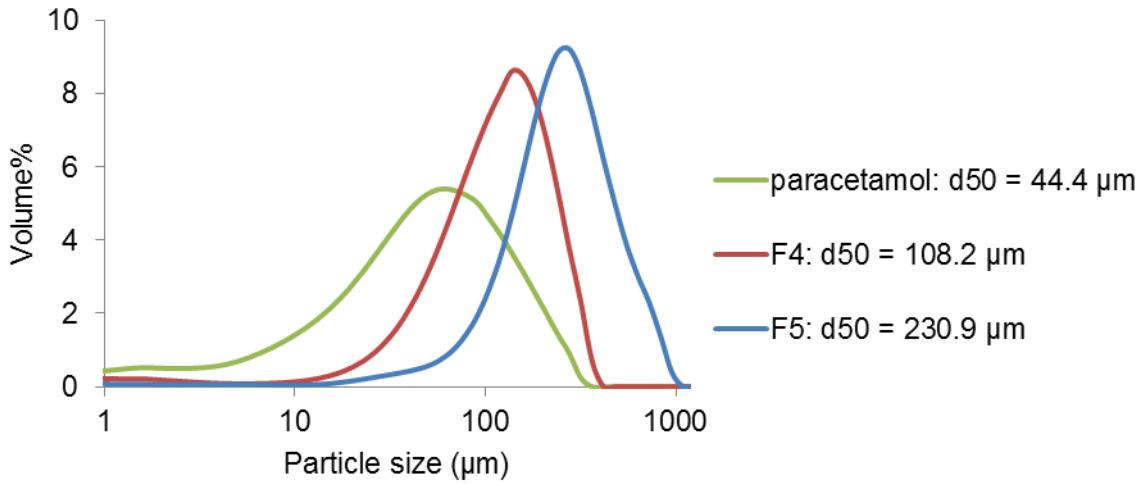

Figure 10. Particle size distribution of paracetamol starting material and coprocessed samples F4 and F5.

The tabletability of the coprocessed samples (F4 and F5) was compared to the tabletability of physical mixtures (PM3 and PM4) with the same composition (Figure 11). The tabletability of coprocessed sample F4 was slightly but significantly better than of its physical mixture PM4. In contrast, the tabletability of coprocessed sample F5 was clearly superior to the tabletability of physical mixture PM3: the TS of PM3 tablets was 0.9 MPa at a MCP of 300 MPa, whereas F5 tablets yielded a TS of 2.1 MPa. This demonstrated the added value of the applied coprocessing method which is due to the coating of paracetamol crystals with δ-mannitol and PVP.

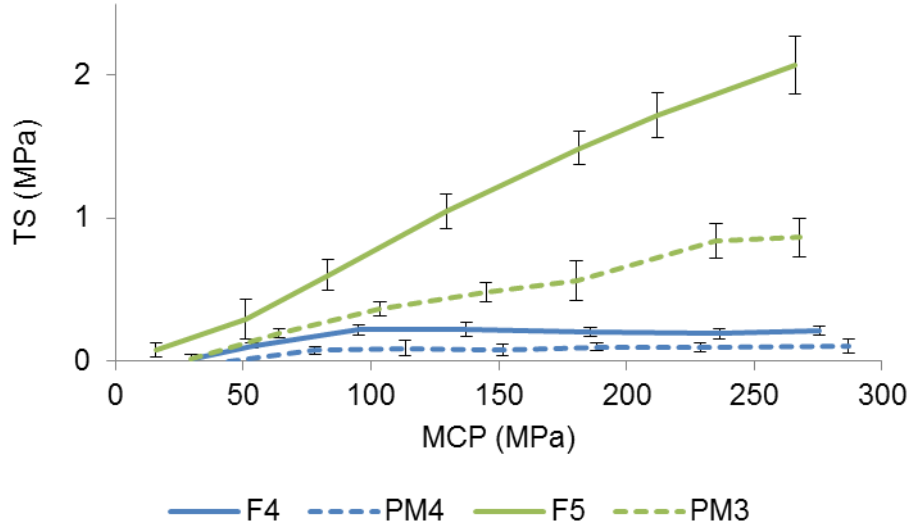

Figure 11. Tabletability of coprocessed samples F4 and F5 and corresponding physical mixtures PM4 and PM3.

While the tablet friability of coprocessed sample F4 (30.5%) and the corresponding physical mixture PM4 (46.8%), which contained 25% β-mannitol and 75% paracetamol, was too high, the friability of the coprocessed sample F5, formulated with 5% PVP, 20% δ-mannitol and 5% paracetamol was excellent (0.5%) and considerably lower than of the corresponding physical mixture PM3 (3.0%) which again illustrated the added value of the coprocessing method.

Stability of the spray dried samples

It is well known that thermodynamically unstable polymorphs can convert over time to a more stable crystal form. As the δ-polymorph is not the thermodynamically stable crystal form of mannitol at ambient conditions, the physical stability of the spray dried samples (F1-3) stored in open cups at 60% relative humidity and 25 °C during 6 months was investigated by Raman spectroscopy [8]. No spectral differences were detected after storage which indicated stability of all mannitol polymorphs over at least 6 months. Kinetic stability of α- and δ-

mannitol was also proven by Burger et al. during mechanical stress and storage for over five years at 25 °C at a relative humidity of 43% [8].

CONCLUSIONS

Spray drying an aqueous solution of mannitol and PVP (mannitol:PVP 4:1) resulted in formation of δ-mannitol which exhibited excellent tabletability and friability in comparison to α- and β-mannitol. Spray drying at higher outlet temperature resulted in higher process yield but negatively affected the purity of the spray dried sample as traces of α-mannitol were present next to δ-mannitol. Inclusion of PVP in the spray dried mannitol solution positively influenced the flowability since the resulting agglomerates were larger.

Additionally, a coprocessing method was applied for the production of δ-mannitol in a continuous way by spray drying aqueous solutions of mannitol and PVP and to agglomerate these particles with paracetamol crystals in the same process. The tabletability and friability of the resulting particles was excellent which was attributed to the superior tabletability of δ-mannitol over α- and β-mannitol and to the application of the coprocessing method which enabled coating of paracetamol crystals with δ-mannitol and PVP.

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4

IMPROVED TABLETABILITY AFTER A POLYMORPHIC TRANSITION OF DELTA-MANNITOL DURING TWIN SCREW GRANULATION

Parts of this chapter are published in:

V. Vanhoorne, B. Bekaert, E. Peeters, T. De Beer, J. P. Remon, C. Vervaet, Improved tabletability after a polymorphic transition of delta-mannitol during twin screw granulation, Int. J. Pharm. 506 (2016) 13-24.

Abstract

In most formulations processed via continuous twin screw granulation microcrystalline cellulose (MCC) and/or lactose are used as excipients, but mannitol is also a preferred excipient for wet granulation and tableting due to its non-hygroscopicity and inertness. Therefore, the aim of the current study was to investigate the influence of process parameters on critical quality attributes of granules (moisture content, solid state, morphology, size distribution, specific surface area, friability, flowability and hygroscopicity) and tablets (tensile strength and friability) after twin screw granulation of δ-mannitol. The δ-polymorph was selected since a moisture-induced transformation to β-mannitol was observed during batch wet granulation, which exhibited a unique morphology with a large surface area and improved tabletability. A full factorial experimental design was performed, varying screw speed (400 - 900 rpm), granulation temperature (25 - 40 °C), number of kneading elements (6 or 12) and liquid-to-solid (L/S) ratio (0.08 – 0.16), on the granulation unit of a ConsiGma^{TM}-25 line (a continuous powder-to-tablet manufacturing system). After tray drying the granules were milled and tableted. The results showed that the polymorphic transition from δ- to β-mannitol also occurred during twin screw granulation, although the residence time and L/S ratios were much lower in continuous twin screw granulation compared to batch processing. However, the polymorphic transition was not complete in all experiments and depended on the L/S ratio, screw speed and number of kneading elements. Nevertheless all granules exhibited the unique morphology linked to the polymorphic transition and had a superior tabletability compared to granules produced with β-mannitol as starting material. This was attributed to enhanced plastic deformation of the granules manufactured using δ-mannitol as starting material. In addition, it was concluded that mannitol was granulated via a different mechanism than other, less-soluble, excipients (e.g. lactose, microcrystalline cellulose) due to its high solubility and dissolution rate as the influence of process parameters on the mannitol granule characteristics was different.

KEYWORDS: δ-mannitol, Polymorphism, Tabletability, Continuous production, Twin screw granulation, Plastic deformability

INTRODUCTION

The interest in twin screw granulation is growing as it is a continuous process that can be implemented into a fully continuous from-powder-to-tablet line. This concept offers economic advantages, improved product quality and a lower environmental impact of processing [1, 2, 3]. Moreover regulatory authorities recently recognized the potential of continuous manufacturing and encouraged adoption of it by the pharmaceutical industry [4].

Only a limited number of studies on twin screw granulation addressed formulation development while most studies focused on the influence of process parameters on granule quality [5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20]. Moreover, most studies used formulations with lactose or microcrystalline cellulose as fillers. Mannitol is a preferred excipient for the formulation of tablets due to its non-hygroscopic character, compatibility with primary amines, high sweetness, cooling mouth sensation, high solubility and fast disintegration [21, 22, 23, 24]. Although it is a frequently used tablet diluent in the nutraceutical and pharmaceutical industry, no literature reports about the use of mannitol as an excipient during twin screw granulation are available [23].

Three polymorphs of mannitol have been described: α-, β- and δ-mannitol. However, most commercially available mannitol grades consist of α- or β-mannitol or mixtures thereof. During high shear granulation of δ-mannitol a moisture mediated polymorphic transition from δ- to β-mannitol was reported which resulted in a unique granule morphology with a high specific surface area and enhanced plastic deformability [22]. As a result the δ-polymorph of mannitol (commercialized as Parteck Delta M by Merck) is specifically promoted for wet granulation processes to take advantage of the improved tableting properties associated with the moisture-induced polymorphic transition from δ- to β-mannitol during wet granulation [25].

It was our aim to use δ-mannitol during a continuous wet granulation process using a twin screw granulator and to evaluate how process parameters (number of kneading elements, granulation temperature, screw speed, liquid-to solid (L/S) ratio) affected the critical quality attributes of granules and tablets. In addition, it was investigated if the polymorphic transition from δ- to β-mannitol, which has only been reported during batch high shear granulation, also occurred during twin screw granulation and whether this transition depended on process parameters as the residence time as well as the liquid content during twin-screw granulation are considerably lower compared to batch granulation processes [6, 14, 17, 19, 26, 27, 28, 29].

MATERIALS AND METHODS

Materials

δ-mannitol (Parteck® Delta M), β-mannitol (C*PharmMannidex) and α-mannitol (Pearlitol 200) were kindly donated by Merck Millipore (Darmstadt, Germany), Cargill Italy (Castelmassa, Italy) and Cargill Belgium (Vilvoorde, Belgium), respectively. These samples were used as reference materials. Distilled water was used as granulation liquid. Magnesium stearate (Fagron, Waregem, Belgium) was used as lubricant for tableting. Raman spectra of reference materials of α-, β- and δ-mannitol were adopted from De Beer et al. [30].

Preparation of granules

Pure β- or δ-mannitol was added to the loss-in-weight feeder (KT20, K-Tron Soder, Niederlenz, Switzerland) of the ConsiGma™-25 system (GEA Pharma Systems Collette™, Wommelgem, Belgium). In this continuous oral solid dosage manufacturing line a twin screw granulator is directly connected to a six-segmented fluid bed dryer, a mill and finally a tablet press. The barrel of the twin screw granulator (length-to-diameter ratio 20:1) can be divided into a feed zone with conveying elements and a working zone where the powder is intensively mixed with granulation liquid by kneading elements. Water as granulation liquid was pumped into the barrel just before the first kneading element via a double liquid addition port, injecting granulation liquid on top of each screw. The equipment has a built-in torque gauge which monitors the torque at 1-second intervals. The torque values obtained after equilibrium of the process were averaged to give the overall torque during each run. A PT-100 temperature sensor was integrated in the working zone of the barrel and linked to a feedback control system which regulates the temperature in the barrel jacket and compensates for temperature increase during the process due to friction. As the aim of the study was to evaluate the polymorphic transition of δ-mannitol during granulation, the fluid bed dryer was not used to avoid interference of dynamic drying on the product properties. The granules were collected after the granulation unit and oven dried at 40 °C for 24 h until the moisture content (as measured by loss on drying (LOD)) was below 1%. After drying, 800 g of the granules was milled through a 1500 µm grater screen with square impeller at 900 rpm using the comill (U10, Quadro, Ontario, Canada) incorporated in the ConsiGma™-25 line.

Design of experiments

A full factorial experimental design (20 runs) including four process parameters was performed using pure δ-mannitol: L/S ratio (0.08 – 0.16), barrel temperature (25 – 40 °C),

screw speed (400 – 900 rpm), number of kneading elements (6 or 12). The throughput was fixed at 20 kg/h in all experiments. The screw configuration with 6 kneading elements consisted of 1 block of kneading elements whereas the screw configuration with 12 kneading elements consisted of 2 kneading zones of 6 kneading elements (2x6) separated by a conveying zone. Reference is made to these configurations as 1x6 and 2x6, respectively. For both screw configurations the distance between liquid addition and the first kneading element was kept constant. Two center points (with screw configurations 1x6 and 2x6) were run in duplicate. An overview of the experiments is given in Table 1. The results were analyzed using Modde 10.1 (Umetrics, Umeå, Sweden) software. As the applied design was a full factorial design, interactions could be detected. However, the statistically non-significant interactions were not shown in the effect plots throughout the paper. Additionally two granulation experiments (runs 21 and 22) were performed with pure β-mannitol to allow comparison with the granules prepared with pure δ-mannitol (Table 1).

Run	L/S ratio	Temperature (°C)	Screw speed	Number of kneading elements	Starting material
1	0.12	32.5	650	12	δ-mannitol
2	0.08	40	900	12	δ-mannitol
3	0.08	40	400	12	δ-mannitol
4	0.08	25	400	12	δ-mannitol
5	0.08	25	900	12	δ-mannitol
6	0.16	25	900	12	δ-mannitol
7	0.16	25	400	12	δ-mannitol
8	0.16	40	400	12	δ-mannitol
9	0.16	40	900	12	δ-mannitol
10	0.12	32.5	650	12	δ-mannitol
11	0.12	32.5	650	6	δ-mannitol
12	0.08	25	400	6	δ-mannitol
13	0.08	25	900	6	δ-mannitol
14	0.16	25	400	6	δ-mannitol
15	0.16	25	900	6	δ-mannitol
16	0.16	40	900	6	δ-mannitol
17	0.16	40	400	6	δ-mannitol
18	0.08	40	400	6	δ-mannitol
19	0.08	40	900	6	δ-mannitol
20	0.12	32.5	650	6	δ-mannitol
21	0.16	25	400	12	β-mannitol
22	0.08	25	900	6	β-mannitol

Table 1. Overview of the granulation experiments.

Preparation of tablets

The milled granules (runs 1 - 22) and β- and δ-mannitol starting material were blended with 1.5% magnesium stearate in a tumbling blender for 3 minutes (T2F, W.A. Bachofen, Basel, Switzerland) before tableting. Tablets were prepared in manual mode at a speed of 20 tablets per minute on the Modul^{TM} P tablet press (GEA Pharma Systems Courtoy^{TM}, Halle, Belgium) part of the ConsiGma^{TM}-25 line.

The press was equipped with 1 pair of round flat-faced Euro B punches (GEA Pharma Systems, Halle, Belgium) (diameter 10 mm) and an overfill cam of 12 mm. A single-paddle feed frame equipped with a paddle with round thin fingers (n = 8) rotating counter-clockwise at 20 rotations per minute (rpm) (GEA Pharma Systems, Halle, Belgium) was used. This setup allowed producing tablets on a rotary press with a minimal amount of granules (± 50 g). Tablets (320 mg ± 20 mg) were compressed at 3 different main compression pressures (MCP): 150, 250 and 350 MPa, for assessment of their tabletability. Tablets compressed at 350 MPa were selected for friability testing.

To elucidate the bonding mechanisms during compression, tableting experiments were performed with monitoring of punch stroke movements by linear variable displacement transducers clamped on the pair of punches (GEA Pharma Systems, Halle, Belgium). Data from these sensors was acquired continuously and transmitted wireless to a data acquisition and data analysis system (CDAAS, GEA Pharma Systems, Halle, Belgium). The CDAAS system measured signals (pre- and main compression force and displacement, punch strokes) and allowed reviewing and analysis of the recorded data. From the punch stroke signals, in-die elastic recovery (IER) and energy plots were calculated. For each formulation the punch stroke movements were monitored during compression at 150 MPa.

Evaluation of the granules

Loss-on-drying

The residual moisture content of the granules was determined via LOD using a moisture analyzer (Mettler LP16, Mettler-Toledo, Zaventem, Belgium) including an infrared dryer and a balance. A sample of 5 g was dried at 105 °C until the weight was constant for 30 s.

Solid state characterization

Raman spectra (Rxn1, Kaiser Optical Systems, Ann Arbor, USA) of the reference materials, unmilled (runs 1 – 22) and milled granules (runs 1 – 20) were recorded using exposure times of 10 s with 3 accumulations. Additionally, unmilled granules were measured after 6 months storage at 40 °C and 75% relative humidity (RH) and at 25 °C and 40% RH in open cups. At least 5 spectra were recorded for each sample. For the tablets, one spectrum was collected at each compression pressure. A PLS model was constructed to determine the ratio of δ- and β-mannitol in the granulated samples (Simca 13.0.3 software, Umetrics, Umeå, Sweden). This model was developed from the Raman spectra (5 spectra for each calibration sample) of calibration samples (i.e., powder mixtures) with a ratio of δ-mannitol:β-mannitol varying between 0 - 100% with increments of 10%. Data were corrected by standard normal variate preprocessing and center-scaled prior to analysis. Standard Normal Variate preprocessing was applied to eliminate the additive baseline offset variations and multiplicative scaling effects in the spectra which may be caused by small variations in distance between the Raman probe and the sample and possible differences in product density. The results of the PLS analysis were averaged for each sample.

Additionally, XRD was performed on the reference materials and unmilled granules on a CuKα diffractor (ARL^{TM} X'TRA, Thermo Fischer Scientific, Waltham, United States) with a voltage of 40 mV in the angular range of $8° < 2\theta < 60°$ using a step scan mode with step size of 0.02° and counting time of 1 s / step.

Morphology

The unmilled granules and reference materials of β- and δ-mannitol were examined by scanning electron microscopy (SEM) (FEI QuantaTM 200F, FEI, Hillsboro, USA) after sputtering with a gold coating (Emitech SC7620, Quorum Technologies, East Grinstead, UK) to improve the electron conductivity of the samples.

Particle size analysis

Granule size was analyzed before and after milling via dynamic image analysis using the QICPIC^{TM} system (Sympatec, Clausthal-Zellerfeld, Germany) equipped with a vibrating feeder system (Vibri/L^{TM}) for gravimetrical feeding of the granules. Samples of 20 g were measured in duplicate. Windox 5 software (Sympatec, Clausthal-Zellerfeld, Germany) was used to calculate the median granule size (d_{50}) as the equivalent projected circle diameter based on a volume distribution. The amounts of fines and oversized granules were defined

as the fractions <150 µm and >1500 µm, respectively. The yield of the process was defined as the percentage of granules between 150 and 1500 µm.

Flowability testing

The flowability expressed as the flowability index (ffc) of the milled granules was measured in duplicate by ring shear testing (Type RST-XS, Dietmar Schulze Schüttgutmesstechnik, Wolfenbuttel, Germany). The powders were tested using three consolidation stresses, 400, 600 and 800 Pa, at a preshear of 1000 Pa.

Additionally, the compressibility index (C%) was calculated from the bulk and tapped densities of the milled granules. The bulk volume (V_0) of 30 g milled granules was measured in a 100 ml graduated cylinder as well as the tapped volume after 1250 taps (V_{1250}) in a tapping machine (J. Englesman, Ludwigshafen, Germany). Experiments were performed in duplicate. Bulk and tapped densities were calculated as 30 g/V_0 and 30 g/V_{1250}, respectively. The compressibility index was calculated from the bulk (ρ_i) and tapped (ρ_f) densities using the following equation: $C\% = [(\rho_f - \rho_i)/ \rho_f]*100$.

Friability testing

The granule friability was determined in duplicate using a friabilator (PTF E Pharma Test, Hainburg, Germany) at a speed of 25 rpm for 10 min, by subjecting 10 g (I_{wt}) of milled granules together with 200 glass beads (mean diameter 4 mm) to falling shocks. Prior to determination, the granule fraction <250 µm was removed to assure the same starting conditions. Afterwards, the glass beads were removed and the weight retained on a 250 µm sieve (F_{wt}) was determined. The friability was calculated as $[(I_{wt} – F_{wt})/I_{wt}]*100$.

Dynamic vapor sorption (DVS)

Dynamic vapor sorption (DVS Advantage, Surface Measurement Systems, Middlesex, UK) was used to assess the overall hygroscopicity of the materials. Approximately 10 – 20 mg of unmilled sample was placed into the instrument's microbalance and dried by a stream of dry nitrogen at 25 °C until equilibrium (i.e. a weight change of less than 0.002% per min during at least 15 min). The samples were subsequently exposed to varying RH, 0, 20, 40, 60, 80, 90 and 95% and equilibrated at each interval. Sorption and desorption of the samples were recorded at these RH conditions.

Specific surface area analysis

Nitrogen adsorption measurements were performed at 77 K on a selection of unmilled granules and β- and δ-mannitol reference material using a TriStar 3000 gas sorption apparatus (Micromeritics Inc., Norcross, USA). The specific surface area of the powder samples was determined from the adsorption isotherm using the Brunauer-Emmett-Teller–theory.

Evaluation of the tablets

The hardness, thickness and diameter of the tablets (n = 10) were determined using a hardness tester (Type HT 10, Sotax, Basel, Switzerland) and the tensile strength (TS) of the tablets was calculated according to the formula of Fell and Newton [31]:

$$T = 2F/\pi dt$$

Where F, d and t denote the diametral crushing force, tablet diameter and tablet thickness, respectively.

The tablet friability was determined using a friabilator (PTFE, Pharma Test, Hainburg, Germany) as described in the European Pharmacopeia at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

Energy plots were calculated based on the punch stroke movements. In the energy plot the punch stroke is plotted against the compression force. An example of an energy plot is shown in Figure 1 where B is the punch stroke when the punch force is zero, C is the punch stroke when the punch force is maximal (A) and D is punch stroke after decompression when punch force is zero again. The areas of ABC, ABD and ADC show the total compression energy, plastic energy and elastic energy, respectively [22]. Based on the energy plot, the plasticity constant (PLC) was calculated as: plastic energy/total compression energy*100. This parameter expresses the plasticity of a material under deformation.

The in-die elastic recovery (IER) was calculated using the Armstrong and Haines-Nutt equation:

$$IER = (T_a - T_{id}) / T_{id} * 100$$

where T_a denotes the tablet height immediately after ejection and T_{id} the tablet height under maximum compression force [32].

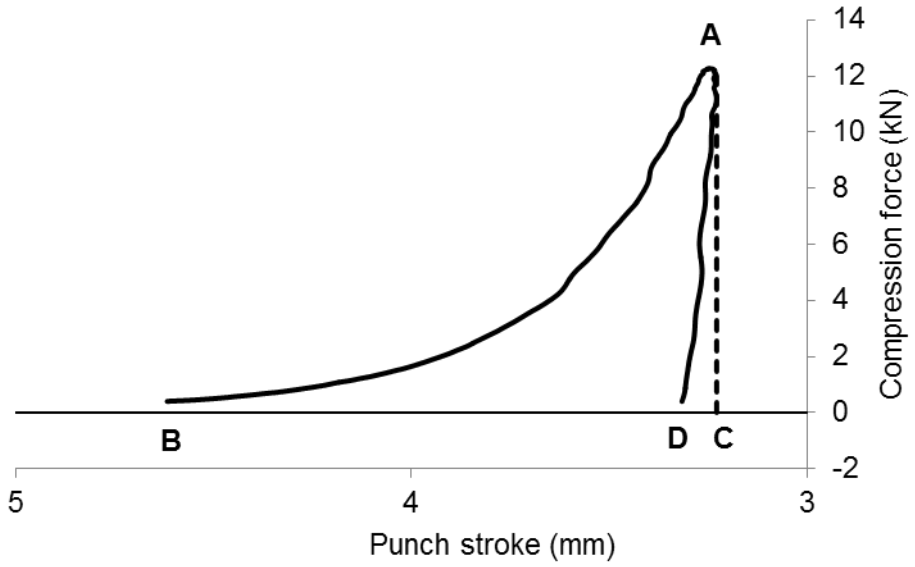

Figure 1. Energy plot of punch stroke against compression force for β-mannitol reference material compressed at 150 MPa.

RESULTS AND DISCUSSION

Although mannitol is a preferred excipient for wet granulation and tableting, its behavior during twin screw granulation was not studied yet. In contrast to frequently used excipients during twin screw granulation (lactose, MCC), mannitol exhibits a high solubility and solubility rate. Therefore mannitol was expected to behave differently during granulation. Moreover polymorphic transitions are possible during recrystallization of mannitol. Such transition of δ- to β-mannitol was reported during high shear granulation and promoted the tabletability of the granules. An experimental design was performed to investigate the influence of four process parameters on the process and critical quality attributes of mannitol granules and tablets.

Evaluation of the granulation process

The torque varied strongly across all experiments. Torque values as low as 0.9 - 1.0 Nm (runs 13 and 19) were recorded, whereas in runs 7 and 8 the torque exceeded 20 Nm, the maximal torque tolerated by the granulator. These runs were conducted with 12 kneading elements, at a low screw speed and using a high L/S ratio. Run 7 was excluded from the design as no material could be collected. During run 8 a limited amount of granules was collected after equilibration which allowed solid state characterization and size and shape analysis but no further characterization. A torque value of 20 Nm was assigned to this run in

the experimental design. The influence of the granulation parameters on torque is shown in the effect plot in Figure 2.

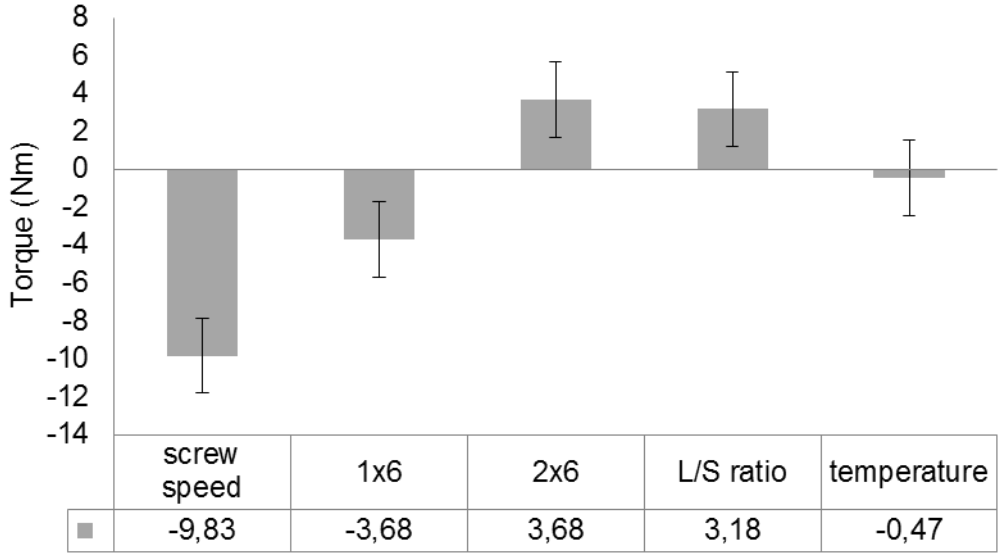

Figure 2. Effect plot showing the influence of the process parameters on torque.

The screw speed, which was varied over a broad range of 400 - 900 rpm in the current study, proved the major factor affecting torque. Since the throughput was constant in all experiments, increasing the screw speed resulted in a lower filling degree of the barrel which in turn yielded lower torque values. This is in accordance with research from Kumar et al., Tan et al., Tu et al. and Keleb et al. (on formulations with mainly lactose, microcrystalline cellulose (MCC) or paracetamol), but is opposed to the report of Vercruysse et al. (on a formulation with lactose and theophylline) stating that screw speed did not influence torque [5, 7, 17, 26, 29]. The influence of screw speed on torque is possibly formulation dependent, but could also be more prominent at lower screw speeds (and consequently higher filling degrees) since the research of Kumar et al. (500 - 900 rpm), Tan et al. (100 - 150 rpm) and current study (400 - 900 rpm) were conducted at lower screw speeds than the study of Vercruysse et al. (600 - 950 rpm).

Increasing the L/S ratio resulted in higher torque values. This is in agreement with research of Dhenge et al. (on a formulation with mainly lactose and MCC) who reported that a higher L/S ratio prolonged the residence time in the barrel as the material behaved like paste [27]. However, an inverse relationship between L/S ratio and torque was established by Tan et al. and Kumar et al. (on formulations with mainly paracetamol and lactose, respectively) [6, 17]. They explained that at a higher L/S ratio the material was more malleable, thus requiring less energy to deform and compress [17]. Finally, Tu et al. reported (on a formulation with MCC) that the torque increased until a critical L/S ratio was reached and then decreased with

formation of over-wetted particles. The effect of the L/S ratio on torque appears again formulation dependent.

A higher number of kneading elements resulted in higher torque values due to the retaining character of the kneading elements causing more friction. Additionally, more mannitol could go into solution and participate in bond formation which could increase the torque. Varying the granulation temperature did not have a significant effect on torque.

Influence of the design variables on granule quality

Solid state characterization

Raman spectra of the unmilled and milled granules were compared to reference spectra of α-, β- and δ-mannitol. The data showed that a polymorphic transition occurred from δ- to β-mannitol during twin screw granulation, similar to the observations of Yoshinari et al. for batch granulation [22]. This is noteworthy since the residence time during twin screw granulation is short, typically 5 - 20 s, compared to batch granulation where granulation times are in the order of tens of minutes [6, 19, 26, 27]. Moreover, Keleb et al., Beer et al. and Tan et al. demonstrated that lower L/S ratios are used in twin screw granulation in comparison to batch granulation [17, 28, 29]. The L/S ratio that could be applied during granulation in the current study varied between 0.08 and 0.16, whereas Yoshinari et al. used an L/S ratio of 0.25 during batch granulation [22]. However, the polymorphic transition was not complete in all samples of current study. Therefore a PLS model was constructed to quantify the percentage of δ-mannitol left in the samples. The model gave a rough quantitative estimation of the composition of the samples since its root mean square error of cross validation (RMSECV) was relatively high (8.15). As β- and δ-mannitol particles where physically mixed in the PLS calibration samples, the variability on the spectra of these samples was higher than of the measured granules (where β- and δ-mannitol are homogeneously mixed during granulation), resulting in a model with a high RMSECV value. An overview of the percentage δ-mannitol in the granulated samples before and after milling is presented in Table 2 and it is clear that milling did not change the polymorphic content of the samples. Stability of δ-mannitol, although thermodynamically the least stable mannitol polymorph, under mechanical stress was also demonstrated by Burger et al. [34].

Run	% δ-mannitol before milling	% δ-mannitol after milling	% δ-mannitol after 6 months at 25 °C and 40% RH	% δ-mannitol after 6 months at 40 °C and 75% RH	Moisture content at 95% RH (%)	Specific surface area (m^2/g)
1	10	7	6	7	1.87	-[c]
2	14	12	9	9	1.54	-[c]
3	9	9	6	7	1.84	-[c]
4	10	9	7	6	1.84	1.7620
5	23	26	26	12	2.08	-[c]
6	8	8	5	6	1.81	-[c]
7	-[a]	-[a]	-[a]	-[a]	-[a]	-[c]
8	6	-[b]	3	6	-[c]	-[c]
9	7	5	4	6	1.74	1.4312
10	9	6	4	6	1.80	1.1167
11	14	10	8	9	1.18	-[c]
12	15	16	11	10	1.27	-[c]
13	31	28	24	13	0.87	-[c]
14	8	8	4	6	1.83	-[c]
15	15	13	10	10	1.57	-[c]
16	13	9	10	11	1.48	-[c]
17	9	8	6	6	1.83	1.0907
18	19	20	15	10	1.40	2.4289
19	45	40	39	13	1.34	1.7945
20	13	14	10	10	1.33	2.0907
21	6	-[d]	4	-[c]	0.43	-[c]
22	6	-[d]	4	-[c]	0.56	0.2346
β-mannitol reference	-[c]	-[c]	-[c]	-[c]	0.26	0.1355
δ-mannitol reference	-[c]	-[c]	-[c]	-[c]	0.60	0.5169

[a]Run 7 was eliminated from the experimental design because of too high torque values immediately after start-up.
[b]The amount of granules collected was too limited to mill the samples.
[c]No data collected.

Table 2. Overview of the percentage δ-mannitol in the unmilled and milled granules and unmilled granules after 6 months storage (25 °C and 40% RH or 40 °C and 75% RH), the maximal moisture content absorbed during DVS analysis and the specific surface area.

These results were also included as responses in the experimental design to investigate the influence of the process parameters on the polymorphic transition from δ- to β-mannitol. The corresponding effect plots showed that the L/S ratio, screw speed and number of kneading elements influenced the polymorphic transition during granulation and confirmed that milling did not significantly influence the polymorphic content (Figure 3).

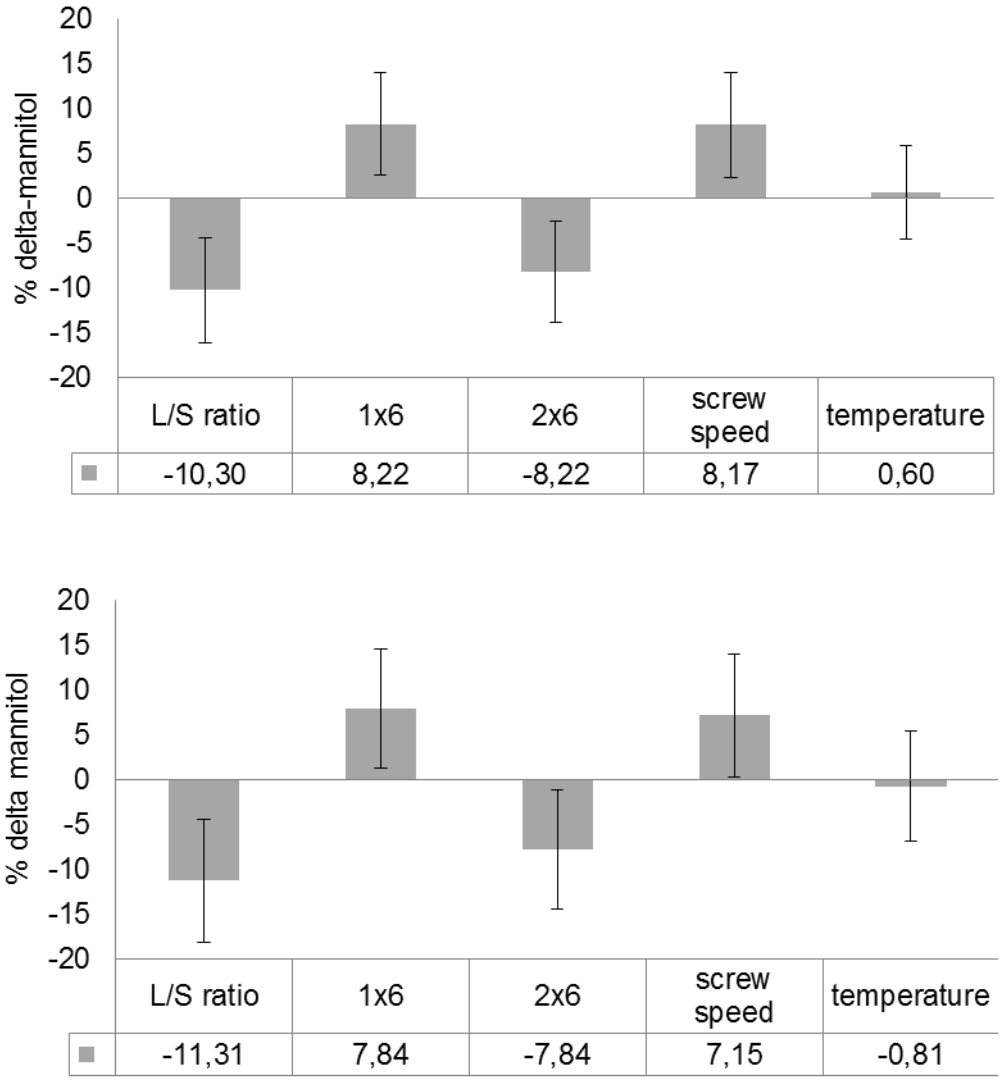

Figure 3. Effect plot showing the influence of the process parameters on the percentage residual δ-mannitol in the granules before (top) and after milling (bottom).

The L/S ratio was the strongest influencing process parameter as more mannitol could go into solution at higher L/S ratios which favored recrystallization to the β-polymorph [35]. Increasing the screw speed resulted in more residual δ-mannitol in the samples as it shortened the residence time and consequently also the duration of granulation during which the polymorphic transition could occur. Mixing of mannitol and water induced by the kneading

elements also affected the polymorphic composition of the granulated samples. More kneading elements resulted in more β-mannitol as more mixing promoted mannitol to go into solution. Run 8, which was performed with a high L/S ratio, low screw speed and 12 kneading elements, yielded the sample with the lowest fraction of residual δ-mannitol. However, combining these process parameters was not feasible because of too high torque. In the section on tablet quality it will be investigated if complete transition of δ- to β-mannitol is necessary to obtain improved tablet properties.

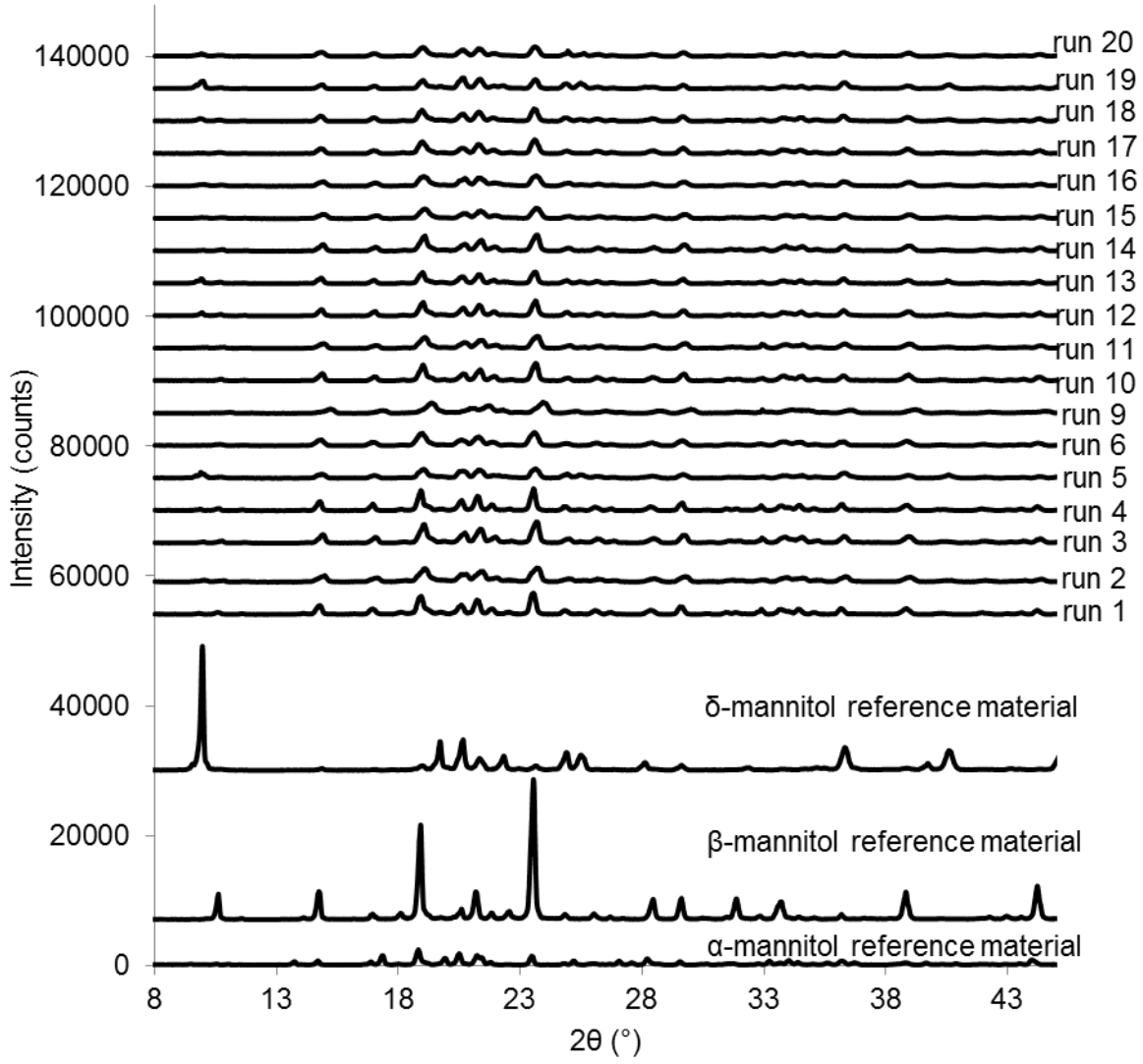

Figure 4. XRD patterns of reference material of α-, β- and δ-mannitol and runs 1-20.

The results of the Raman analysis were confirmed by XRD measurements (Figure 4). β-mannitol was identified in all samples by its unique peak at 14.74°. Moreover, a small peak at 9.90°, selective for δ-mannitol, in the diffractograms of runs 5, 12, 13, 18 and 19 indicated a significant residual percentage of δ-mannitol in these samples [21, 22, 30, 34, 36, 37]. The

overall lower intensity of the peaks in the diffractograms of the granules was attributed to a different crystal habit of the granules in comparison to the reference materials (powders) [38].

Morphology and specific surface analysis

SEM images of the granulated samples were compared to those of β- and δ-mannitol reference materials. The granules derived from δ-mannitol as starting material (e.g. runs 14 and 19) possessed a completely different morphology than the granules derived from β-mannitol (runs 21 and 22) and the reference materials of β- and δ-mannitol (Figure 5). They consisted of aggregates of many small needle-shaped primary crystals, similarly as described by Yoshinari et al. after a polymorphic transition from δ- to β-mannitol during high shear granulation [22, 35]. This specific morphology was observed in all granules derived from δ-mannitol and was not correlated to the percentage of residual δ-mannitol in the granules.

Yoshinari et al. also reported on a higher specific surface area associated with this specific surface morphology. Therefore, the specific surface area (SSA) of a selection of granules was determined (Table 2). The SSA of the granules derived from δ-mannitol was at least twice the SSA of δ-mannitol reference material, at least 8 times the SSA of β-mannitol reference material and at least 4 times the SSA of granules derived from β-mannitol. This confirmed the microscopic observations.

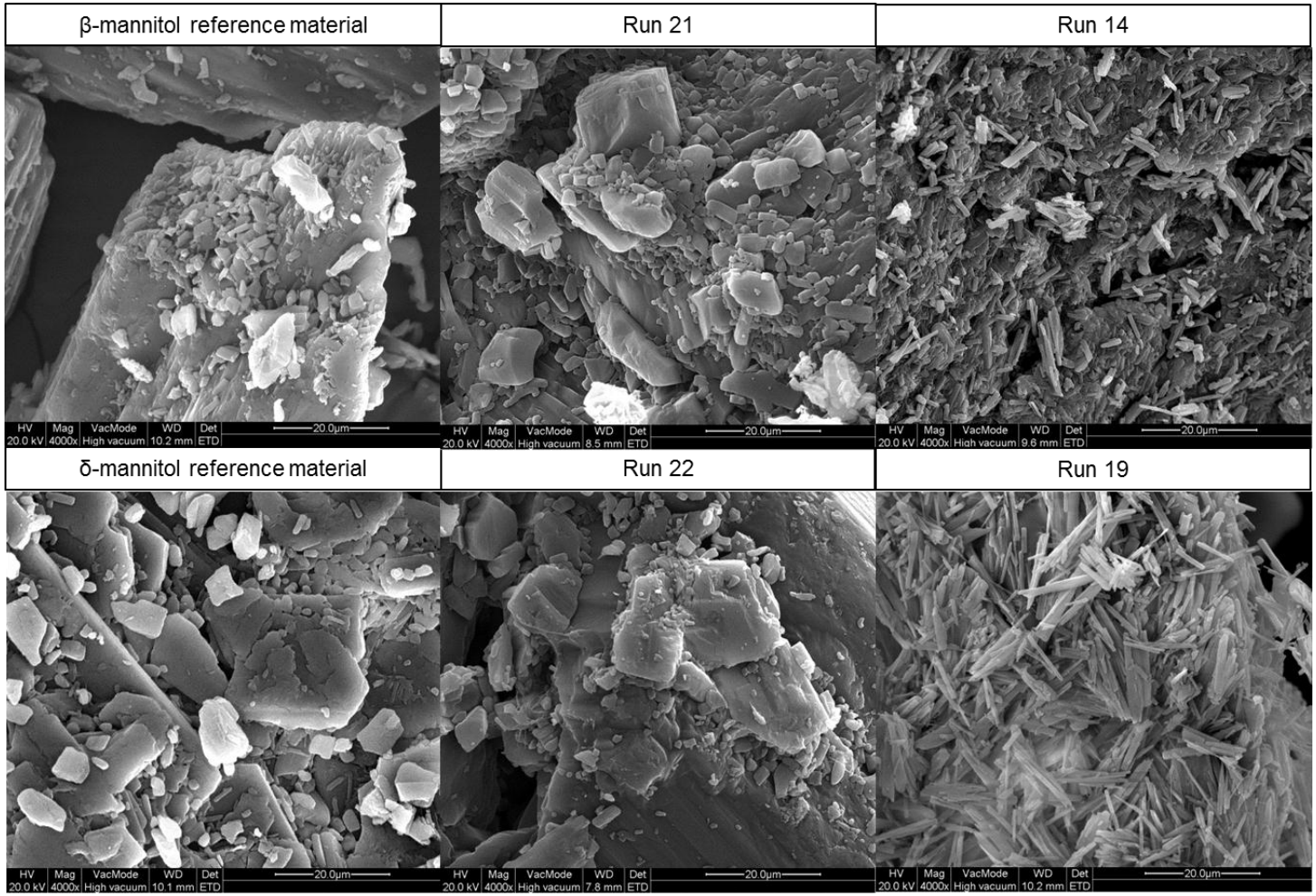

Figure 5. SEM images of β- and δ-mannitol reference material and representative samples of granulated β-mannitol (runs 21 and 22) and of granulated δ-mannitol (runs 14, 19).

Size analysis

The particle size distributions of granules before and after milling were determined. They were evaluated with regard to d_{50}, fines fraction (<150 µm), oversized fraction (>1500 µm) and yield (150 - 1500 µm).

A significant relationship between the L/S ratio and the d_{50}, fines fraction and oversized fraction was detected: by adding more water, more liquid and solid bonds were formed, resulting in a larger d_{50}, less fines and more oversized particles (Figure 6). This effect of L/S on particle size is generally recognized in literature [1, 5, 14, 19, 27].

A direct relationship was established between screw speed and the d_{50} and oversized fraction. This is in contrast to most literature reports (on a variety of formulations), indicating no correlation between screw speed and d_{50} [1, 7, 16, 17, 29] or an inverse relationship [1, 5, 8]. They attributed the larger particle size at lower screw speeds to higher torque values, resulting in higher compressive forces in the granulator barrel. However, it is clear from the effect plot in Figure 6 that the directly proportional relation was dominant for all size parameters in the current study. The solubility and the solubility rate of the formulation could be determining factors for the influence of screw speed on granule size. Pure mannitol was used as excipient in current study and has a higher solubility and solubility rate constant than most other commonly used excipients for twin screw granulation (lactose, MCC, active drug substances…) [1, 7, 8, 10, 12, 13, 17, 19, 20, 26, 27, 39, 40]. Whereas higher compressive forces at low screw speed generally favor granule growth with less soluble excipients, granulation of mannitol could be driven by its high and fast solubility, rather than by compressive forces. It can even be concluded that compressive forces at low screw speeds induce breakage of the mannitol granules due to collision and friction. Additionally, an interaction between screw speed and L/S ratio influenced the d_{50} and oversized fraction: the positive influence of screw speed on the d_{50} and oversized fraction was more pronounced at high L/S ratios. This is illustrated by the interaction plot in Figure 7.

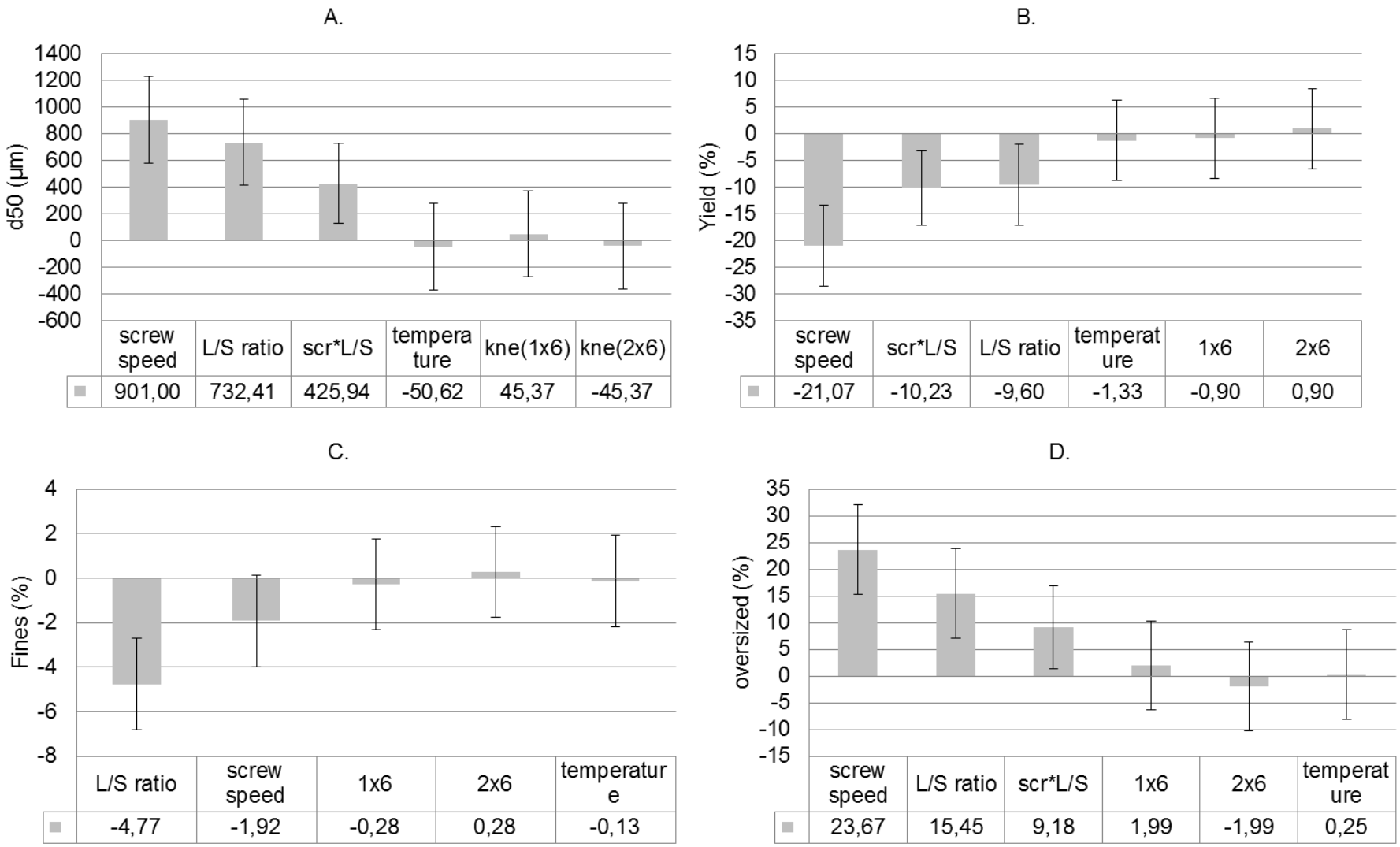

Figure 6. Effect plots visualizing the influence of the process parameters on d_{50} (A), yield (B), fines (C) and oversized fraction (D) of the granules before milling.

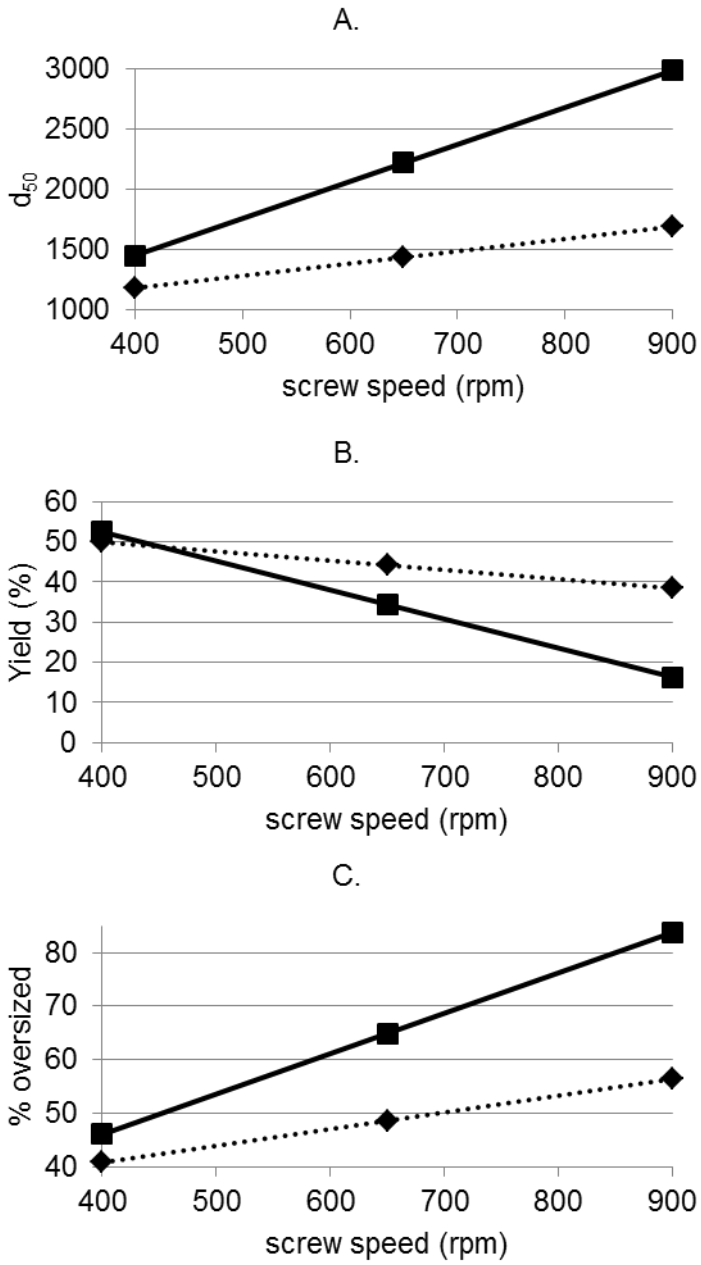

Figure 7. Interaction plots showing the combined effect of the L/S ratio (full line: L/S = 0.16 and dotted line: L/S = 0.08) and screw speed on the d_{50} (A), yield (B) and the fraction of oversized granules (C).

Although the torque was increased by a higher number of kneading elements, no influence of the number of kneading elements on the granule size distribution was detected (Figure 6). This is most remarkable since compaction of the powder mass takes place along the kneading zone and kneading elements favor mixing between the granulation liquid and the powder. Taking into account that the compressive forces at low screw speed due to a high filling degree of the granulator barrel did not favor granule growth either, this confirmed the hypothesis that granule growth of mannitol particles was not caused by compressive forces but rather by formation of liquid and solid bridges after crystallization of solubilized material.

The yield of the granulation process varied between 13 and 56% before milling and was strongly affected by a high oversized fraction (varying between 36 and 86%). Consequently, the process yield was inversely related to the screw speed and L/S ratio (Figure 6).

After milling with a grater screen of 1500 µm, the oversized fraction was eliminated but the fines fraction was generally larger. Nevertheless, the yield of particles suitable for tableting increased after milling and varied between 79 and 89%. No influence of the process parameters on fines and oversized fraction or yield was detected after milling. The d_{50} after milling was only influenced by the L/S ratio (Figure 8). No effect of the screw speed on d_{50} was observed since the oversized fraction, created at high screw speed, was eliminated by milling.

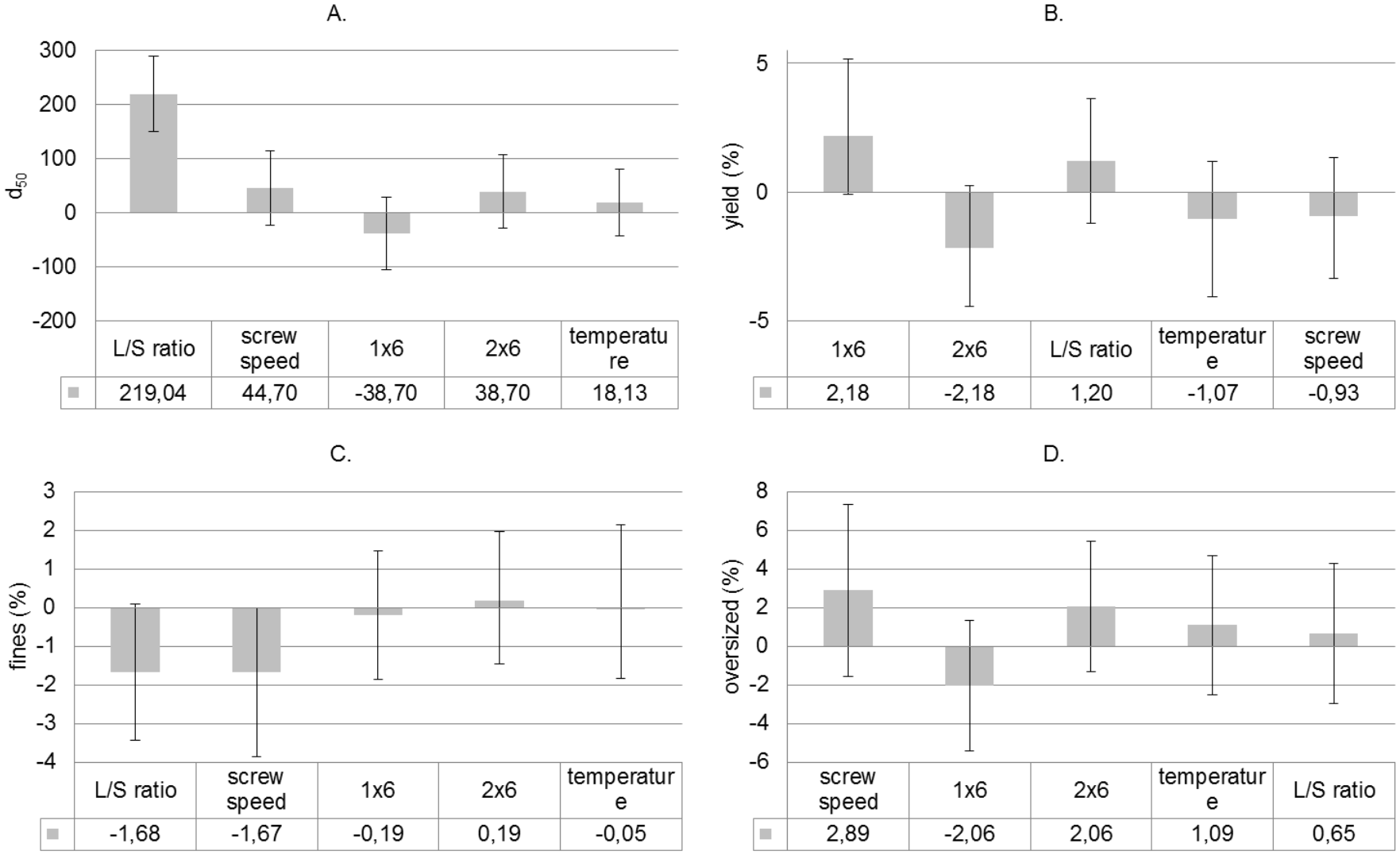

Figure 8. Effect plots visualizing the influence of the process parameters on d_{50} (A), yield (B), fines (C) and oversized fraction (D) of the granules after milling.

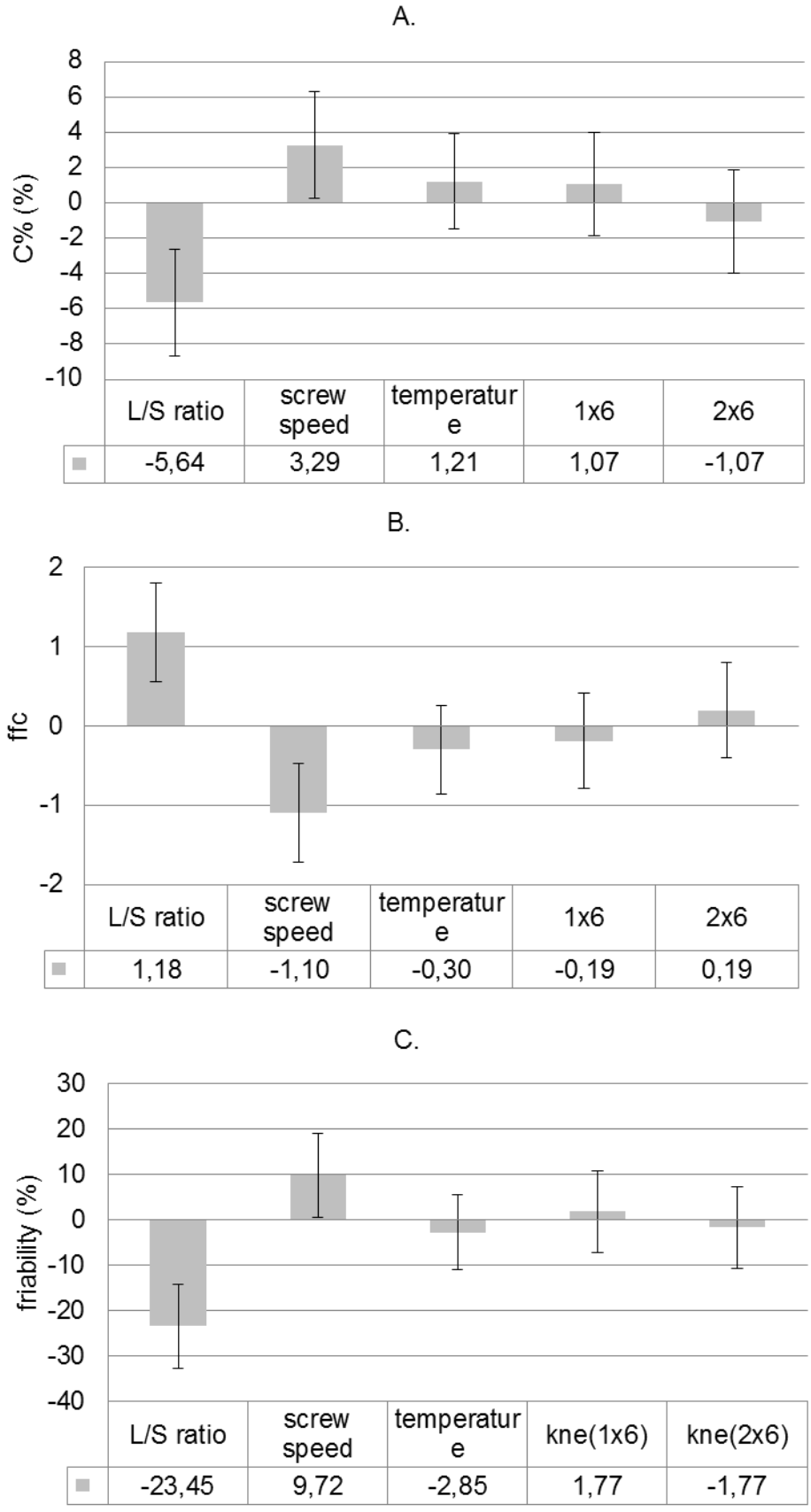

Figure 9. Effect plots visualizing the influence of the process parameters on compressibility index (C%) (A), flowability index (ffc) (B) and granule friability (C).

Flowability and friability

The compressibility index (C%) and flowability index (ffc) were influenced by the L/S ratio and screw speed (Figure 9). Increasing the L/S ratio resulted in higher d_{50} values of the milled granules and consequently yielded better flowing granules. Overall the granules were classified as very cohesive to easy flowing based on their ffc value, and as having a fair to excellent flowability based on the C% value [41].

The friability of the granules ranged from 6.1 to 50.5% and mainly depended on the L/S ratio. At higher L/S ratios more material dissolved in the granulation liquid which formed strong solid bridges after crystallization, resulting in less friable granules. The screw speed had a minor influence on the granule friability (Figure 9). Fewer compaction forces acted on the material at high screw speeds and consequently weaker bonds were formed inside the granules.

Dynamic vapor sorption

Mannitol is considered as a non-hygroscopic excipient [24, 35]. Nevertheless, the hygroscopicity of the granules was investigated by DVS analysis since a strong increase in specific surface area was microscopically observed. Sorption and desorption curves of β- and δ-mannitol starting material, granules derived from β-mannitol starting material (runs 21 and 22) and a selection of representative granules derived from δ-mannitol starting material (runs 14 and 19) are shown in Figure 10. The maximal moisture uptake of β- and δ-mannitol starting material and the granules derived from β-mannitol starting material did not exceed 0.60%, whereas the maximal moisture uptake of the granules derived from δ-mannitol starting material varied between 0.87 and 2.08% (Table 2). The maximal moisture uptake was linked to the percentage of residual δ-mannitol. Granules with a high percentage of residual δ-mannitol (e.g. run 19 in Figure 10) absorbed less moisture compared to samples where the polymorphic transition of δ- to β-mannitol was almost complete (e.g. run 14 in Figure 10). No significant difference in level of hysteresis between sorption and desorption was observed in the samples.

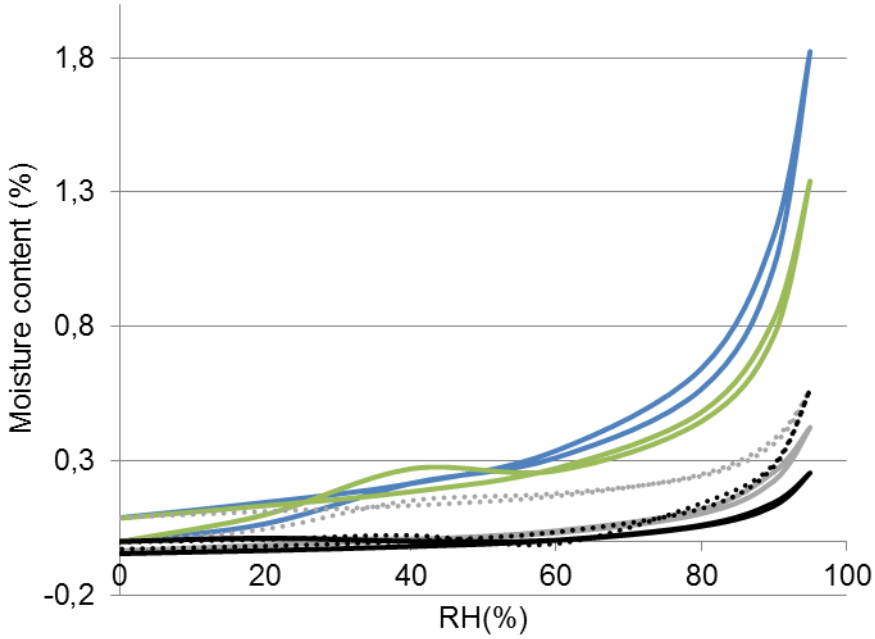

Figure 10. DVS sorption and desorption curves of β-mannitol (full black line) and δ-mannitol (dotted black line) reference material, granulated β-mannitol samples 21 (full grey line) and 22 (dotted grey line) and granulated δ-mannitol samples 14 (full blue line) and 19 (full green line).

Influence of the design variables on tablet quality

Tabletability and compression mechanism

The tensile strength (TS) of tablets produced with β- and δ-mannitol reference material and granules manufactured using β-mannitol was compared to the TS of tablets manufactured with granules using δ-mannitol as starting material (Figure 11). The tabletability of four samples (runs 2, 5, 13 and 19) was not investigated as they lacked sufficient flowability for tableting on a rotary tablet press. These samples were produced at low L/S ratios and at high screw speed, conditions that negatively influenced the flowability (Figure 9).

The tabletability of δ-mannitol reference material was significantly higher than of β-mannitol reference material, reaching a maximal TS of 2.1 MPa. Superior compaction properties of δ-mannitol were also reported by Burger et al., Wagner et al. and Vanhoorne et al. [23, 34, 42]. The TS of granules derived from β-mannitol starting material did not exceed 1.6 MPa and was independent of the applied MCP. However, the tabletability of all granules that used δ-mannitol as starting material underwent a transition to β-mannitol during granulation and their tabletability was significantly enhanced compared to the other tested materials. A linear relationship between MCP and TS was observed and maximal TS values of 4.2 - 5.7 MPa were obtained. This was attributed to the polymorphic transition from δ- to β-mannitol during

granulation resulting in granules with a specific morphology (aggregates of small needle-shaped primary crystals) and an increased specific surface area. Yoshinari et al. demonstrated that this unique particle structure resulted in enhanced plastic deformability and increased tabletability [22]. No correlation between the investigated properties (e.g. residual percentage of δ-mannitol) of granules derived from δ-mannitol and their tabletability was established. Therefore a full polymorphic transition from δ- to β-mannitol must not be pursued to obtain granules with improved tabletability and there is no optimum in the ratio of δ-:β-mannitol with regard to tabletability. This was in agreement with the microscopic observations and SSA measurements since the specific morphology (aggregates of small needle-shape primary crystals) and increased SSA were present in all granules derived from δ-mannitol, independently of the percentage residual δ-mannitol in the granules. It was therefore concluded that the specific granule morphology associated with the polymorphic transition was key to the improved tabletability. Moreover the process was considered to be robust since variation in the process parameters could not influence the tabletability.

The compression mechanism of the granules derived from β- and δ-mannitol was also investigated in the current study. Therefore the in-die elastic recovery (IER), plasticity constant (PLC) and the elastic energy were calculated based on the energy plots (Table 3). Based on IER and elastic energy, no difference in elastic behavior was detected between the mannitol granules and β- and δ-mannitol reference material. However, granules derived from δ-mannitol and δ-mannitol reference material exhibited higher plasticity constants than granules derived from β-mannitol or β-mannitol reference material. Therefore it was concluded that the superior tabletability of granules derived from δ-mannitol over granules derived from β-mannitol was due to better plastic deformation characteristics of the former. This confirmed the research of Yoshinari et al. [22].

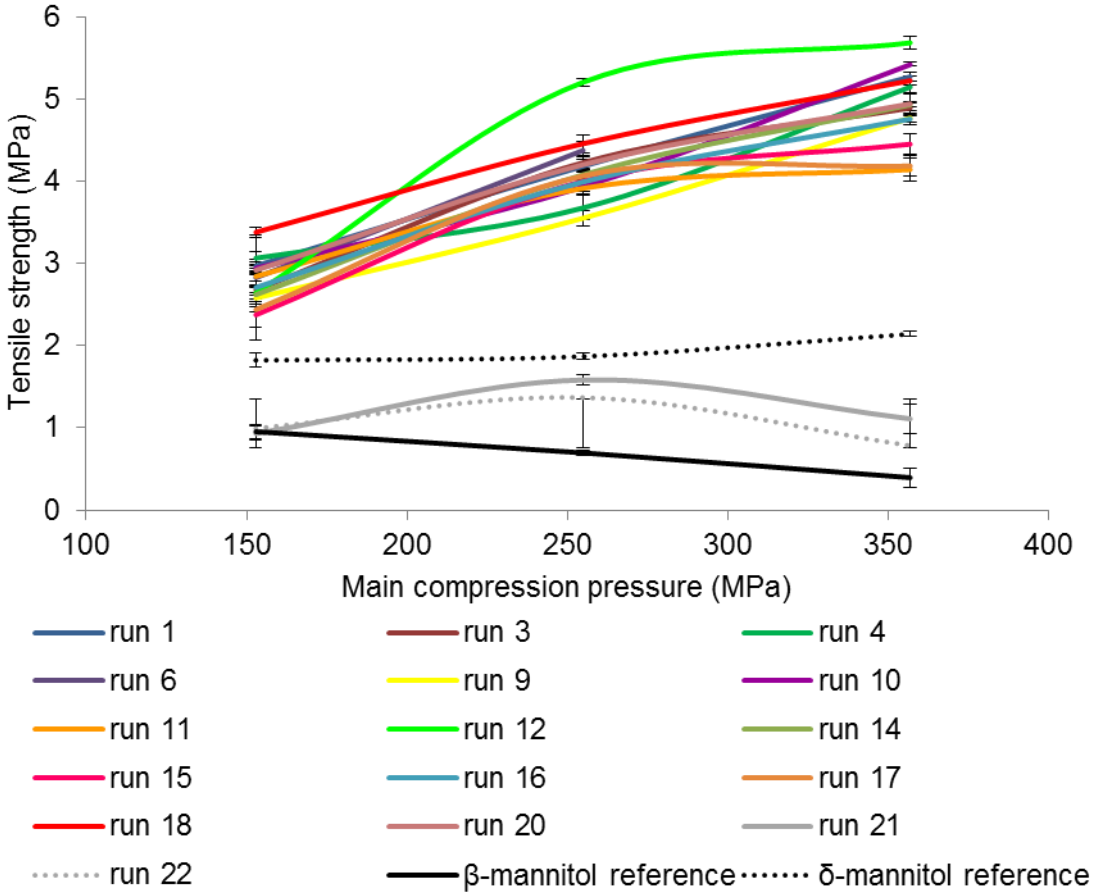

Figure 11. Tabletability of β- and δ-mannitol reference material, granulated β-mannitol (run 21 and 22) and granulated δ-mannitol samples.

Friability

The friability of tablets produced with granules of runs 1 - 20 (δ-mannitol starting material) and with δ-mannitol reference material was lower than 1%. In contrast, granulation with β-mannitol starting material resulted in highly friable tablets (4.7 and 21.5% for runs 21 and 22, respectively). This confirmed the tabletability experiments as the enhanced plastic deformation of granules derived from δ-mannitol resulted in tablets with a higher tensile strength and lower friability. The friability of tablets with β-mannitol starting material was excessively high as these tablets completely fragmented during friability testing.

Stability

Samples of the unmilled granules were stored at 25 °C / 40% RH and at 40 °C / 75% RH in open cups. They were analyzed by Raman spectroscopy after 6 months and the percentage δ-mannitol was calculated by the PLS model (Table 2).

run	IER (%)	PLC	elastic E (J)
1	2.6	93.3	0.5
3	3.1	92.1	0.6
4	2.8	92.8	0.5
6	2.9	93.3	0.5
9	2.5	93.2	0.5
10	3.0	93.1	0.6
11	3.4	94.2	0.4
12	2.4	94.1	0.4
14	3.0	92.4	0.5
15	2.3	94.6	0.4
16	3.0	92.4	0.5
17	2.5	92.2	0.4
18	2.4	94.0	0.5
20	2.9	94.2	0.4
21	2.3	89.0	0.4
22	2.7	91.2	0.5
β-mannitol reference	2.9	90.0	0.5
δ-mannitol reference	2.2	94.0	0.4

Table 3. Overview of in-die elastic recovery (IER), plasticity constant (PLC) and elastic energy (E).

After storage, a lower amount of δ-mannitol was found in the samples, irrespectively of the storage conditions. However, a significant decrease in the percentage of residual δ-mannitol was only detected in three samples (runs 5, 13, 19) after storage at 40 °C / 75% RH. These samples were produced at a low L/S ratio and a high screw speed and contained a relatively large fraction of residual δ-mannitol. The limited moisture uptake during storage at higher RH apparently induced a further moisture-mediated transition from δ- to β-mannitol. Hence, storage at lower RH is preferred to avoid polymorphic transition.

CONCLUSIONS

A different granulation behavior of mannitol was identified during continuous twin-screw granulation compared to other commonly used excipients such as lactose and MCC as the effect of granulation parameters (filling degree, screw speed, number of kneading elements) on the granule size distribution of mannitol granules was different compared to literature reports on formulations containing lactose and/or MCC as filler. Based on the higher solubility and faster dissolution rate of mannitol it was concluded that granulation of mannitol was principally driven by formation of liquid and solid bridges of solubilized material, rather than by compressive forces in the granulator barrel.

A polymorphic transition of mannitol was reported during twin screw granulation, which allowed to improve the tabletability of this material. Despite the short residence times and low L/S ratios used in twin screw granulation in comparison to batch granulation, the polymorphic transition of δ- to β-mannitol was observed, yielding a unique granule morphology with a higher specific surface area and enhanced plastic deformability. The superior tabletability of these granules derived from δ-mannitol as starting material over granules derived from β-mannitol as starting material was attributed to this unique granule morphology which was not dependent on the process parameters. Therefore, the process was considered as robust. The excellent tabletability of granules derived from δ-mannitol is promising and its potential in combination with highly dosed, poorly compressible drugs will be investigated in a next study.

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5

DEVELOPMENT OF A CONTROLLED RELEASE FORMULATION BY CONTINUOUS TWIN SCREW GRANULATION: INFLUENCE OF PROCESS AND FORMULATION PARAMETERS

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V. Vanhoorne, B. Vanbillemont, J. Vercruysse, F. De Leersnyder, P. Gomes, T. De Beer, J.P. Remon, C. Vervaet, Development of a controlled release formulation by continuous twin screw granulation: influence of process and formulation parameters, Int. J. Pharm. 505 (2016) 61-68.

Abstract

The aim of this study was to evaluate the potential of twin screw granulation for the continuous production of controlled release formulations with hydroxypropylmethylcellulose as hydrophilic matrix former. Metoprolol tartrate was included in the formulation as very water soluble model drug. A premix of metoprolol tartrate, hydroxypropylmethylcellulose and filler (ratio 20/20/60, w/w) was granulated with demineralized water via twin screw granulation. After oven drying and milling, tablets were produced on a rotary Modul^{TM} P tablet press. A D-optimal design (29 experiments) was used to assess the influence of process (screw speed, throughput, barrel temperature and screw design) and formulation parameters (starch content of the filler) on the process (torque), granule (size distribution, shape, friability, density) and tablet (hardness, friability and dissolution) quality attributes. The torque was dominated by the number of kneading elements and throughput, whereas screw speed and filling degree only showed a minor influence on torque. Addition of screw mixing elements after a block of kneading elements improved the yield of the process before milling as it resulted in less oversized granules and also after milling as less fines were present. Temperature was also an important parameter to optimize as a higher temperature yielded less fines and positively influenced the aspect ratio. The shape of hydroxypropylmethylcellulose granules was comparable to that of immediate release formulations. Tensile strength and friability of tablets were not dependent on the process parameters. The use of starch as filler was not beneficial with regard to granule and tablet properties. Complete drug release was obtained after 16 - 20 h and was independent of the design's parameters within the experimental space.

KEYWORDS: Continuous production, twin screw granulation, wet granulation, controlled release, hydroxypropylmethylcellulose, process variables

INTRODUCTION

Twin screw granulation has received much attention in recent years as this continuous manufacturing concept can be implemented by the pharmaceutical industry to make the switch from batch to continuous processing in order to improve time and cost efficiency, flexibility, quality and environmental impact during manufacturing of oral solid dosage forms [1-4]. Additionally, regulatory authorities also encouraged the pharmaceutical industry to adopt continuous processing [5].

Up to now most studies on twin screw granulation focused on the influence of process parameters on granule quality [6-15] while only a limited number of papers addressed formulation parameters [16-21]. In most studies excipients intended for immediate release formulations were used such as lactose, microcrystalline cellulose (MCC) and blends thereof. Occasionally formulation parameters were investigated such as different lactose isomers [12], lactose grades with different size characteristics [12, 20] and the hydrophobicity and solubility of excipients [2, 22]. More complex formulations however require special attention.

Continuous granulation of controlled release formulations was up to now exclusively examined by Thompson et al. [23]. They studied the granulation behavior of two placebo formulations with hydroxypropylmethylcellulose (HPMC) or polyvinylacetate/povidone (5-20% w/w) as matrix formers and a mixture of MCC and lactose as filler (MCC/lactose ratio 20/80, w/w) on a 27 mm Leistritz extruder. This process yielded large granules with a twisted morphology, especially using HPMC as matrix former. The poor shape of the granules (the aspect ratio of the individual granules was as low as 0.25) could not be eliminated by changing the liquid-to-solid ratio (L/S), screw speed, throughput or polymer concentration. It was observed that these twisted granules were formed immediately after a non-conveying zone. Screw configurations with a kneading block or comb mixing elements at the end were the only effective means of eliminating the formation of these aberrant granules.

It was the aim of this study to investigate the potential of continuous twin screw granulation with water as granulation liquid, for the production of a controlled release formulation with HPMC as hydrophilic matrix former and metoprolol tartrate (MPT) as very water soluble model drug. Therefore the influence of process (throughput, screw speed, temperature and screw design) and formulation (starch content of the filler) parameters on critical quality attributes of the process, granules and tablets were investigated using an experimental design.

MATERIALS AND METHODS

Materials

MPT was used as model drug and was purchased from Utag (Almere, The Netherlands). HPMC grade 90SH-4000 (substitution type 2208 according to the USP and Ph. Eur.) was kindly donated by ShinEtsu (Tokyo, Japan). Native maize starch (C*Gel™, Cargill, Mechelen, Belgium), MCC (Avicel PH101, FMC Health and Nutrition, Cork, Ireland) and α-lactose monohydrate (Pharmatose 200M, DMV-Fronterra, Veghel, The Netherlands) were used as fillers. Distilled water was used as granulation liquid. Magnesium stearate (Fagron, Waregem, Belgium) was used as lubricant during tableting.

Preparation of granules

MPT (20% w/w), HPMC (20% w/w) and filler (lactose or 1/1-mixture of lactose/starch) were preblended in a tumbling mixer (Inversina Bioengineering, Wald, Switzerland) for 10 minutes at 25 rpm and transferred to the loss-in-weight feeder (DDW-MD2-DDSR20, Brabender, Duisburg, Germany) of the ConsiGma™-1 (GEA Pharma Systems, Collette™, Wommelgem, Belgium) system. This system is a laboratory-scale continuous granulator with an integrated fluid bed dryer intended for early R&D work (Figure 1). The granulation unit consists of a co-rotating twin screw granulator without a die plate and has a length-to-diameter ratio of 20/1. The barrel can be divided in a feed zone with conveying elements and a working zone where the powder is intensively mixed with the granulation liquid by kneading elements. Water as granulation liquid was pumped into the barrel just before the first kneading element via a double liquid addition port, dripping granulation liquid on top of each screw. For all experiments the distance between liquid addition and the first kneading element was kept constant. The L/S ratio was kept constant at 0.08 and 0.10 in MPT/HPMC mixtures using lactose and a lactose/starch (1/1-ratio) mixture as filler, respectively. The barrel jacket was equipped with an active cooling system in order to maintain the set temperature during processing, and torque was monitored by a built-in torque gauge at 1-second intervals. For each run, 1000 g of granules were collected at the outlet of the granulator and tray dried in an oven at 40 °C for 24 h. After drying, 750 g of the granules were milled through a 1000 µm grater screen with square impeller at 900 rpm using the Quadro comil (U10, Quadro, Ontario, Canada).

Figure 1. ConsiGma™-1 system with (a) high-shear granulator barrel, (b) liquid addition on both screws, (c) gravimetric feeder and (d) granulator exit to be optionally coupled to a fluid bed dryer.

In addition a formulation used by Thompson et al. (2014), consisting of 20% HPMC, 16% MCC and 64% lactose was granulated using the granulation unit of the ConsiGma™-25 system (GEA Pharma Systems, Collette™, Wommelgem Belgium) in order to evaluate the tendency of this formulation to form noodle-like granules on the ConsiGma™-25 system [23]. The HPMC type used in current study was identical to the HPMC type used by Thompson et al. according to classification of the USP and Ph. Eur. with regard to substitution degree and viscosity. Screw speed, temperature and throughput were fixed at 900 rpm, 25 °C, 25 kg/h, respectively, and a screw configuration with one block of six kneading elements was used. The L/S ratio was varied between 0.10 and 0.30.

Preparation of tablets

The milled granules were blended with 0.5% w/w magnesium stearate in a tumbling blender (T2F, W.A. Bachofen, Basel, Switzerland) before tableting. Tablets were prepared using a Modul™ P tablet press (GEA Pharma Systems, Courtoy™, Halle, Belgium) in manual mode at a speed of 230 tablets per minute. The press was equipped with 10 round flat-faced bevel-edged Euro B punches (SPC, Rillieux-la-Pape, France) of 13 mm diameter and an overfill cam of 16 mm. The paddles in the feed frame were rotating at a speed of 15 and 20 rpm. Filling depths between 9.8 and 10.5 mm were used, in function of the density of the samples. Tablets were compressed at 7 different main compression forces: 54, 126, 230, 352 and 521

MPa after precompression at 16 MPa in order to assess the tabletability of the granulates. Tablets compressed at 352 MPa were selected for friability testing and dissolution.

Design of experiments

Based on preliminary experiments the different L/S ratios (0.08 and 0.10 using lactose and a 1/1-ratio lactose/starch mixture as fillers, respectively) and experimental ranges for throughput, screw speed, barrel temperature and screw design were determined. A D-optimal design (G-efficiency 84, condition number 2.13) with 29 experiments was applied to study the influence of four process parameters: screw speed (600-900 rpm), throughput (10-25 kg/h), temperature (10-40 °C) and screw design, and one formulation parameter: starch content of the filler (0-50%) on the granulation process, granule and tablet properties. Three different screw configurations were evaluated: 1 kneading zone of 6 kneading elements without (1x6) or with (1x6+SME) addition of screw mixing elements (SME) and 2 kneading zones of 6 kneading elements (2x6) separated by a conveying zone. A description of SME is given by Vercruysse et al. [15]. An overview of the screw configurations is shown in Figure 2. Two centerpoints (with screw configurations 1x6 and 1x6+SME) were run in duplicate. An overview of the experiments is given in Table 1. The results were analyzed using Modde 10.1 (Umetrics, Umeå, Sweden) software, and error bars represent 95% confidence intervals.

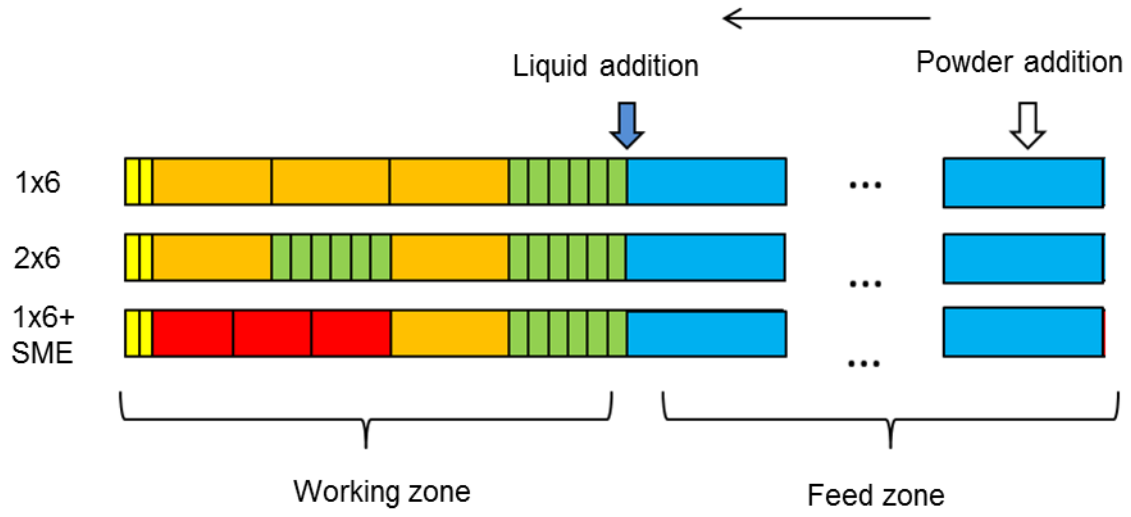

Figure 2. Schematic overview of the screw configurations with: kneading elements with a length-to-diameter (L/D) ratio of L/D 1/6 (yellow), kneading elements with L/D ratio of 1/4 (green), conveying elements (blue), SME (red). The process direction is indicated with an arrow.

Run	Temperature (°C)	Screw speed (rpm)	Throughput (kg/h)	Starch content of the filler (%)	Screw configuration(*)
1	40	600	10	0	2x6
2	25	900	10	0	2x6
3	25	600	25	0	2x6
4	40	900	25	0	2x6
5	25	600	10	50	2x6
6	40	900	10	50	2x6
7	40	600	25	50	2x6
8	25	900	25	50	2x6
9	25	600	10	0	1X6+SME
10	40	900	10	0	1X6+SME
11	40	600	25	0	1X6+SME
12	25	900	25	0	1X6+SME
13	40	600	10	50	1X6+SME
14	25	900	10	50	1X6+SME
15	25	600	25	50	1X6+SME
16	40	900	25	50	1X6+SME
17	40	600	10	0	1x6
18	25	900	10	0	1x6
19	40	900	10	0	1x6
20	25	600	25	0	1x6
21	40	900	25	0	1x6
22	25	600	10	50	1x6
23	40	900	10	50	1x6
24	40	600	25	50	1x6
25	25	900	25	50	1x6
26	32.5	750	17.5	50	1x6
27	32.5	750	17.5	50	1x6
28	32.5	750	17.5	0	1X6+SME
29	32.5	750	17.5	0	1X6+SME

(*)Screw configurations: 1x6: 1 kneading zone of 6 kneading elements, 1x6+SME: 1 kneading zone of 6 kneading elements with addition of screw mixing elements (SME), 2x6: kneading zones of 6 kneading elements (2x6) separated by a conveying zone.

Table 1. Overview of the experimental design.

Evaluation of granules

Particle size and shape analysis

Granule size and shape was analyzed before and after milling via dynamic image analysis using the QICPIC™ system (Sympatec, Clausthal-Zellerfeld, Germany) equipped with a vibrating feeder system (Vibri/L™) for gravimetrical addition of the granules. Samples of 3 g were measured in triplicate. Windox 5 software was used to calculate the median granule size (d_{50}) as the equivalent projected circle diameter. In addition, the sphericity and aspect ratio of the granules were determined. The aspect ratio is defined as the ratio of the maximal Feret diameter to the minimal diameter orthogonal to it, and sphericity is the ratio of the perimeter of the equivalent circle to the real perimeter. The amounts of fines, coarse and oversized granules were defined as the fractions <150 µm, >900 µm and >1500 µm, respectively. The yield of the process was defined as the percentage of granules between 150 and 1500 µm. All particle diameters were calculated based on volume.

Bulk and tapped density

The bulk volume (V_0) of 30 g milled granules was measured in a 100 ml measuring cylinder as well as the tapped volume after 1250 taps (V_{1250}) in a tapping machine (J. Englesman, Ludwigshafen, Germany). Experiments were performed in duplicate. Bulk and tapped densities were calculated as 30 g/V_0 and 30 g/V_{1250}, respectively. The compressibility index (C%) was calculated from the bulk (ρ_i) and tapped (ρ_f) densities using the following equation:

$$C\% = \left[\frac{\rho f - \rho i}{\rho f}\right] * 100$$

Friability analysis

The granule friability was determined in duplicate using a friabilator (PTF E Pharma Test, Hainburg, Germany) at a speed of 25 rpm for 10 min, by subjecting 10 g (I_{wt}) of milled granules together with 200 glass beads (mean diameter 4 mm) to falling shocks. Prior to determination, the granule fraction <250 µm was removed to assure the same starting conditions. Afterwards, the glass beads were removed and the weight retained on a 250 µm sieve (F_{wt}) was determined. The friability was calculated as:

$$\text{Friability } (\%) = \left[\frac{Iwt - Fwt}{Iwt}\right] * 100$$

Tablet evaluation

The hardness, thickness and diameter of the tablets (n=10) were determined (Sotax HT 10, Basel, Switzerland) and the tensile strength (TS) was calculated using the equation described by Fell and Newton [24]:

$$TS = 2F/\pi dt$$

Where F, d and t denote the diametral crushing force, tablet diameter and tablet thickness, respectively.

The tablet friability was determined using a friabilator described in the European Pharmacopeia (PTF E Pharma Test, Hainburg, Germany) at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

Dissolution tests were performed (n=3) in 900 ml demineralized water using the paddle method (VK 7010, Vankel, Cary, NC, USA). The temperature of the dissolution medium was maintained at 37 ± 0.5 °C, while the rotation speed was set at 100 rpm. Samples of 5 ml were withdrawn after 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h. The drug content in these samples was derived from the absorbance of the samples at 222 nm using a UV spectrophotometer (UV-1650PC, Shimadzu Benelux, Antwerp, Belgium). From the drug release profile, the time point of 50% drug release was determined.

RESULTS AND DISCUSSION

Evaluation of the granulation process

For all experiments the torque was lower than about 5.5 Nm (which was far below 20 Nm, the maximum torque tolerated by the granulator) and was mainly influenced by screw design, screw speed and throughput. More kneading elements, which retain the material in the extruder, resulted in higher torque readings. An interaction between high throughput and the number of kneading elements was also detected as the torque was especially high when running at high throughput with the 2x6 screw configuration. This is in agreement with continuous wet granulation of immediate release formulations [6, 7, 8, 25, 26].

Addition of SME after a kneading block did not result in lower and more stable torque values as described by Vercruysse et al. [15]. As the geometry of SME is based on conveying elements, their conveying capacity is higher than of kneading elements, resulting in less shear and lower torque with an immediate release formulation. However, the HPMC-formulation behaved differently when processed using SME which was attributed to swelling

and stickiness of HPMC upon hydration. This reduced the free volume between the screws and the barrel wall, resulting in more shear on the screws.

Screw speed as such and in an interaction with throughput also affected the torque. At higher screw speed, lower torque values were recorded as the material residence time in the barrel is shorter and therefore swelling of HPMC was less pronounced [26, 7]. This is in accordance with the research of Dhenge et al. on a formulation containing 5% hydroxypropylcellulose and 20% microcrystalline cellulose, components that also swell upon hydration [7]. In addition, the interaction between throughput and screw speed affected torque: at high throughput an increase of screw speed reduced the torque, whereas it only had a minor impact at low throughput since the filling degree was more affected at higher screw speed (Figure 3).

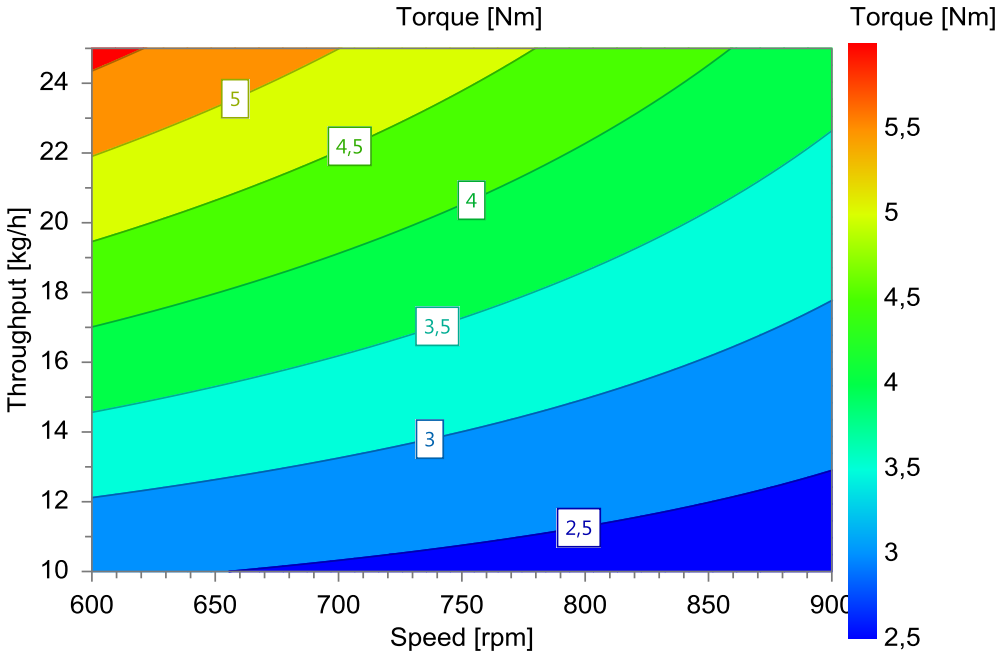

Figure 3. Contour plot of torque (Nm) as a function of throughput (kg/h) and speed (rpm) at a temperature of 32.5 °C, filler ratio of 25% and screw configuration 2x6.

Influence of design variables on granule quality

Granule size

Narrow granule size distributions with all particles between 150 – 1500 µm are preferred as they prevent content uniformity issues after tableting due to poor flow. However, in current study all granule size distributions were relatively broad after granulation with a process yield varying between 21.4 – 70.1%. This was mainly due to an extensive oversized fraction, varying between 26.1 – 78.2 %. Oversized granules are not desirable as they prevent homogeneous dosing during tableting. Therefore milling of the oversized fraction was

necessary and the granule size distributions of the granules before and after milling were evaluated. Although during milling fines were created, the yield of the process after milling generally increased and varied between 77.7 - 89.4%.

Increasing the number of kneading elements resulted in high d_{50} values, an extensive fraction of oversized granules and a small fraction of fines, both before and after milling (Figure 4). Addition of SME after a block of kneading elements reduced the d_{50} and the fraction of oversized granules before milling but yielded slightly more fines which was in accordance with the results of Vercruysse et al. [15]. Overall a narrower granule size distribution and higher yield were obtained before milling when SME were added after a block of kneading elements which could improve the drying uniformity of the granules and potentially eliminate a milling step prior to tableting, making the manufacturing process more cost effective. This is illustrated for the centerpoints with screw configuration 1x6 (runs 26 and 27) and 1x6+SME (runs 28 and 29) in Figure 5. After milling there was no significant difference between the d_{50} and the coarse fraction produced with screw configurations 1x6 and 1x6+SME, while less fines were present in the granulate produced with screw configuration 1x6+SME (Figure 4). This was due to the absence of a large oversized fraction after the granulator if SME were added after a kneading block as milling of oversized granules created fines during the milling process.

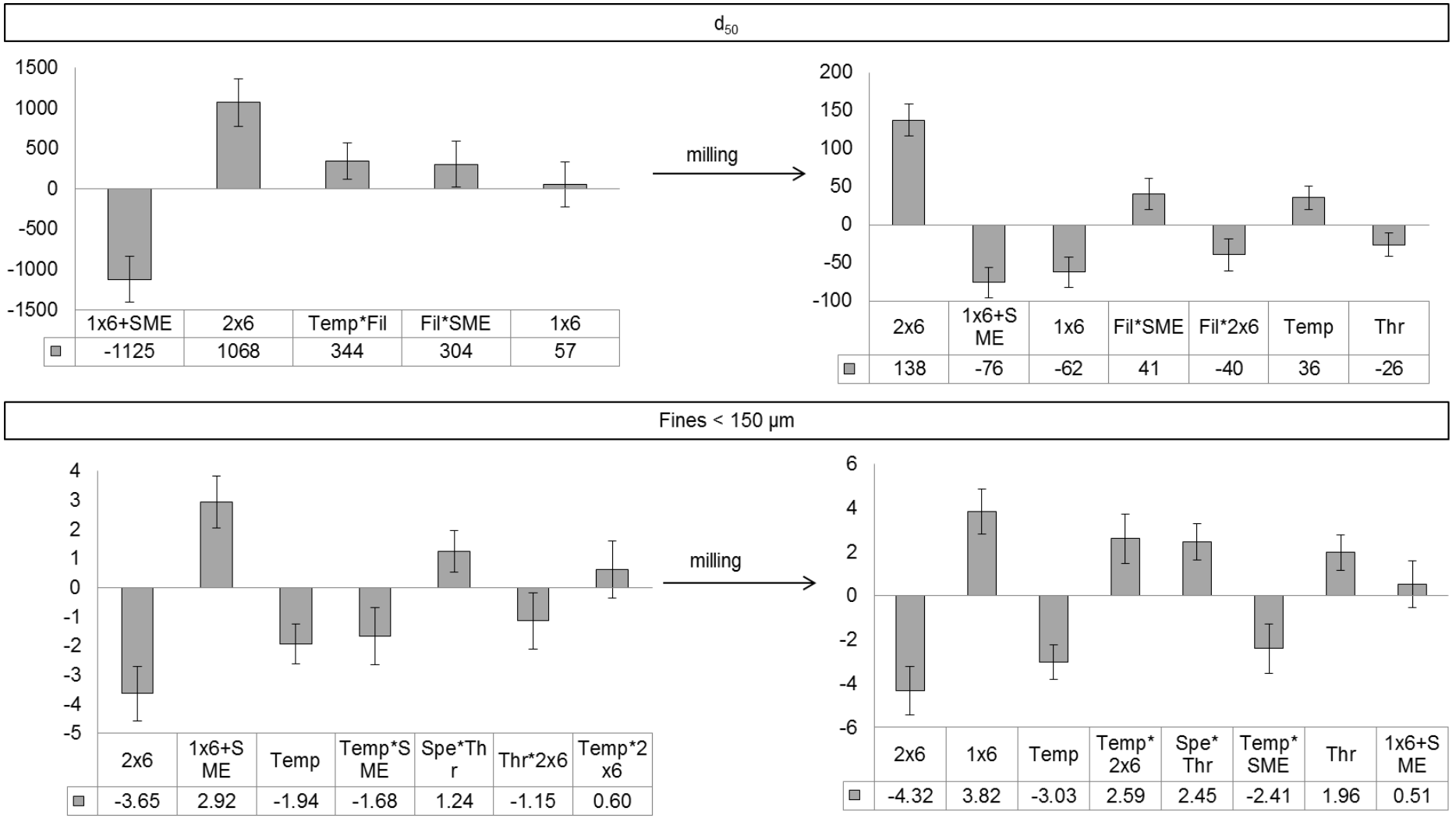

Figure 4. Top: effect plot (effects > 25 µm) of d_{50} of unmilled (left) and milled (right). Bottom: effect plot of the fines fraction (<150 µm) of unmilled (left, effects > 1.2 %) and milled (right, effects >2%).

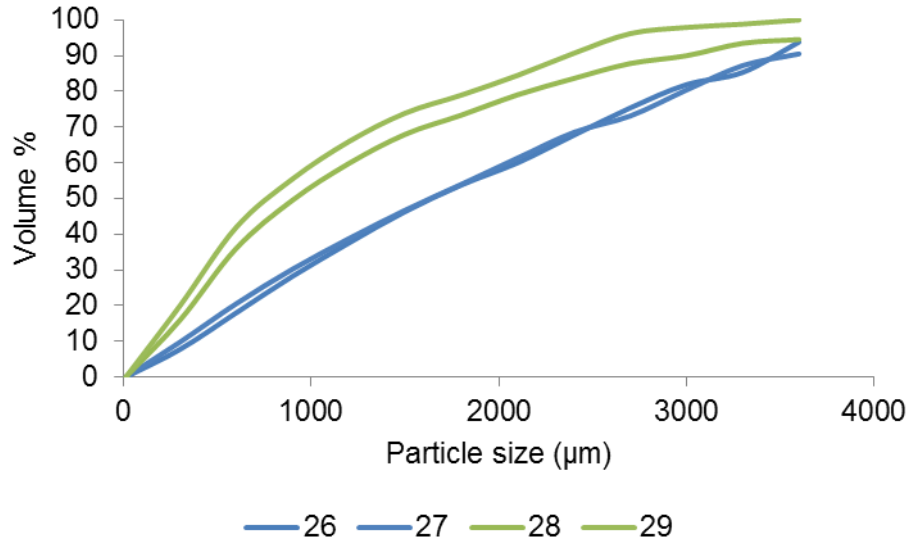

Figure 5. Granule size distributions of centerpoints produced with screw configurations 1x6 (runs 26 and 27) and 1x6+SME (runs 28 and 29) before milling.

The filler ratio as such did not significantly affect the granule size distribution. However, two interactions including the filler were detected with respect to the d_{50} of the unmilled granules: an interaction between screw configuration and filler, and an interaction between temperature and filler. Whereas addition of SME after a kneading zone resulted in a considerable decrease in d_{50} when lactose was used as filler, this decrease was less pronounced in combination with starch as a filler in the formulation. This could be explained by the hypothesis that SME are responsible for breaking up the oversized granules and that the starch-containing formulation is more resistant to breakage during granulation as a higher L/S ratio was used. The interaction between the filler and temperature demonstrated a directly proportional relation between d_{50} and the barrel temperature when the lactose/starch mixture was used as filler, whereas an inversely proportional relation was found for the granules exclusively formulated with lactose as filler. At higher processing temperature the solubility of lactose and MPT increased, the solubility of HPMC decreased and the solubility of starch is not affected since this component is not water soluble at temperatures below the gelation point. It appears that the reduction in solubility of HPMC at higher temperatures only affected the formulation with lactose as filler as in this formulation the applied L/S ratio is lower, hence the decrease in HPMC solubility was not compensated by the higher solubility of lactose and MPT.

A significant relationship between the barrel temperature and fines fraction of milled and unmilled granules was established (Figure 4). The reduction of fines at higher barrel temperature was attributed to the increased solubility of lactose and MPT and to the lower viscosity of HPMC at these settings (HPMC can act as binder next to its function as matrix

former). According to the supplier's information, there is a sharp decrease in viscosity of a 1% HPMC solution in water when the temperature is increased over 40 °C. Although the product temperature was monitored and kept constant at 40 °C, higher temperatures might temporarily been reached in the kneading zone due to high shear. A lower viscosity of the granulation liquid could improve the penetration of the granulation liquid in the powder bed, resulting in improved distribution of granulation liquid. This induced granule growth with layering of fines on granules. As a consequence, a high temperature positively influenced the yield of the milled granules. An interaction between temperature and screw design was also detected with respect to the fines fraction (Figure 4). The decrease in fines at higher temperatures was more distinct when using SME. Assuming that SME break oversized granules during granulation and thereby create fines, this effect can also be explained by the higher solubility of lactose and MPT and the lower viscosity of HPMC at higher temperatures. Therefore barrel temperature is an important process parameter to optimize when granulating HPMC-based formulations.

An increase in throughput resulted in a lower d_{50} and a larger fines fraction of milled granules. This is in contrast to most reports in literature where denser and larger granules at higher throughput are linked to higher compressive forces during granulation [11, 19, 21, 28]. However, similar results were found by Dhenge et al. on a formulation containing 20% microcrystalline cellulose and 5% hydroxypropylcellulose, components that also swell upon hydration [7, 8]. At a higher throughput, less free volume in the barrel is available which could hinder the penetration of granulation liquid in the powder bed. Although this reasoning could be applicable for formulations with non-swelling components, it appeared to be exclusively valid for formulations with cellulose derivatives that swell upon hydration and consequently strongly hinder penetration of the granulation liquid [7, 8].

There was no influence of screw speed on the particle size distribution of the granules. This is in contrast to the research of Thompson et al. on an HPMC formulation where higher screw speeds resulted in larger granules [23]. However an interaction of screw speed and throughput was detected for the fines fraction of the milled and unmilled granules (Figure 4). At low throughput, the fines fraction decreased as screw speed increased. This could be attributed to the higher energy input in the process at high screw speed. At high throughput the effect of screw speed on fines was reversed. This is correlated to a decrease in torque at higher screw speed (section 3.1), resulting in lower compressive forces and therefore more fines.

Granule shape

Overall the aspect ratio and sphericity varied between 0.61-0.69 and 0.69-0.75 (unmilled granules), and 0.64-0.69 and 0.75-0.79 (milled granules), respectively. Screw configuration and temperature showed a minor but significant influence on the granules' shape. Screw configurations 2x6 and 1x6+SME yielded granules with the highest aspect ratio and sphericity, respectively, meaning that more kneading elements improved the overall shape of the granules and that the addition of SME smoothened the surface of the granules. Temperature positively influenced the aspect ratio as at a higher processing temperature the viscosity of HPMC in solution is lower and a higher fraction of lactose and MPT can dissolve, increasing the deformability during processing. The use of exclusively lactose as filler yielded granules with a higher aspect ratio as lactose can dissolve in the granulation liquid which makes it easier to deform during granulation than starch which is not soluble in the granulation liquid. No significant influence of screw speed or throughput on the granule shape was detected.

In contrast to Thompson et al. who reported the formation of long (3-10 mm), twisted noodle-like granules (Figure 6) using HPMC as controlled release excipient, the aspect ratios of the granules in the current study were comparable to those reported for immediate release formulations (typically between 0.64 and 0.70) [2, 23, 27].

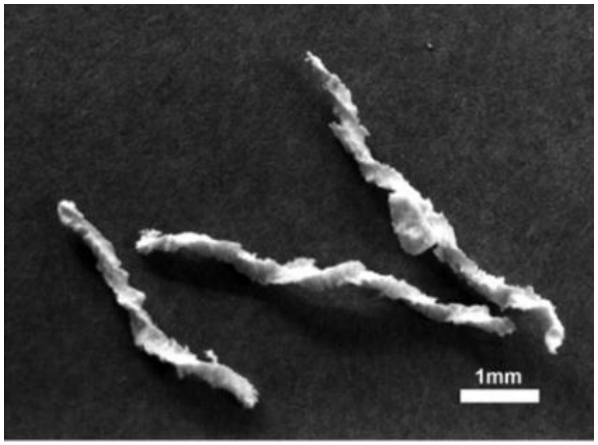

Figure 6. Twisted noodle-like granules reported by Thompson et al. [adopted from 23].

Thompson et al. suggested that the twisted, noodle-like HPMC-based granules were formed at the flight tips of the conveying elements, a process which mainly occured at the kneading zone where forces squeezed the liquid to the periphery of the granules [23]. The formation of these noodle-like granules could only be eliminated through inclusion of a kneading block at the end of the screws. As in the current study no such granules were formed, independent of the process parameters and screw design, it was evident that the granulator design and/or the composition of the formulation are vitally important to create controlled release granules

with acceptable size and shape. Thompson et al. used a formulation with 5 - 20% HPMC and filler mixture consisting of 20% MCC and 80% lactose [23]. Since MCC has a high water absorption capacity and is practically insoluble in water, formulations with MCC require more water for successful granulation [29, 30]. As a consequence a higher L/S ratio (0.25 w/w) was used in the study of Thompson et al. in comparison to the current study (L/S ratios of 0.08 and 0.10 w/w using lactose or a 1/1-ratio mixture of lactose and starch, respectively) [23].

In order to clarify whether the formation of twisted, noodle-like granules as described by Thompson et al. was due to a different granulator design or the use of MCC as filler in combination with a high L/S ratio, an identical formulation was granulated in the current study. The screw configuration applied in current study (1 block of 6 kneading elements followed by conveying elements) was as similar as possible to one of the screw configurations (1 block of 5 kneading elements followed by conveying elements) used by Thompson that resulted in noodle-like granules. An L/S ratio of 0.16 yielded granules with an acceptable shape having a mean aspect ratio of 0.60. Increasing the L/S ratio to 0.26 resulted in oversized granules with a flake-like structure, while a further increase of the L/S ratio to 0.29 resulted in twisted elongated granules as described by Thompson et al. [23]. Their aspect ratio could not be reported as their size exceeded the measuring range of image analysis detector. However, in contrast to Thompson et al., the formation of these granules depended on the moisture content [23]. This indicated that both granulator design and composition of the formulation are essential parameters during continuous granulation of controlled release formulations with HPMC.

Bulk and tapped density, flowability, friability

The bulk and tapped density of the milled granules ranged between 0.46-0.53 and 0.58-0.67 g/ml, respectively, with the granules containing starch displaying lower densities. This could be correlated to the lower aspect ratio of the granules with starch included in the filler. A higher number of kneading elements induced more densification during the granulation process, resulting in higher bulk and tapped densities, similar to the observations for immediate release formulations [6]. Furthermore, an interaction between screw design and temperature was detected (Figure 6). An increase in temperature only resulted in a higher density for granules produced with the 2x6 screw configuration. Apparently there was a synergy between a high temperature (solubilizing lactose and MPT which increased the plasticity and deformability of the powder mass in the granulator) and the higher number of kneading elements (which enhanced the compaction of the granules).

The compressibility index varied between 15 and 23%, indicating acceptable flow properties. No relevant relationships between flow properties and the design variables were detected.

The friability of the milled granules ranged between 9 and 34% and was mainly affected by the screw design. Increasing the number of kneading elements yielded less friable granules, whereas addition of SME after a kneading block had no significant effect on friability. In addition an interaction between temperature and screw design influenced the friability of the granules (Figure 7): barrel temperature only determined friability using the 2x6 screw configuration due to the more extensive densification at higher temperatures.

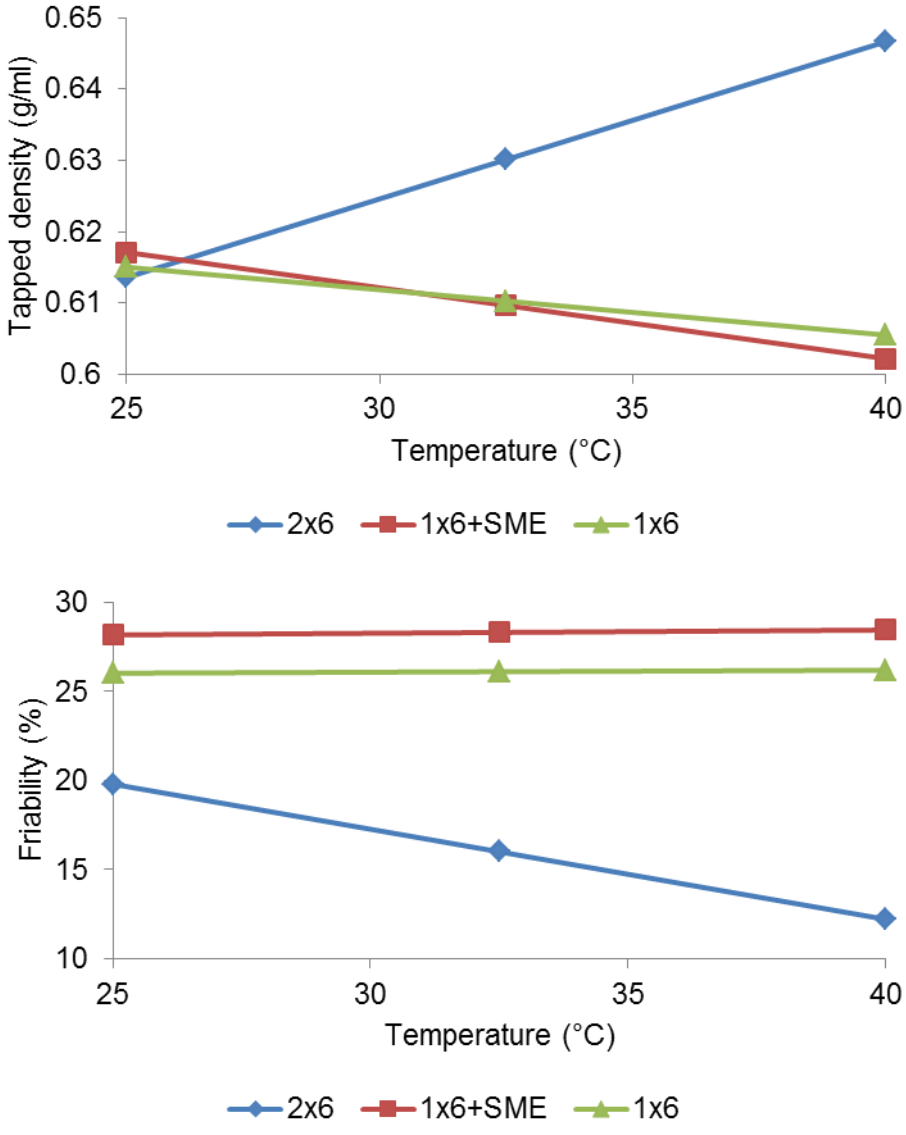

Figure 7. Interaction plot of tapped density (top) and granule friability (bottom) as a function of screw configuration and temperature.

Influence of design variables on tablet quality

The tensile strength of the tablets was clearly affected by the fillers used. As starch exhibited elastic behavior during tableting, the tabletability of tablets containing exclusively lactose was superior [31]. However, in contrast to immediate release formulations, no significant influence of process parameters on tabletability was detected although it should be noted that the studies on immediate release formulations were performed at low tableting speeds [6, 9] and that no magnesium stearate was added before tableting [9].

Representative tabletability plots for formulations containing only lactose as filler and containing a 1/1-ratio lactose/starch mixture as filler are shown in Figure 8. Based on the tabletability plots, tablets compressed at 352 MPa were selected for friability and dissolution testing as from this compression force onwards the tablet hardness was constant.

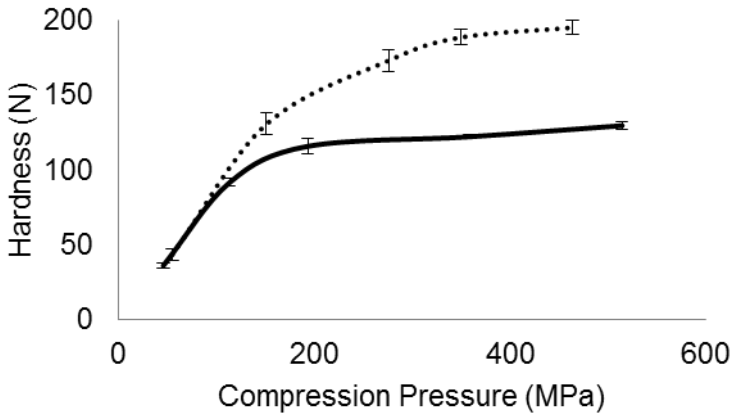

Figure 8. Representative tabletability plots of formulations with only lactose as filler (dotted line) and with a 1/1-ratio lactose/starch mixture (full line) as filler.

The friability of all tablets was compliant to the European Pharmacopeia and ranged between 0.13 and 0.53%.

Release profiles of selected runs (4, 22 and 28) showed that MPT was released over 16-20 h (Figure 9). The release was independent of the parameters included in the design. This is in contrast to the reports of Dhenge et al. and Vercruysse et al. on immediate release formulations showing an effect of screw design and throughput on the drug release rate [6, 8]. However, in our study the effect of HPMC as matrix former for controlled release and the high solubility of metoprolol tartrate dominated over the process parameters.

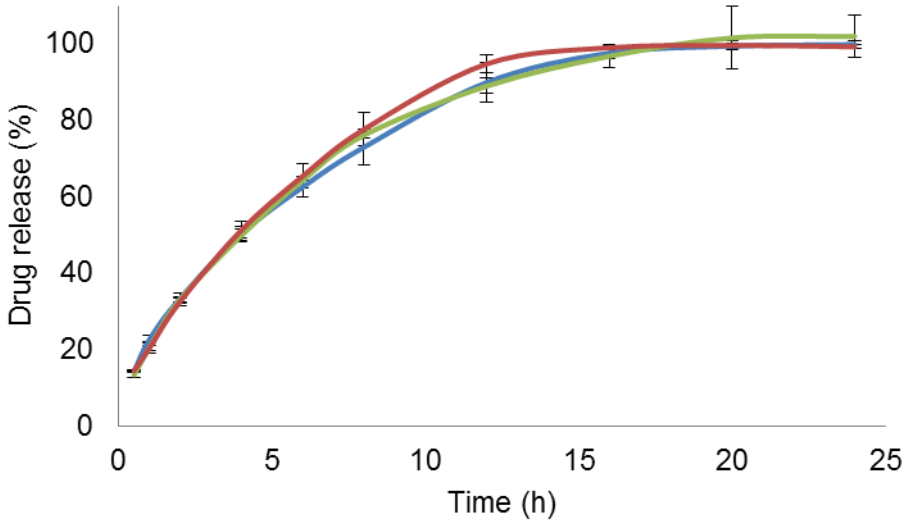

Figure 9. Drug release profile of selected runs: 4 (blue), 22 (green) and 28 (red).

CONCLUSIONS

The influence of process parameters and filler on the granule and tablet properties of a controlled release formulation was investigated using a D-optimal experimental design with 29 experiments. Torque could be modulated by adjusting the filling degree and the screw configuration. Addition of SME after a block of kneading elements increased the yield of the process before and after milling. The shape of the controlled release granules was comparable to that of immediate release granules. No elongated granules were formed when lactose and/or starch were used as filler. However, combination of HPMC and MCC resulted in elongated granules at high L/S ratios. Therefore combination of HPMC with other cellulose derivatives was discouraged. The use of native starch as filler was not beneficial with regard to granule or tablet properties. Release of MPT was sustained over 16 - 20 h and was independent of the process and formulation parameters, signifying that the process is very robust with regard to dissolution. Twin screw granulation with water as granulation liquid followed by tableting proved to be an attractive technique for the continuous production of controlled release tablets with HPMC as hydrophilic matrix former.

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6

CONTINUOUS TWIN SCREW GRANULATION OF CONTROLLED RELEASE FORMULATIONS WITH VARIOUS HPMC GRADES

Parts of this chapter are accepted for publication by International Journal of Pharmaceutics (August 9th 2016):

V. Vanhoorne, L. Janssens, J. Vercruysse, T. De Beer, J.P. Remon, C. Vervaet, Continuous twin screw granulation of controlled release formulations with various HPMC grades, accepted manuscript (August 9th 2016).

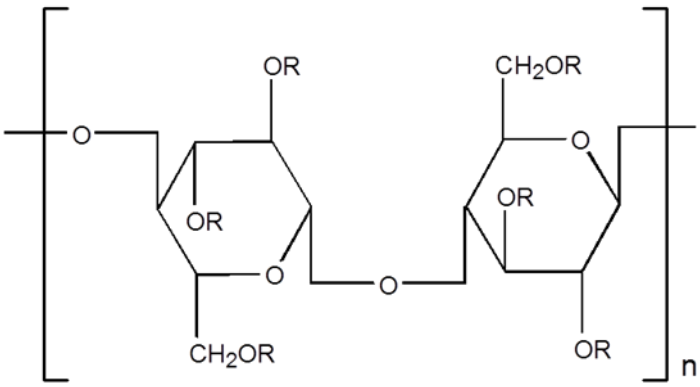
Abstract

HPMC is a popular matrix former to formulate tablets with extended drug release. Tablets with HPMC are preferentially produced by direct compression. However, granulation is often required prior to tableting to overcome poor flowability of the formulation. While continuous twin screw granulation has been extensively evaluated for granulation of immediate release formulations, twin screw granulation of controlled release formulations including the dissolution behavior of the formulations received little attention. Therefore, the influence of the HPMC grade (viscosity and substitution degree) and the particle size of theophylline on critical quality attributes of granules (continuously produced via twin screw granulation) and tablets was investigated in the current study. Formulations with 20 or 40% HPMC, 20% theophylline and lactose were granulated with water at fixed process parameters via twin screw granulation. The torque was influenced by the viscosity and substitution degree of HPMC, but was not a limiting factor for the granulation process. An optimal L/S ratio was selected for each formulation based on the granule size distribution. The granule size distributions were influenced by the substitution degree and concentration of HPMC and the particle size of theophylline. Raman and UV spectroscopic analysis on 8 sieve fractions of granules indicated an inhomogeneous distribution of theophylline over the size fractions. However, this phenomenon was not correlated with the hydration rate or viscosity of HPMC. Controlled release of theophylline could be obtained over 24 h with release profiles close to zero-order. The release of theophylline could be tailored via selection of the substitution degree and viscosity of HPMC.

KEYWORDS: HPMC, continuous production, twin screw granulation, theophylline, controlled release

INTRODUCTION

Hydroxypropylmethylcellulose (HPMC) is widely applied in oral, ophtalmic and topical pharmaceutical formulations. In oral products, HPMC is applied as binder, film coating and hydrophilic matrix former. As matrix former, it sustains drug release resulting in a prolonged therapeutic effect, minimization of side effects, reduced administration frequency and improved patient compliance. Hydrogen bonding between HPMC and water forms a gel layer at the surface of a wetted tablet, controlling the drug release via diffusion through and erosion of the highly viscous polymer matrix. The matrix forming and drug release mechanisms have been thoroughly studied by several research groups [1-3]. HPMC has a polymeric backbone of cellulose substituted with hydroxypropyl and methyl groups (Figure 1). The ratio of hydroxypropyl and methyl substitutions is referred to as the degree of substitution and will determine the characteristics of the polymer (e.g. solubility, hydration rate). Additionally, commercially available HPMC grades differ with regard to molecular weight and therefore viscosity.



R = -H, -CH_3, -$CH_2CH(CH_3)OH$

Figure 1. Chemical structure of HPMC.

HPMC is the most popular hydrophilic matrix former for production of controlled release tablets as it is non-ionic, stable over a broad pH range, enzyme resistant, odourless and tasteless, extensively studied and understood, non-toxic and cost-effective [4-8]. Moreover the available variety of HPMC grades with different substitution degrees and viscosities make it a versatile matrix former for controlled release of a wide range of drugs with varying solubilities and doses [8]. Tablets with HPMC can be produced by direct compression but often granulation is necessary [4, 9]. High shear and fluid bed granulation were successfully applied to improve the flowability of formulations with HPMC [4, 5, 9, 10-16], often requiring hydro-alcoholic granulation liquids as granulation with water yielded lumps as well as fines due to the irregular wetting of the formulation.

Twin screw granulation is an emerging continuous granulation technique that can be implemented in a fully continuous from-powder-to-tablet manufacturing line. This concept offers economic advantages, improved product quality and a lower environmental impact [17, 18, 19, 20]. However, up to now only two studies addressed continuous granulation of formulations with HPMC [21, 22]. Whereas these studies used the same HPMC grade and investigated the influence of process parameters, in current study the impact of formulation variables on critical quality attributes of granules and tablets was studied. Three HPMC grades (in two concentrations), varying in substitution degree and viscosity, and two theophylline grades, varying in particle size, were included in the formulations.

MATERIALS AND METHODS

Materials

Theophylline, in a micronized and powdered grade, was used as model drug and was kindly donated by BASF (Ludwigshafen, Germany). Three HPMC grades (90SH-4000-SR, 90SH-100000-SR and 60SH-4000) were kindly donated by ShinEtsu (Tokyo, Japan). The substitution types (according to the USP and Ph. Eur.) and viscosities of these HPMC grades are included in Table 1. Magnesium stearate (Fagron, Waregem, Belgium) and α-lactose monohydrate (Pharmatose 200M, DMV-Fronterra, Veghel, The Netherlands) were used as lubricant and filler, respectively.

Product	Substi-tution type[a]	Viscosity (mPa*s)	d_{10} (µm)	d_{50} (µm)	d_{90} (µm)	span	True density (g/cm³)
HPMC Metolose 90SH-4000-SR	2208	4000	18.8	80.4	208.5	2.4	1.32
HPMC Metolose 90SH-100000-SR	2208	100000	14.5	49.7	287.6	5.5	1.32
HPMC Metolose 60SH-4000	2910	4000	16.6	42.6	253.2	5.6	1.29
α-lactose monohydrate	-	-	6.6	41.4	113.8	2.6	1.46
Micronized theophylline	-	-	0.5	8.6	25.6	2.9	1.49
Powdered theophylline	-	-	4.5	41.7	95.0	2.2	1.48

Table 1. Overview and characterization of the starting materials.

Preparation of the granules

Theophylline (20% w/w), HPMC (20 or 40% w/w) and lactose were preblended in a tumbling mixer (Inversina Bioengineering, Wald, Switzerland) for 10 minutes at 25 rpm. An overview of the formulations is shown in Table 2. Subsequently they were transferred to the loss-in-weight feeder (DDW-MD2-DDSR20, Brabender, Duisburg, Germany) of the ConsiGma™-1 (GEA Pharma Systems, GEA Pharma Systems, Wommelgem, Belgium) system. This system is a laboratory-scale continuous granulator with an integrated fluid bed dryer intended for early R&D work. The granulation unit consists of a co-rotating twin screw granulator without a die plate and has a length-to-diameter ratio of 20/1. The barrel can be divided in a feed zone with conveying elements and a working zone where the powder is intensively mixed with the granulation liquid by kneading elements. A PT-100 temperature sensor was integrated in the working zone of the barrel and linked to a feedback control system which regulates the temperature in the barrel jacket and compensates for temperature increase during the process due to friction. Torque was monitored by a built-in torque gauge at 1-second intervals. All torque values were smoothed by application of moving average (over a period of 5 measurements). Water as granulation liquid was pumped into the barrel just before the first kneading element via a double liquid addition port (internal diameter 0.8 mm), injecting granulation liquid on top of each screw. For all experiments the distance between liquid addition and the first kneading element was kept constant. Granulation of the formulations was performed at constant process parameters (screw speed 900 rpm, throughput 10 kg/h, barrel temperature 25 °C) using a fixed screw configuration consisting of two kneading blocks with each 6 kneading elements at an angle of 60°. This screw configuration was schematically presented by Vanhoorne et al. [22]. The liquid-to-solid (L/S) ratio was varied between 0.08 and 0.18 with intervals of 0.02. After stabilization of torque at least 100 g granules were collected at the outlet of the granulator at each L/S ratio, while 1000 g granules was collected at an L/S ratio considered optimal for each formulation. The optimal L/S ratio (listed in Table 2) was dependent on the HPMC grade and percentage HPMC included in the formulation. The granules were tray dried in an oven at 40 °C for 24 h. After drying, the granules processed with an optimal L/S ratio were milled through a 1000 µm grater screen with square impeller at 900 rpm using the Quadro comil (U10, Quadro, Ontario, Canada) incorporated in the ConsiGma™-25 line.

Formulation	Theophylline (%)		HPMC (substitution type – viscosity)			lactose	Optimized L/S ratio
	micronized	powdered	2208-4000	2208-100000	2910-4000		
F1	20	-	20	-	-	60	0.10
F2	20	-	-	20	-	60	0.10
F3	20	-	-	-	20	60	0.12
F4	-	20	20	-	-	60	0.10
F5	-	20	-	20	-	60	0.10
F6	-	20	-	-	20	60	0.12
F7	-	20	40	-	-	40	0.12
F8	-	20	-	40	-	40	0.12
F9	-	20	-	-	40	40	0.16

Table 2. Composition of the granulated formulations.

Preparation of tablets

The milled granules were blended with 0.5% magnesium stearate in a tumbling blender for 2 minutes at 49 rpm (T2F, W.A. Bachofen, Basel, Switzerland) before tableting. Tablets were prepared in manual mode at a speed of 230 tablets per minute on the Modul^{TM} P tablet press (GEA Pharma Systems Courtoy^{TM}, Halle, Belgium). The press was equipped with 10 pairs of round flat-faced bevel-edged Euro B punches (GEA Pharma Systems, Halle, Belgium) (diameter 12 mm) and an overfill cam of 16 mm. The paddles in the feed frame were rotating at 15 and 20 rpm. Filling depths between 5.75 and 7.50 mm were used, dependent on the density of the samples. Tablets were compressed at 7 different main compression pressures in order to assess the tabletability of the granules: 60, 110, 150, 190, 260, 330, 410 MPa after precompression at 15 MPa. Tablets compressed at 190 and 330 MPa were selected for friability and dissolution testing.

Characterization methods

Laser diffraction

The particle size distributions of all starting materials were measured in duplicate by laser diffraction (Mastersizer S long bench, Malvern Instruments, Worcestershire, UK) and the average particle size distributions were calculated via the Mastersizer 2000 software. The dry dispersion technique was applied using a 1000 mm lens at a jet pressure of 3.2 bar (Malvern 220 Instruments, Worcestershire, UK). The results were expressed as volume diameters d_{10},

d_{50} and d_{90}. The span was calculated as $(d_{90}-d_{10})/d_{50}$ and was an indication of the width of the particle size distribution.

Loss on drying

The residual moisture content of the milled granules was determined via loss-on-drying using a moisture analyzer (Mettler LP16, Mettler-Toledo, Zaventem, Belgium) including an infrared dryer and a balance. A sample of 5 g was dried at 105 °C until the weight was constant for 30 s.

Particle size and shape analysis

The granule size and shape of all granules was analyzed before and after milling via dynamic image analysis using the QICPIC™ system (Sympatec, Clausthal-Zellerfeld, Germany) equipped with a vibrating feeder system (Vibri/L™) for gravimetrical feeding of the granules. Samples of 20 g were measured in duplicate. Averaged granule size distributions are shown, as the measurements were done in duplicate and the respective results did not differ from each other. Windox 5 software (Sympatec, Clausthal-Zellerfeld, Germany) was used to calculate the median granule size (d_{50}) as the equivalent projected circle diameter based on a volume distribution. The amounts of fines and oversized granules were defined as the fractions <150 µm and >1500 µm, respectively. The yield of the process was defined as the percentage of granules between 150 and 1500 µm. The aspect ratio (i.e. the ratio of the minimal Ferret diameter to the maximal diameter orthogonal to it) of the granules was determined to evaluate the shape of the granules. The median aspect ratio (a_{50}) of the granules was calculated by the Windox 5 software.

For analysis of drug content in the granules by Raman and UV spectroscopy, different size fractions of the milled granules were isolated by sieve analysis using a Retsch VE 1000 sieve shaker (Haan, Germany). Granules were placed on the shaker during 10 min at an amplitude of 2 mm using a series of sieves (150, 250, 500, 710, 1000, 1400 and 2000 µm). The amount of granules retained on each sieve was determined and isolated.

Flowability testing

The flowability expressed as the flowability index (ffc) of the milled granules was measured in duplicate by ring shear testing (Type RST-XS, Dietmar Schulze Schüttgutmesstechnik, Wolfenbuttel, Germany). The powders were tested using three consolidation stresses (250, 525 and 800 Pa) at a preshear of 1000 Pa.

Additionally, the compressibility index (C%) was calculated from the bulk and tapped densities of the milled granules. The bulk volume (V_0) of 30 g milled granules was measured in a 100 ml graduated cylinder as well as the tapped volume after 1250 taps (V_{1250}) in a tapping machine (J. Englesman, Ludwigshafen, Germany). Experiments were performed in duplicate. Bulk and tapped densities were calculated as 30 g/V_0 and 30 g/V_{1250}, respectively. The compressibility index was calculated from the bulk (ρ_i) and tapped (ρ_f) densities using the following equation:

$$C\% = [(\rho_f - \rho_i)/ \rho_f]*100$$

Friability analysis

The granule friability of the milled granules was determined in duplicate using a friabilator (PTF E Pharma Test, Hainburg, Germany) at a speed of 25 rpm for 10 min, by subjecting 10 g (I_{wt}) of milled granules together with 200 glass beads (mean diameter 4 mm) to falling shocks. Prior to determination, the granule fraction <250 µm was removed to assure the same starting conditions. Afterwards, the glass beads were removed and the weight retained on a 250 µm sieve (F_{wt}) was determined. The friability was calculated as:

$$[(I_{wt} – F_{wt})/I_{wt}]*100$$

Raman spectroscopy

Raman spectroscopy was applied on isolated sieve fractions to evaluate the distribution of theophylline over the sieve fractions. Raman spectra (Raman Rxn1, Kaiser Optical Systems, Ann Arbor, United States) of the samples were recorded (n = 5) using exposure times of 5 s with 3 accumulations. All spectra were recorded with a resolution of 4 cm^{-1}. The spectral region between 300 and 1500 cm^{-1} was selected for evaluation. Principal component analysis (PCA) was applied on the spectra with Simca 13.0.3 software (Umetrics, Umeå, Sweden). Data were corrected by standard normal variate preprocessing and center-scaled prior to analysis. Standard normal variate preprocessing was applied to eliminate the additive baseline offset variations and multiplicative scaling effects in the spectra which may be caused by small variations in distance between the Raman probe and the sample and possible differences in product density.

UV spectroscopy

The isolated sieve fractions were dissolved in water (1 mg/ml), diluted 20 times and measured by UV spectroscopy (UV-1650PC, Shimadzu Benelux, Antwerp, Belgium). The theophylline content in these samples was derived from their absorbance at 272 nm.

Tablet characterization

The hardness, thickness and diameter of the tablets (n = 10) were determined using a hardness tester (Type HT 10, Sotax, Basel, Switzerland) and the tensile strength (TS) of the tablets was calculated according to the formula of Fell and Newton [23]:

$$T = 2F/\pi dt$$

Where F, d and t denote the diametral crushing force, tablet diameter and tablet thickness, respectively.

The tablet friability of tablets compressed at 190 and 330 MPa was determined using a friabilator (PTFE, Pharma Test, Hainburg, Germany) as described in the European Pharmacopoeia at a speed of 25 rpm for 4 min. The percentage weight loss was expressed as the tablet friability.

Dissolution tests were performed (n = 3) in 900 ml demineralized water using the paddle method (VK 7010, Vankel, Cary, NC, USA). The temperature of the dissolution medium was maintained at 37 ± 0.5 °C, while the rotation speed was set at 100 rpm. Samples of 5 ml were withdrawn after 0.5, 1, 2, 4, 6, 8, 12, 16, 20 and 24 h. The drug content in these samples was derived from the absorbance of the samples at 272 nm using a UV spectrophotometer (UV-1650PC, Shimadzu Benelux, Antwerp, Belgium).

RESULTS AND DISCUSSION

Evaluation of the granulation process

Since HPMC swells upon hydration, excessive torque values might limit the processing of formulations with HPMC. Although inclusion of 40% HPMC in the formulations resulted in higher torque values compared to 20% HPMC, the torque was lower than 10 Nm for all experiments, which was far below the maximal torque (20 Nm) tolerated by the granulator.

Increasing the L/S ratio resulted in higher torque values until a critical L/S ratio was reached where torque became independent of L/S ratio. This is illustrated in Figure 2 for F9 where the L/S ratio was increased up to 0.18. Reports on the influence of L/S ratio of immediate release formulations on torque are contradictory, indicating linear or inverse relationships depending on the formulation [24, 25, 26]. Nevertheless, the results in current study were compatible with the regime map presented by Tu et al. on an immediate release formulation with microcrystalline cellulose (MCC), a component also known to swell upon hydration, reporting that the torque increased until a critical L/S ratio was reached and then decreased [27]. First

the torque increased at higher L/S ratios due to interparticle bond formation but after reaching a critical L/S ratio over-wetted malleable particles were formed resulting in lower torque readings.

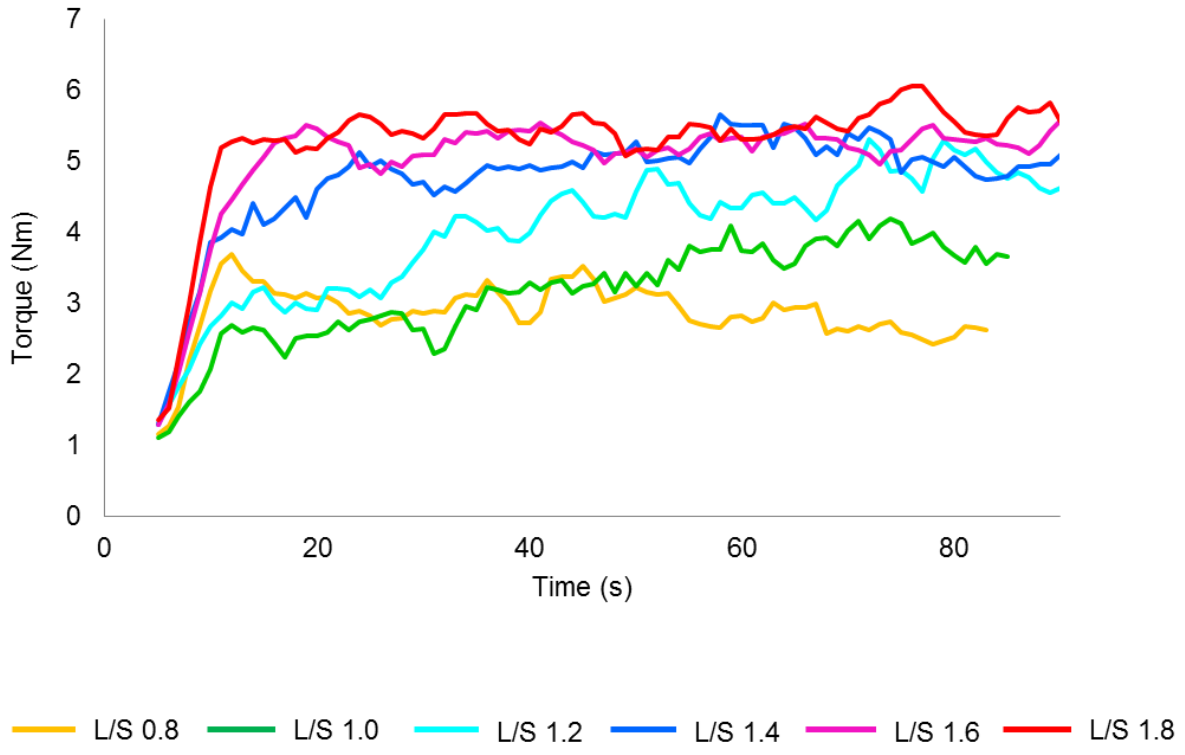


Figure 2. Torque profiles in function of L/S ratio for formulation F9.

Longer runs (at least 10 min) were performed using the optimized L/S ratio selected for each formulation (Table 2). The torque of these runs was compared to evaluate the influence of viscosity and the substitution degree of the HPMC grade on torque. The effect of these variables was most obvious with the formulations containing 40% HPMC. Inclusion of HPMC grades with a high viscosity and a high degree of hydroxypropyl substituents increased the torque. As viscous materials caused frictional resistance of the material to flow, the torque during granulation of F8 was higher compared to F7 (Figure 3). This is similar to literature reports on high torque values recorded during twin screw granulation with viscous liquids [24, 25]. Granulation of a formulation with HPMC substitution type 2208 (F7) resulted in higher torque values than with HPMC substitution type 2910 (F9) (Figure 3). The former type has more hydroxypropyl substituents and consequently swells faster upon hydration in the granulation process. This resulted in faster formation of a highly viscous gel structure, yielding high torque values. The particle size of the theophylline grade did not influence the torque.

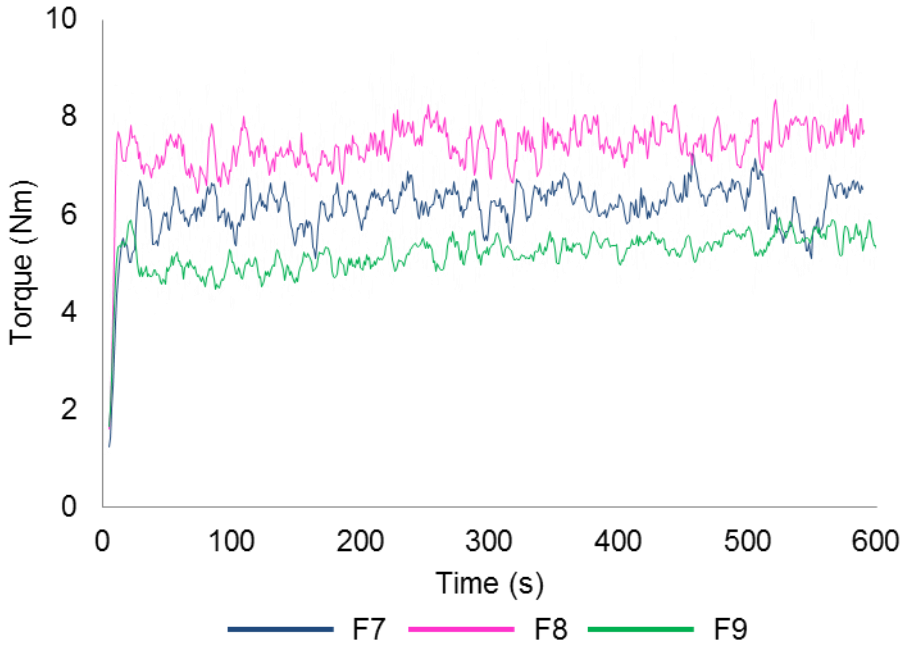


Figure 3. Torque profiles of F7, F8 and F9 granulated with optimized L/S ratios.

Influence of formulation variables on granule quality

Overall the granule size distribution (GSD) was broad which is a common observation for twin screw granulation, independently of the formulation [17, 24, 26, 27 28, 29, 30, 31, 32, 33, 34]. These multimodal distributions can potentially result in segregation during downstream processing and have a negative effect on the drying uniformity. Efforts have been made to obtain monomodal GSD after continuous granulation through optimization of the feeder performance, screw design, binder addition, liquid pump, nozzle design and operation at low filling degree [22, 28, 30, 35, 36]. However, for granulation of HPMC bimodal distributions were also reported on high shear granulation which was attributed to the specific granulation mechanism of HPMC [11]. HPMC grades used as matrix former quickly absorb water and develop a gel layer during granulation. This hinders uniform distribution of granulation liquid in the powder bed. Moreover the viscous gel layer is resistant against shear forces and consequently limits breakage of the granules, resulting in a bimodal distribution [11]. Thus, obtaining a monomodal GSD by twin screw granulation is even more challenging for controlled release formulations with HPMC compared to immediate release formulations.

The GSD (d_{50}, fines and oversized fraction) was evaluated in function of the L/S ratios and formulation parameters (substitution degree, viscosity and concentration of HPMC, particle size of theophylline). The d_{50}, fines and oversized fraction in function of L/S ratio are shown

in Figure 4 and Figure 5. Increasing the L/S ratio yielded granules with a higher d_{50}, fewer fines and more oversized granules. The formulations with HPMC substitution type 2910 (F3, F6 and F9) required more water for efficient granulation compared to HPMC type 2208 (F1 vs. F3, F4 vs. F6 and F7 vs. F9 in Figure 4). At a specific L/S ratio the granules with HPMC grade 2910 contained more fines and less oversized granules compared to the granules with HPMC grade 2208. This is linked to the higher hydrophilicity and faster polymer hydration of HPMC type 2208, which has less methoxy substituents than HPMC type 2910. This allows a faster interaction with water during twin-screw granulation, hence more bonds are formed between water and HPMC type 2208, yielding larger granules at a specific L/S ratio.

The molecular weight (and therefore the viscosity) of the polymers did not influence GSD (F1 vs. F2, F4 vs. F5 and F7 vs. F8 in Figure 5). The influence of the viscosity of cellulose-ether derivatives during twin screw granulation of immediate release formulations was studied in literature by varying the amount of binder in the granulation liquid. In these studies more binder resulted in larger granules which was linked to the higher binder viscosity [24, 36]. However, the viscosity of cellulose-ether derivatives used as binders in immediate release formulations is 100 to 100000-fold lower than the grades used for controlled release purposes. In addition, in immediate release applications the polymeric binder is often added to the process as an aqueous dispersion (i.e. via the granulation liquid), while HPMC in sustained release formulations can only be added dry (i.e. mixed with the other powder components prior to the addition of granulation liquid). Hence, the granulation behavior of cellulose-ether derivatives as binders in immediate release formulations cannot be compared to that of cellulose-ethers used as matrix former in sustained release formulations.

While granule growth was affected by the substitution degree of HPMC during twin screw granulation, the viscosity of HPMC and not the substitution degree influenced GSD during high shear granulation [9]. This difference is likely due to the difference in residence time between continuous (5 – 20 s) and high shear granulation (tens of minutes) as the substitution degree (and thus hydration rate) only influences granule growth when the contact time between water and polymer is short [24, 26, 32, 36].

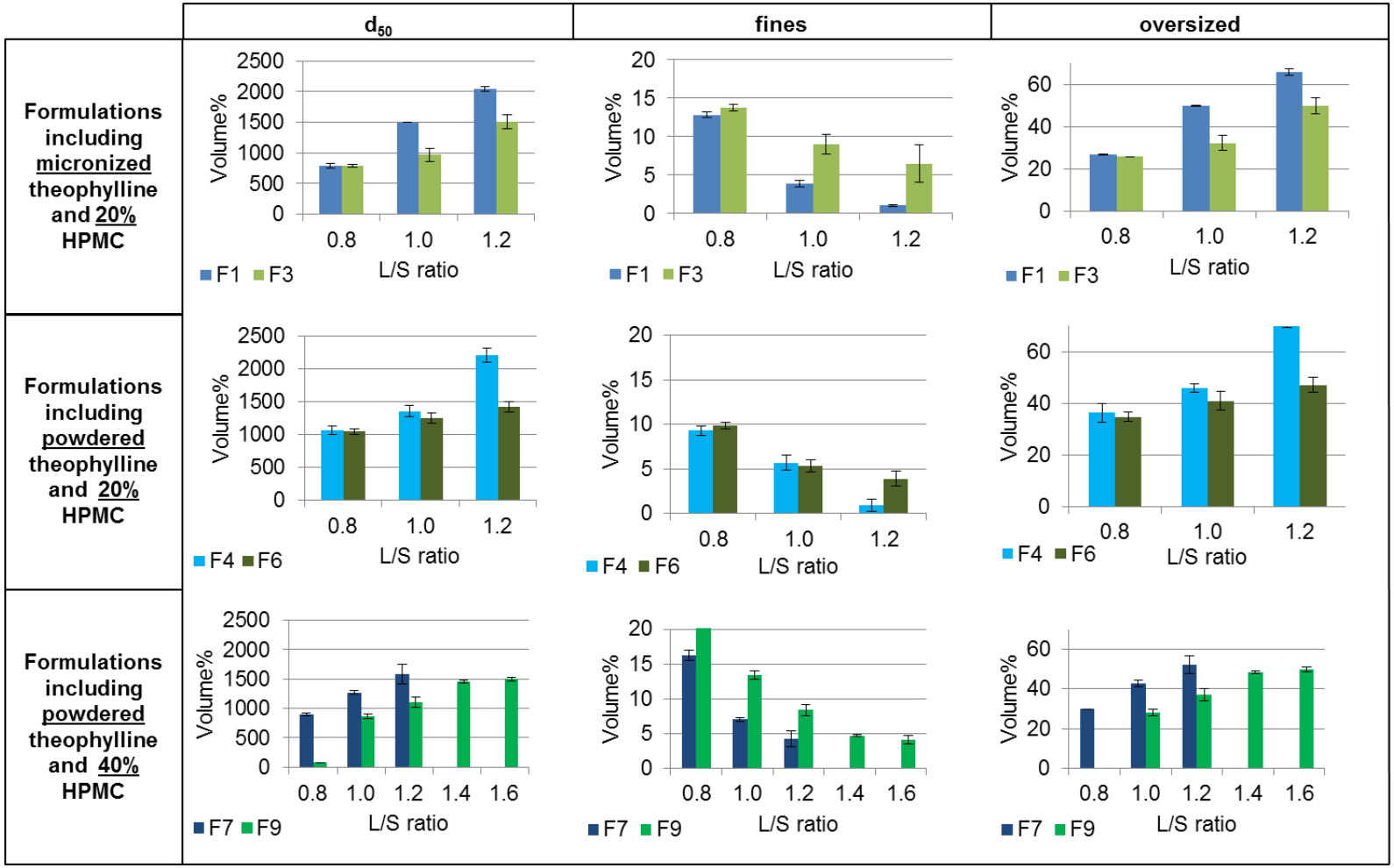


Figure 4. Influence of HPMC substitution degree on granule size distribution: d_{50}, fines fraction and oversized fraction of F1 and F3 (formulations with micronized theophylline and 20% HPMC), F4 and F6 (formulations with powdered theophylline and 20% HPMC) and F7 and F9 (formulations with powdered theophylline and 40% HPMC) as a function of the applied L/S ratio.

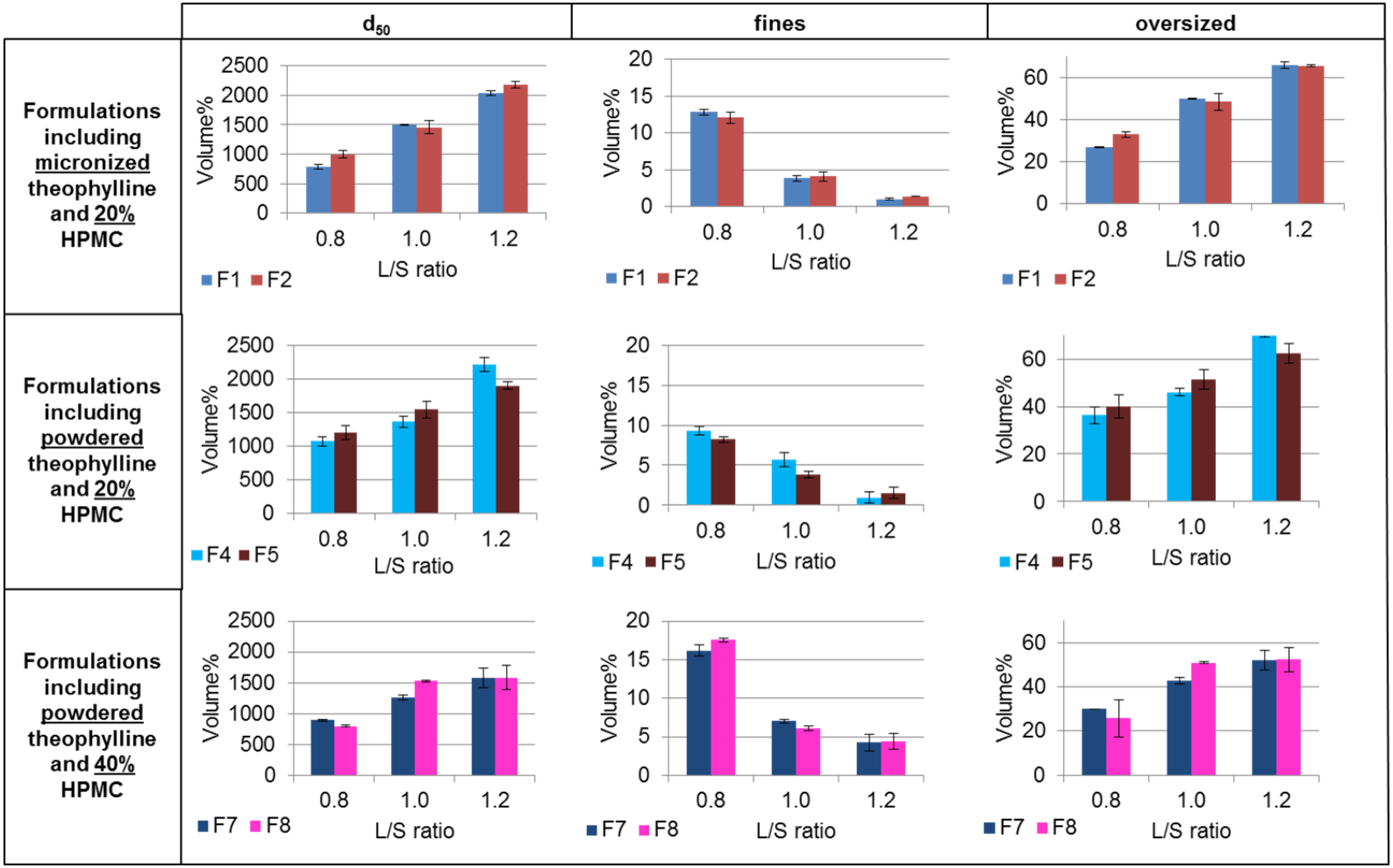


Figure 5. Influence of HPMC viscosity on granule size distribution: d_{50}, fines fraction and oversized fraction of F1 and F2 (formulations with micronized theophylline and 20% HPMC), F4 and F5 (formulations with powdered theophylline and 20% HPMC) and F7 and F8 (formulations with powdered theophylline and 40% HPMC) as a function of the applied L/S ratio.

Inclusion of a higher HPMC concentration in the formulation required more water to obtain granules with a similar GSD. This is illustrated in Figure 6 for the formulation with HPMC type 2910 and was attributed to the high water binding capacity of HPMC. To evaluate the influence of raw material variability on processability, granule and tablet critical quality attributes, two theophylline grades (F1-3: micronized, F4-6: powdered grade) were included in the formulations. The particle size distributions of all starting materials were summarized by their d_{10}, d_{50}, d_{90} and span (Table 2). The particle size of micronized theophylline was significantly smaller than of the powdered grade. However, the primary particle size of theophylline starting material did not influence the GSD of the formulations. This is in agreement with research of El Hagrasy et al. on immediate release formulations, reporting limited differences in GSD among formulations with different lactose grades at low L/S ratios [32]. At higher L/S ratios a direct correlation between the primary particle size of lactose and GSD was established by El Hagrasy et al. [32]. Furthermore, Fonteyne et al. linked the primary particle size of theophylline to differences in the GSD [37]. In the current study the inclusion of a high percentage of HPMC, which in addition to its function as matrix former also acts as binder, probably eliminated the effect of primary particle size on GSD.

For each formulation an optimal L/S ratio was selected based on the GSD results: yielding granules with less than 10% fines, less than 52% oversized granules and a d_{50} between 1300 and 1600 µm. As the GSD was broad, milling was necessary to narrow down the GSD before tableting. Therefore, a large fraction of oversized granules was tolerated in these samples. After milling, the samples were further analysed with regard to flowability, friability, distribution of theophylline over the sieve fractions and finally tableted. The yield of the process before milling varied between 40 and 49% which was mainly due to an extensive oversized fraction. This fraction was eliminated by milling, resulting in a yield varying between 78 and 86%.

The median aspect ratios varied between 0.57 and 0.63 (Figure 7). This is slightly lower than typically reported for immediate release formulations [17, 21, 24]. The aspect ratios of the formulations with HPMC substitution type 2910 were higher compared to formulations with HPMC substitution type 2208, although the differences were minor. As the viscous gel layer of HPMC type 2910 formed slower due to the lower number of hydrophilic substituents, granules containing type 2910 are more deformable during the granulation process, yielding a higher aspect ratio. No correlation between the median aspect ratios and the applied L/S ratio was detected.

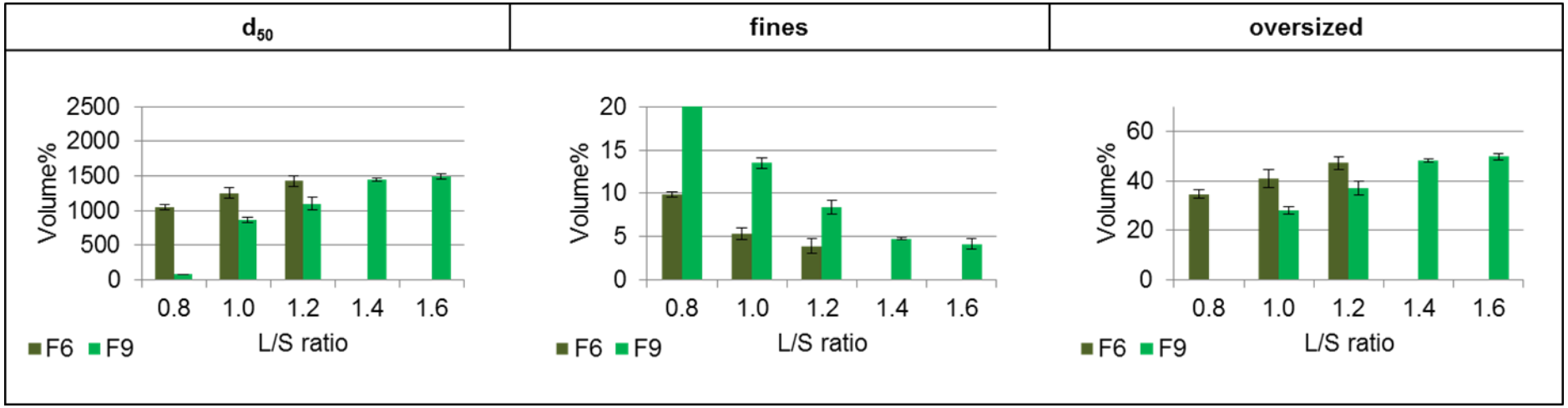


Figure 6. Influence of HPMC concentration on granule size distribution: d_{50}, fines fraction and oversized fraction of F6 and F9, containing 20 and 40% HPMC, respectively.

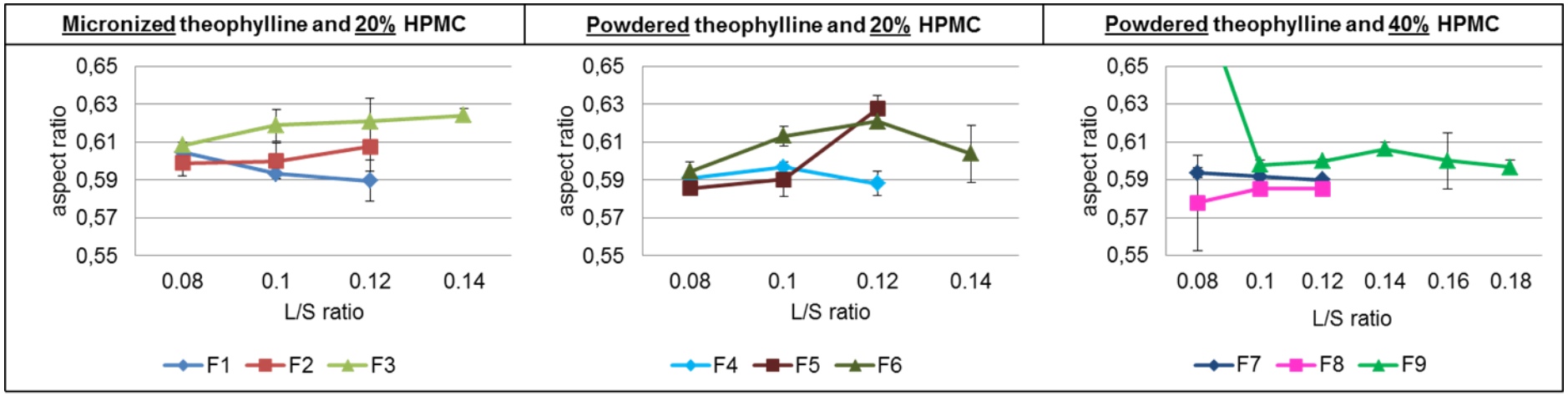


Figure 7. Aspect ratios at varying L/S ratios.

Thompson et al. reported the formation of elongated noodle-like granules (3-10 mm) during granulation with HPMC type 2208, even with formulations containing only 5% HPMC. In the current study a similar screw design was used but no elongated granules were formed with either HPMC grade. This confirmed previous research of our group, studying the influence of process parameters on the granulation behaviour of a formulation with HPMC type 2208, where no elongated granules were formed [22]. Thus, granule shape was not an issue for granulation of formulations with different types of HPMC.

All granules were classified as passable and easy-flowing according to the C% and ffc values, respectively [38]. The friability of the granules was low, varying between 8.1 and 13.9 % (friability lower than 30% is considered acceptable, using the applied method).

The content uniformity of theophylline over 8 sieve fractions was evaluated by Raman and UV spectroscopy for all formulations. The results of the Raman analysis were summarized in a PC 1 vs. PC 2 scores plot of the first and second principal components (PC) explaining 54 and 25% of variation in the dataset, respectively (Figure 8). The spectra of the fines fraction (< 150 µm) were clustered in the negative part of PC 2 while the spectra of fractions 150-250 µm and 250-500 µm were clustered in the positive part of PC 2. The other size fractions were distributed homogeneously over the PC 1 vs. PC 2 scores plot. Comparison of the spectra of lactose and theophylline to the loading plot of PC 1 and PC 2 learned that PC 1 represented variation due to baseline offset variations while the maxima and minima of the PC 2 loading plot were characteristic for theophylline and lactose, respectively (Figure 9). This signified that theophylline was underdosed in the fines fraction (on average 15% less theophylline) and overdosed in the fractions 150 - 250 µm and 250 - 500 µm (an excess of 7 and 6%, respectively). The uneven distribution of theophylline over the size fractions was present in all formulations, independently of the viscosity and substitution degree of HPMC. Comparable observations were made after batch granulation of immediate release formulations [39, 40]. These studies pointed at differences in primary particle size between drug and fillers to explain preferential granule growth and consequently inhomogeneous drug distribution over the size fractions. Despite the similar primary particle size of lactose and powdered theophylline in formulations F4-6, theophylline was not evenly distributed over the size fractions of these formulations. This was also observed by Fonteyne et al. after continuous granulation of an immediate release formulation [37]. However, no explanation was found for the observations. Thorough characterization of the starting materials (e.g. solubility, solubility rate, wettability) could help to reveal the granulation mechanism leading to uneven API distribution over the size fractions of granules produced by twin screw granulation.

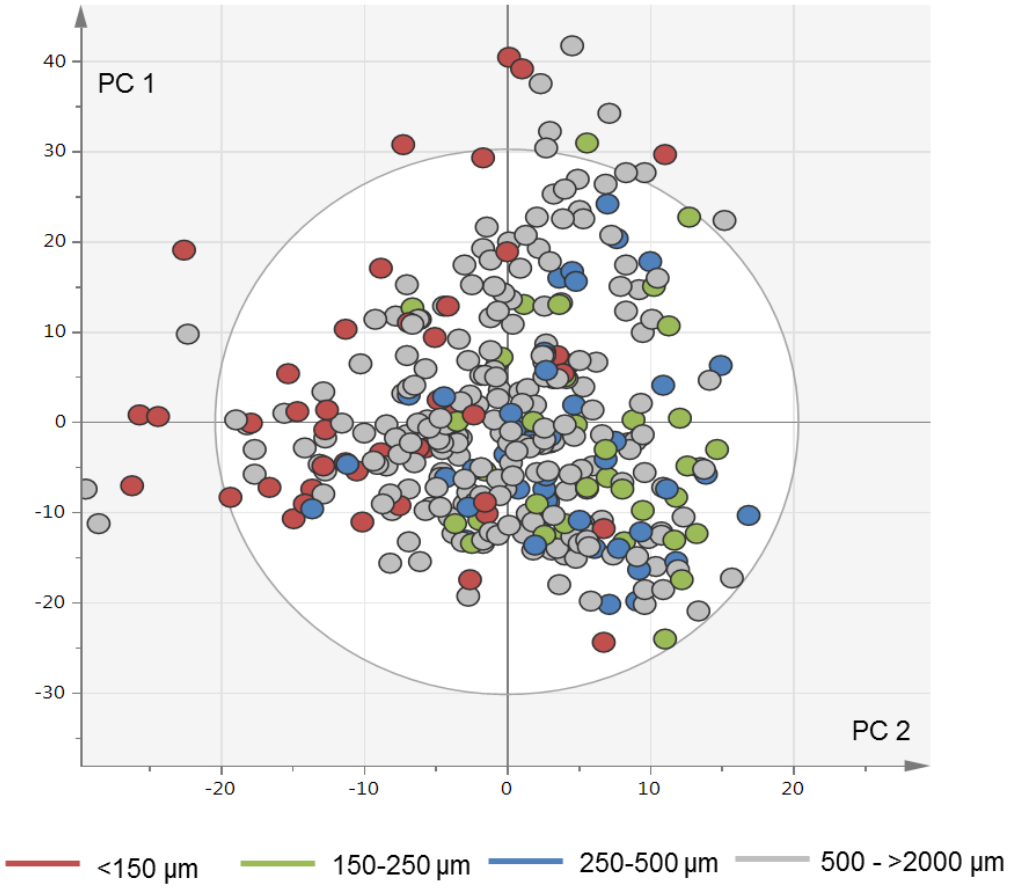


Figure 8. PC1 vs. PC2 scores plot obtained after PCA analysis on 8 sieve fractions of all formulations.

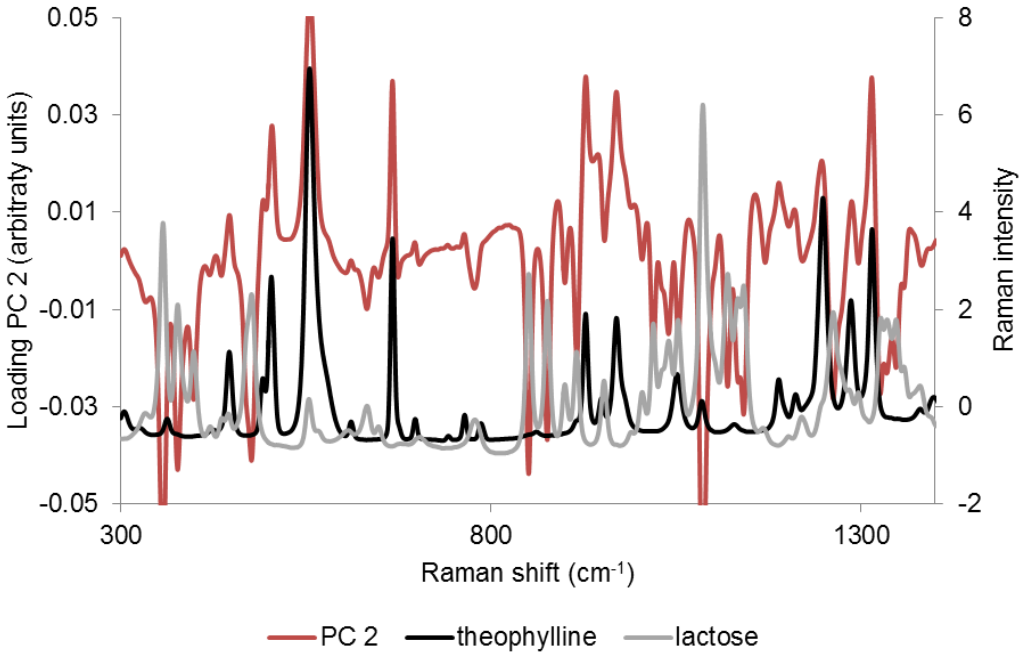


Figure 9. Raman spectra of pure lactose and theophylline and loading plot of PC 2 after PCA analysis.

Influence of the formulation variables on tablet quality

The tensile strength (TS) of the milled formulations tableted at 7 main compression pressures (MCP) was measured. The particle size distributions and moisture content of the different formulations were similar and could not bias the comparison of the formulations. A linear relationship between TS and MCP was established for all formulations. No differences in TS were detected between the formulations containing 20% HPMC, whereas the viscosity and substitution degree of HPMC influenced the TS of the formulations containing 40% HPMC (Figure 10). F7, containing an HPMC grade with a lower viscosity, showed a lower TS than F8, containing an HPMC grade with a higher viscosity. Similar observations were made after high shear granulation of HPMC with different viscosities [9]. This was attributed to the stronger plastic deformation during compression of HPMC grades with a high viscosity [9]. Comparing F7 (containing HPMC type 2208) and F9 (containing HPMC type 2910), it is clear that the substitution degree of HPMC also affected the TS of formulations containing 40% HPMC. HPMC type 2208 contains more hydrophilic substituents that can form hydrogen bonds during compression, yielding harder tablets. This in agreement with research on the compaction behavior of HPMC with different substitution degrees after direct compression and batch granulation [4, 9, 41, 42, 43, 44]. The particle size of theophylline starting material did not influence the TS.

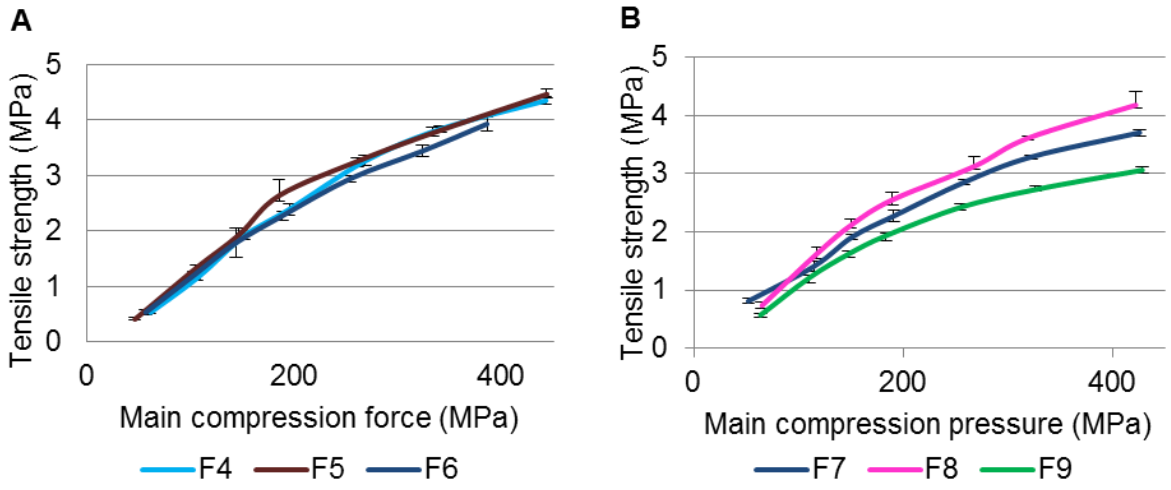


Figure 10. Tabletability of (A) F4 - 6 (containing 20% HPMC) and (B) F8 - 10 (containing 40% HPMC).

Considering the linear relation between TS and MCP, the friability of tablets compressed at an intermediate (190 MPa) and high (330 MPa) MCP was determined. The friability of all tablets was low, varying between 0.05 and 0.16%. The tablets compressed at a higher MCP were harder and consequently less friable. No correlation between HPMC or theophylline grade and the friability of the corresponding tablets was detected.

The influence of viscosity and substitution degree of HPMC on the drug release rate after direct compression and batch granulation was already extensively studied [4, 9, 12]. However, a comparative study between twin screw granulation and high shear granulation demonstrated that granules produced by twin screw granulation were denser and that the drug release rate from tablets derived from these dense granules was slower [34]. Therefore the influence of viscosity and substitution degree of HPMC on drug release was investigated after twin screw granulation in the current study.

The release of tablets compressed at 190 MPa and 330 MPa was measured but MCP did not significantly influence the release, a similar observation was already reported after high shear granulation [43]. Inclusion of 20% HPMC type 2208 resulted in controlled release of theophylline over 24 h, while complete drug release was obtained after 16 h with 20% HPMC type 2910 (F4 vs. F6 in Figure 11). The viscosity of HPMC also influenced the release rate of theophylline, a higher viscosity resulting in a slightly slower release (F4 vs F5 in Figure 11). At 40% polymer load, the drug release was only affected by the viscosity of HPMC and not by its substitution degree. Incomplete release (80%) of theophylline was obtained with the highest viscosity HPMC grade (F8), while F7 (HPMC type 2208) and F9 (HPMC type 2210) showed identical dissolution profiles and complete release after 24 h. These dissolution profiles also approached zero-order kinetics. Thus, at low polymer load the faster hydration of HPMC type 2208 resulted in a faster formation of the matrix and at both polymer loads the higher viscosity of HPMC formed a more tortuous and resistant barrier to diffusion and erosion, resulting in slower release rates. These results are in accordance with dissolution studies of HPMC after direct compression and batch granulation [4, 9, 12, 14, 41, 43, 45, 46]. The particle size of theophylline starting material did not influence the release of the formulations.

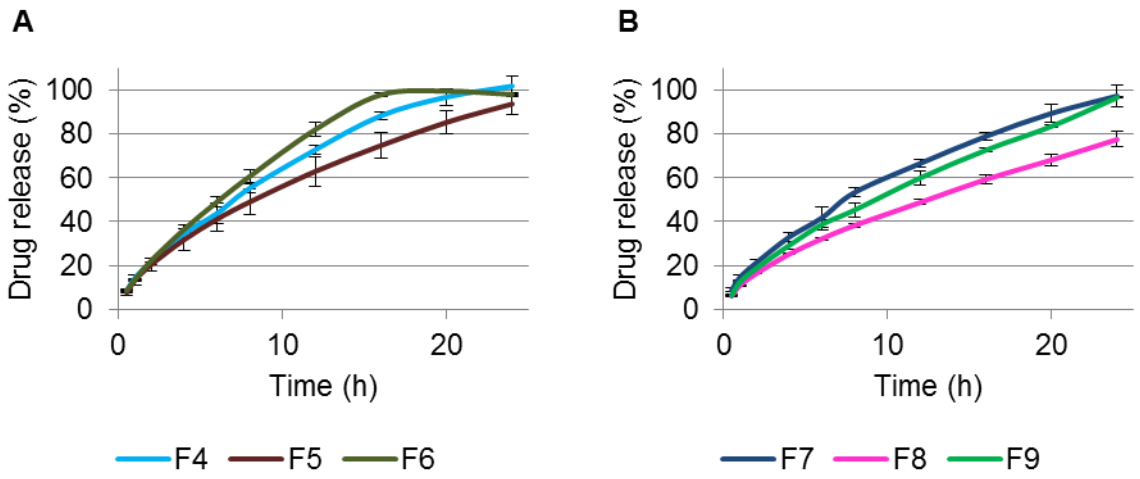


Figure 11. Dissolution profiles of (A) F4 - 6 (containing 20% HPMC) and (B) F7 - F9 (containing 40% HPMC).

CONCLUSIONS

HPMC was identified as versatile matrix former for manufacturing of controlled release formulations via twin screw granulation using water as granulation liquid. The torque during processing was linked to viscosity and hydration rate of HPMC, but the recorded torque values did not limit the process. HPMC type 2910 required more water during granulation to obtain a similar granule size distribution compared to HPMC type 2208 which was attributed to its lower hydrophilicity. Although theophylline was not homogenously distributed over the size fractions (with a lower theophylline content in the fines fraction), this phenomenon was not correlated to the hydration rate or viscosity of HPMC. The release of theophylline was independent of the compression pressure but could be steered by the viscosity and substitution degree of HPMC to obtain sustained release over 24 h.

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7

BROADER INTERNATIONAL CONTEXT, RELEVANCE AND FUTURE PERSPECTIVES

BROADER INTERNATIONAL CONTEXT

The International Council for Harmonization (ICH) issued high-level guidelines concerning pharmaceutical development to promote the 'quality-by-design' principle which signifies that 'quality cannot be tested into products but should be built in by design' [ICH Q8]. This principle encompasses that product and process knowledge is required for the development of a robust process delivering high quality products. Continuous drug manufacturing perfectly meets this principle as a high level of product and process knowledge is also required for effective implementation of PAT and control strategies and eventually to routinely run the continuous production process for a longer period [1].

Implementation of continuous manufacturing in the pharmaceutical industry requires more in-depth process knowledge, innovative technologies, new equipment, strict control strategies and different plant design compared to batch processes. To achieve this academia, industry and equipment manufacturers joined forces in several global consortia:

- C-SOPS (Center of Structured Organic Particulate Systems): is a multi-university consortium (Rutgers University, Purdue University, New Jersey Institute of Technology, University of Puerto Rico) founded in 2006. It is funded by the National Science Foundation, about 40 industrial member companies and several equipment manufacturers. Their research includes three areas: manufacturing science, composite synthesis and characterization and functionalization [2].

- Blue sky vision project: A 10-year, 65-million dollar collaboration between Novartis and the Massachusetts Institute of Technology (MIT) focusing on the development of a truly continuous manufacturing line from the primary manufacturing stage. This involves the development novel technologies and new synthesis approaches [2].

- European Consortium for Continuous Pharmaceutical Manufacturing: a collaboration between the Research Centre Pharmaceutical Engineering (RCPE) (Graz, Austria), industrial partners (AstraZeneca UK, Automatic Pelletizing Systems, Bayer Health Care Germany, GEA Pharma Systems Belgium, Siemens Austria, UCB Belgium) and four academic partners (Graz University of Technology, University of Eastern Finland, Heinrich Heine University Düsseldorf, Ghent University). This consortium focuses on investigation, development and implementation of continuous manufacturing strategies for solid oral dosage forms.

- Britest: a membership based consortium developing innovative approaches to manufacturing and process design. Pharmaceutical companies (e.g. Pfizer, Hovione, Abbvie,

Astra Zeneca) and universities (University of Nottingham, Newcastle University, Purdue University, University of Limerick) joined forces in this consortium [2].

- L. B. Böhle Technology Center: A collaboration between industrial and academic partners working on the development and implementation of a modular production line for continuous manufacturing. Equipment manufacturers (Korsch, Gericke and Böhle), academic partners (Heinrich Heine University Düsseldorf, RWTH Aachen University and RCPE Graz) and companies specialized in PAT equipment and control strategies (Kaiser Optical Systems, Kraemer Elektronik and Sentronic) work together on this project.

A continuous twin screw granulation process using a modified twin screw extruder was developed and patented by the Laboratory of Pharmaceutical Technology (Ghent University). This granulation process was incorporated in the ConsiGma™ continuous tableting line (GEA Pharma Systems). The continuous 'from-powder-to-tablet'-line ConsiGma™-25 as well as the ConsiGma™-1 intended for early R&D work have been sold worldwide (e.g. US, Mexico, UK, Switzerland, Japan, France, Belgium, Korea, Sweden, Singapore, Germany, Italy) over recent years. Currently at least three products are approved by the competent authorities for continuous manufacturing (Severin® and Antiflu-des® by Chinoin on the Mexican market and Kalydeco® by Vertex on the US market). It is however expected that over the coming years much more continuously manufactured drug products will be commercialized as several big pharma companies announced investments in the continuous manufacturing technology (e.g. Novartis, Roche, Pfizer, AstraZeneca, GlaxoSmithKline, Johnson and Johnson) [2-5]. Additionally, the European and US competent drug authorities (EMA and FDA) support the implementation of this innovative technology for manufacturing of drug products [6, 7].

RELEVANCE

Continuous manufacturing offers opportunities for highly educated and skilled staff, delivery of high quality products, cost reduction during drug development and production and lower environmental impact, and consequently has a positive effect on society.

Economical

As explained in the introduction, continuous manufacturing requires sound process knowledge but also tools for implementation of risk management strategies, design of experiments, profound formulation knowledge, advanced data analysis, statistics, process modeling and control. Partnerships and exchange between academia, industry and government play a crucial role in education and training in these areas as future pharmaceutical plants that operate continuously are likely to settle in regions where highly skilled staff is available. Availability of skilled staff in combination with a smaller footprint and

reduced manufacturing costs make continuous pharmaceutical manufacturing ideally suited for implementation in Europe or the US [3, 8]. This is a great opportunity in an era where most industries, including the pharmaceutical industry, moved production sites out of Europe and the US as this makes economically sense for labor-intensive production activities that require low skilled staff. Therefore fundamental process knowledge about continuous processes available at academic institutions in Europe and availability of highly educated and trained staff will be crucial to convince pharmaceutical companies to build new continuously operating manufacturing plants in Europe. Settlement and anchoring of pharmaceutical R&D and manufacturing activities in Europe involves direct and indirect employment and fast availability of new therapies to patients.

Improved product quality

Improved product quality of continuously manufactured drug products is achieved by plug-flow of material during continuous processes and implementation of PAT for continuous monitoring of critical quality attributes. Drug products manufactured in a batch wise manner often suffer from batch-to-batch variability as the heat, mass and momentum experienced by material in a batch process differs with the position in the equipment [9]. In contrast, materials move in plug-flow during continuous processing, resulting in improved and constant product quality. Continuous manufacturing and PAT are inextricably connected as implementation of PAT probes will allow adjustment of process parameters to drive critical quality attributes to the requested target levels during continuous manufacturing and will allow real time release of drug products after continuous manufacturing. Thus by the very nature of continuous manufacturing, quality is built into continuously manufactured products.

Furthermore, the agility, flexibility and robustness offered by continuous manufacturing could prevent drug shortages, accelerate the response to changing market needs and allow faster market access. Drug shortages are a real threat to public health and are often initiated by failing product quality, followed by product recalls. Therefore the FDA recognized the potential of continuous drug manufacturing to prevent these drug shortages [10]. Continuous manufacturing also offers a faster response to changing market needs (e.g. epidemics, emergencies) as real time release testing of the drug product decreases the time-to-market and scale-up issues are eliminated. Additionally, the typically smaller continuous production plants are installed faster than their batch counterparts and can be setup in portable containers that are shipped around the world [11]. This is also a tremendous advantage with regard to breakthrough therapies (therapies for serious and life-threatening diseases that demonstrate substantial improvement over existing therapies in preliminary clinical tests) [3]. A drug product designated as ‘breakthrough therapy’ profits from expedited review by the

competent regulatory authority to accelerate market access. Continuous manufacturing is ideally suited for development and manufacturing of these therapies as less API is necessary during development and manufacturing sites can be installed quickly after approval. Hence, continuous manufacturing enables fast patients' access to therapies for serious and life-threatening diseases.

Reduced environmental impact

A significant smaller environmental impact is associated with continuous manufacturing in comparison to traditional batch manufacturing. This is due to a reduction of solvent use, of resource consumption during continuous manufacturing and of waste. Firstly, as less API is necessary during drug development, less solvent and reagent are consumed. The solvents (often chlorinated and aromatic) and reagents (often polycyclic compounds with hetero-atoms that are little or not biodegradable) involved in API production require special care with regard to their disposal to avoid negative effects on humans and the environment. Secondly, a resource reduction (heating, electromechanical power, chemicals, cleaning agents and their disposal, compressed air) can be achieved through adoption of continuous manufacturing [12]. The typically drastically reduced footprint of a continuous manufacturing plant (with less intermediate storage, stockpiling, material handling and off-line quality control) adds to the reduced resource consumption in comparison to batch wise operating plants since less energy is needed to condition the smaller production areas [8, 13]. Thirdly, the environmental impact of continuous pharmaceutical manufacturing is also less as the risk of quality failures is reduced [9]. In contrast to batch manufacturing, where the entire batch is at risk during production, corrections during the process are possible through in-line monitoring of critical quality attributes of intermediates by PAT and implementation of feedback and –forward loops.

FUTURE PERSPECTIVES

Twin screw granulation

Current research provided more knowledge regarding twin screw granulation of (1) δ-mannitol, a promising novel excipient to improve the tabletability of a formulation, and (2) a controlled release formulation with HPMC. However, much more knowledge and experience is required before continuous lines will routinely be operated for manufacturing of drug products. Future research topics should include process control strategies, development of new PAT interfaces and on-line probes, a design space approach for validation, modeling of variances and their propagation through the process and interactions between process and

formulation parameters. Below a few process and formulation related topics are identified for further investigation.

A controlled release formulation including HPMC was successfully granulated on the twin screw granulator incorporated in the ConsiGma™ system and tableted after tray drying and off-line milling. However, the suitability of the ConsiGma™ system for further downstream processing (i.e. drying, milling, material transport between the unit operations) of controlled release formulations should also be investigated. Additionally, the suitability of twin screw granulation for other commonly used controlled release polymers (e.g. hydroxypropylcellulose, polyvinylacetate/povidone) should be studied.

Formulations with different HPMC types were processable by twin screw granulation and drug release could be steered through variation of their concentration, viscosity and substitution degree. However, the ranges tolerated by the Ph. Eur. and USP with regard to viscosity and substitution degree of HPMC grades are broad and the batch-to-batch variability of HPMC could influence the granulation behavior of formulations with identical HPMC grades. Therefore, the influence of HPMC batch-to-batch variability on critical quality attributes of granules and tablets should be well studied and accounted for in the determination of the design space. In future research, the potential of feed-forward loops to compensate for the batch-to-batch variability of HPMC should be evaluated.

The API distribution over different size fractions of controlled release granules produced by twin screw granulation was investigated in the current study. The recovery of API in the fines fraction (<150 µm) was lower than targeted. Even when the primary particle size and density of API and excipients were similar, less API was retrieved in the fines fractions. Uneven API distribution over different size fractions of granules is undesirable as it can potentially result in content uniformity issues after tableting. Thorough characterization of the starting materials (e.g. solubility, solubility rate, wettability) should be performed to reveal the granulation mechanism leading to uneven API distribution over the size fractions of granules produced by twin screw granulation. Additionally the influence of binder addition (type, concentration, wet or dry addition) on the API distribution should be investigated.

Although twin screw granulation of formulations with HPMC was not limited by excessive torque values, longer runs should be performed to assess the stability of the process over a longer period. Process outcomes (e.g. torque, barrel temperature, pressure over the bag filters) and critical quality attributes of granules and tablets should be monitored over time to investigate if the process is capable of delivering a product with constant properties during routine operation for weeks.

In the current work the release of good soluble drugs was prolonged through twin screw granulation with HPMC. In contrast, the release of poorly soluble drugs processed via twin screw granulation should be fast enough to reach a high bioavailability. Therefore the influence of process and formulation parameters on the release profile of poorly soluble drugs should be investigated. Granules with a low porosity could favor the release rate of poorly soluble drugs. Studies comparing the porosity of granules after batch (high shear and fluid bed granulation) and continuous granulation are also needed as it is expected that over the coming years existing formulations will be switched from batch to continuous processing.

Conversion of δ- to β-mannitol during twin screw granulation was associated with an increased specific surface area and a needle-like surface structure of the granules. This resulted in granules with excellent tabletability. In future work, the potential δ-mannitol as preferred excipient for twin screw granulation of a poorly tabletable API should be investigated. Inclusion of API in the formulation could affect the solubility of δ-mannitol and consequently the crystallization reaction from δ- to β-mannitol. Additionally, the potential of δ-mannitol as excipient for production of tablets on the ConsiGma™ line should also include experiments on the fluid bed dryer incorporated in the ConsiGma™ line as the drying parameters (air flow, temperature, filling degree of the dryer cell) could also affect the polymorphic transition during drying of the granules.

A thin powder layer along the screw chamber wall is frequently observed after twin screw granulation. As in the end continuous processes are intended for production during weeks and months, accumulation of material in the system is not acceptable due to risk of product degradation. Therefore it should be investigated whether the layer covering the screw chamber wall is static or dynamic (i.e. the material sticks temporarily to the barrel) and whether the build-up of the layer is correlated to the process parameters used.

During melt granulation, a molten binder is used instead of an aqueous binder solution, eliminating a (semi-continuous) drying step after granulation. Therefore melt granulation by continuous twin screw granulation is of interest and the feasibility of melt granulation using the granulator barrel of the ConsiGma™ system should be investigated. This might be challenging as the short residence time of material in the granulator barrel could limit the heat transfer needed to melt the binder.

Although scaling-up of continuous processes can be avoided by running the process for a longer time, larger equipment scales are necessary for products requiring a high throughput. Therefore, the ConsiGma™ Continuous Tableting Line is available in different sizes (ConsiGma™-25, 50, 100 with a throughput of 25, 50 and 100 kg/h, respectively). However, practically no information is available concerning the transfer of a formulation from a smaller

to larger scale twin screw granulator. Hence the effect of the dimension of the granulator barrel and dryer cells on the granule quality should be investigated and the most important scaling factors should be identified.

Twin screw granulation received much attention over recent years and a lot of research papers on continuous twin screw granulation were published. Herein, different research groups reported the appearance of wide and multimodal granule size distributions. However, it is often hard to interpret and correlate the data as research was done using non-identical equipment (e.g. GEA Pharma Systems, Thermo Fisher Scientific, Leistritz). Moreover, some of these studies provided contradictory results. Besides the experimental studies, efforts are made for predictive modelling and model-based analysis of the experimental data. In order to be more generic such models also require consideration of these equipment differences to provide more robust predictions and accurate analysis. Therefore, a detailed study comparing process performance as well as product quality after granulation on different twin screw granulators is of interest.

Spray drying

It is expected that in the long run continuous processes will involve homogeneous processing technology in which API's and excipients are processed together with a minimum of in-process product transfer. Spray drying is extremely suited to achieve this aim as – at the end of primary manufacturing - excipients can be mixed into a purified API solution and further processed together. Additionally, the spray dried process is well studied and widely applied. However, before spray drying of dissolved excipients in a purified API solution becomes routinely applicable, more research is needed regarding (1) solvents used during API synthesis and (2) development of a formulation platform to match API characteristics with the appropriate excipients. Ideally, an aqueous solution of API is obtained in the final stages of primary drug manufacturing to eliminate issues of residual solvents after spray drying. Spray dryers in closed loop can handle organic solvents but often the amount of residual solvent in the spray dried product exceeds the acceptance limit, making secondary drying steps necessary. Next, excipients cospray dried with API should be carefully selected as coprocessing can affect the crystal structure and habit of API and excipient which in turn influences the tabletability and bioavailability of the final spray dried product.

In the current project co-spray drying mannitol and PVP yielded δ-mannitol with excellent tableting properties. A mixture of the spray dried δ-mannitol/PVP particles (25%) could be directly tableted with highly dosed paracetamol (75%) that is known for its poor tabletability. Additionally, paracetamol crystals were coprocessed during the spray drying process using an modified setup for crystal coating. In future work, mannitol and PVP could also be

cospray dried with API to deliver a directly compressible powder mixture. Challenges will include (1) the influence of the API on the crystallization of the excipients and vice versa, and (2) continuous mixing of polymer/API/excipient during solution preparation as slow dissolution of polymers can limit the performance.

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GENERAL CONCLUSIONS

Agglomeration processes are often necessary to improve the flowability, homogeneity and tabletability of powders prior to tableting. Spray drying and twin screw granulation, the techniques studied in this thesis, are continuous agglomeration processes with high potential for implementation in continuous 'from-powder-to-tablet' lines.

The first objective of this doctoral thesis was to develop a modified spray drying method to improve the flowability and tabletability of drug formulations with poor tabletability. The developed method included the introduction of solid, dry particles into an atomized spray during spray drying in order to coat and agglomerate individual particles. The setup proved promising to coat paracetamol crystals with amorphous lactose and PVP, resulting in particles with excellent tabletability. Additionally, the proposed method was suitable for the production of direct compression lactose. However, the extent of agglomeration achieved during coprocessing was limited.

The δ-polymorph of mannitol was continuously produced by spray drying of a mannitol/PVP (ratio 4/1) solution. Compression experiments confirmed that δ-mannitol exhibited superior tabletability in comparison to α- and β-mannitol. Next, paracetamol and δ-mannitol were coprocessed through application of the modified spray drying method. The tabletability and friability of the resulting particles was excellent which was attributed to the superior tabletability of δ-mannitol over α- and β-mannitol and to the application of the modified spray drying method which enabled coating of paracetamol crystals with δ-mannitol and PVP.

The second aim of this project was to evaluate the potential of β- and δ-mannitol as excipient during twin screw granulation. A different granulation behavior of mannitol was identified during continuous twin-screw granulation compared to other commonly used excipients such as lactose and microcrystalline cellulose (MCC) as the effect of granulation parameters (filling degree, screw speed, number of kneading elements) on the granule size distribution of mannitol granules was different compared to literature reports on formulations containing lactose and/or MCC as filler. Based on the higher solubility and faster dissolution rate of mannitol it was concluded that granulation of mannitol was principally driven by formation of liquid and solid bridges of solubilized material, rather than by compressive forces in the granulator barrel. A polymorphic transition from δ- to β-mannitol during twin screw granulation was also reported. However, the polymorphic transition was not complete in all experiments and depended on the liquid-to-solid ratio, screw speed and number of kneading elements. Nevertheless all granules exhibited a unique morphology linked to the polymorphic transition and had a superior tabletability compared to granules produced with β-mannitol as

starting material. This was attributed to enhanced plastic deformation of the granules manufactured using δ-mannitol as starting material.

The third aim was to investigate the potential of twin screw granulation with water as granulation liquid, for the production of a controlled release formulation with HPMC as matrix former. Although HPMC swells upon hydration, high torque values did not limit the granulation process. Addition of screw mixing elements after a block of kneading elements and a higher barrel temperature positively influenced the process yield. The shape of the controlled release granules was comparable to the shape of immediate release granules reported in literature. Although the tablet hardness and friability and drug release were not dependent on the process parameters, they could be steered by formulation parameters (substitution degree and concentration of HPMC). HPMC proved to be a useful and versatile matrix former for manufacturing of controlled release formulations via twin screw granulation with water as granulation liquid.

SUMMARY

Over recent years, the advantages offered by continuous manufacturing were recognized by the pharmaceutical industry. Additionally, the competent authorities identified continuous manufacturing as means to comply with the quality-by-design principle of drug manufacturing set out by the International Council for Harmonization. However, process knowledge and understanding of continuous manufacturing techniques is indispensable for successful implementation of continuous pharmaceutical manufacturing. Therefore, spray drying and twin screw granulation, two continuous agglomeration techniques, with potential for implementation in fully continuous 'from-powder-to-tablet' lines were studied in current research work.

In the **introduction (Chapter 1)** batch wise manufacturing is compared to continuous manufacturing. The advantages (improved product quality, improved cost-efficiency and reduced footprint) and challenges related to continuous manufacturing were explained. Additionally, the advantages and limitations of the techniques used for tablet manufacturing are discussed, covering batch, semi-continuous and continuous agglomeration techniques and providing some examples of integrated 'from-powder-to-tablet' lines.

The aim of the research described in **Chapter 2** was to develop a modified spray drying method to improve the flowability and tabletability of drug formulations with poor tabletability. The method included the introduction of solid, dry particles into an atomized spray during spray drying in order to coat and agglomerate individual particles. Paracetamol, a highly dosed API showing poor tabletability and high capping tendency, was used as model drug in the formulation and was injected into a spray of lactose/PVP droplets during spray drying. The spray dried solution consisted of lactose and PVP as these components can act as amorphous binders to induce agglomeration between particles and droplets. The particle size enlargement and flowability were evaluated by laser diffraction and ring shear testing, respectively. The developed method was successful for the production of particles containing 75% paracetamol with excellent tabletability and friability. However, the extent of agglomeration was limited. The excellent tabletability of the coprocessed particles was attributed to the coating of paracetamol crystals with amorphous lactose and PVP and the presence of brittle and plastic components in the formulation. Additionally, the coprocessing method was successfully applied for the production of directly compressible lactose.

Mannitol is a preferred excipient during manufacturing of tablets due to its non-hygroscopic character and low drug interaction potential. Although the δ-polymorph of mannitol exhibits superior tabletability in comparison to α- and β-mannitol, its large-scale production is difficult.

Therefore, **Chapter 3** reported on the development of a continuous production method of δ-mannitol via spray drying. Spray drying an aqueous solution of mannitol and PVP in a ratio of 4:1 resulted in formation of δ-mannitol. The tabletability of a physical mixture of spray dried δ-mannitol (20%) with PVP (5%) and paracetamol (75%) was superior to the tabletability of physical mixtures consisting of spray dried α- and β-mannitol (20%) with PVP (5%) and paracetamol (75%), which confirmed the excellent tabletability of the δ-polymorph of mannitol. In addition, the modified spray drying method developed in Chapter 1 was applied to coat paracetamol crystals (75%) with δ-mannitol (20%) and PVP (5%). The tabletability and friability of these coprocessed samples was superior compared to physical mixtures with the same composition. This was attributed to the coating of paracetamol crystals with δ-mannitol and PVP during coprocessing and illustrated the added value of the modified spray drying method developed in Chapter 1.

Although mannitol is a preferred excipient for the formulation of tablets, most studies on twin screw granulation used lactose or microcrystalline cellulose as fillers. Therefore the potential of δ-mannitol as excipient during twin screw granulation was evaluated in **Chapter 4**. The influence of process parameters on critical quality attributes of granules (moisture content, solid state, morphology, size distribution, specific surface area, friability, flowability and hygroscopicity) and tablets (hardness and friability) was evaluated after twin screw granulation of δ-mannitol. The δ-polymorph was selected since a moisture-induced transformation to β-mannitol was observed during batch wet granulation, which exhibited a unique morphology with a large surface area and improved tabletability. A full factorial experimental design was performed, varying screw speed (400 – 900 rpm), granulation temperature (25 – 40 °C), number of kneading elements (6 or 12) and liquid-to-solid (L/S) ratios (0.08 – 0.16). The results showed that the polymorphic transition from δ- to β-mannitol also occurred during twin screw granulation, although the residence time and L/S ratios were much lower in continuous twin screw granulation compared to batch processing. However, the polymorphic transition was not complete in all experiments and depended on the L/S ratio, screw speed and number of kneading elements. Nevertheless all granules exhibited the unique morphology linked to the polymorphic transition and had a superior tabletability compared to granules produced with β-mannitol as starting material. This was attributed to enhanced plastic deformation of the granules manufactured using δ-mannitol as starting material. In addition, it was concluded that mannitol was granulated via a different mechanism than other, less-soluble, excipients (e.g. lactose, microcrystalline cellulose) due to its high solubility and dissolution rate as the influence of process parameters on the mannitol granule characteristics was different.

In **Chapter 5** the potential of twin screw granulation for the continuous production of controlled release formulations with hydroxypropylmethylcellulose (HPMC) as hydrophilic matrix former was evaluated. Metoprolol tartrate was included in the formulation as very water soluble model drug. A premix of metoprolol tartrate, HPMC and filler (ratio 20/20/60) was granulated with demineralized water via twin screw granulation. After oven drying and milling, tablets were produced on a rotary Modul^{TM} P tablet press. A D-optimal design (29 experiments) was used to assess the influence of process (screw speed, throughput, barrel temperature and screw design) and formulation parameters (starch content of the filler) on the process (torque), granule (size distribution, shape, friability, density) and tablet (hardness, friability and dissolution) critical quality attributes. The torque was dominated by the number of kneading elements and throughput, whereas screw speed and filling degree only showed a minor influence on torque. Addition of screw mixing elements after a block of kneading elements improved the yield of the process before milling as it resulted in less oversized granules and also after milling as fewer fines were present. The barrel temperature was also an important parameter as fewer fines and more spherical granules were produced at higher temperatures. The shape of HPMC granules was comparable to that of immediate release formulations. Hardness and friability of tablets were only dependent on the filler ratio. Complete drug release was obtained after 16-20 h and was independent of the design's parameters.

In **Chapter 6** the influence of formulation parameters during twin screw granulation of a controlled release formulation with HPMC was studied. The influence of the viscosity and substitution degree of HPMC and the particle size of theophylline on critical quality attributes of continuously produced granules (size distribution, shape, flowability, friability, density) and tablets (hardness, friability, dissolution) were investigated. Formulations with 20 or 40% HPMC, 20% theophylline and lactose as filler were granulated with water at fixed process parameters. The torque was influenced by the viscosity and substitution degree of HPMC but was not a limiting factor for the granulation process. An optimal L/S ratio was selected for each formulation based on the granule size distribution. The granule size distributions were influenced by the substitution degree and concentration of HPMC and the particle size of theophylline. Raman and UV spectroscopic analysis on 8 sieve fractions of granules indicated an inhomogeneous distribution of theophylline over the size fractions. However, this phenomenon was not dependent on the hydration rate or viscosity of HPMC. Controlled release of theophylline could be obtained over 24 h with release profiles close to zero-order. The release of theophylline could be tailored via selection of the substitution degree and viscosity of HPMC.

SAMENVATTING

De voordelen verbonden aan continue productie van geneesmiddelen zijn recent erkend door de farmaceutische industrie. Bovendien hebben de bevoegde autoriteiten continue productie van geneesmiddelen aangeduid als middel om te voldoen aan het 'quality-by-design' principe van de International Council for Harmonization (ICH). Proceskennis en begrip van continue productietechnieken is echter noodzakelijk voor een succesvolle implementatie van continue productietechnieken in de farmaceutische industrie. Daarom werden sproeidrogen en dubbeleschroefgranulatie, twee continue agglomeratietechnieken met potentieel voor implementatie in continue 'van-poeder-tot-tablet' lijnen, bestudeerd in deze thesis.

In de **inleiding** (**Hoofdstuk 1**) werden batchgewijze en continue productie vergeleken. De voordelen (betere product kwaliteit, hogere kostenefficiëntie en gereduceerde voetafdruk) en uitdagingen verbonden aan continue productie werden uitgebreid besproken. De voordelen en beperkingen van technieken gebruikt voor productie van tabletten werden bovendien behandeld waarbij batch, semi-continue en continue agglomeratietechnieken aan bod kwamen en enkele voorbeelden van geïntegreerde 'van-poeder-tot-tablet' lijnen gegeven werden.

Het doel van het ondezoek beschreven in **Hoofdstuk 2** was de ontwikkeling van een aangepaste sproeidroogmethode om de vloei-eigenschappen en tableteerbaarheid van geneesmiddelformulaties te verbeteren. De methode omvatte de introductie van vaste, droge partikels in een geatomiseerde spray tijdens sproeidrogen om individuele partikels te coaten en agglomereren. Paracetamol, een hoog gedoseerde geneesmiddelmolecule met slechte tableteerbaarheid en sterke neiging tot capping, werd gebruikt als modelgeneesmiddel in de formulatie en werd in een spray van lactose/PVP druppels gespoten tijdens sproeidrogen. De gesproeidroogde oplossing bestond uit lactose en PVP aangezien deze componenten fungeren als amorfe binders om agglomeratie tussen partikels en druppels te induceren. De deeltjesvergroting en vloei-eigenschappen werden geëvalueerd d.m.v. respectievelijk laserdiffractie en ring shear testing. De ontwikkelde methode was succesvol voor de productie van partikels met excellente tableteerbaarheid en friabiliteit.

Mannitol is een excipiënt dat vaak de voorkeur geniet tijdens formulatie van tabletten omwille van zijn niet-hygroscopisch karakter en laag interactiepotentieel. Alhoewel de δ-polymorf van mannitol een betere tableteerbaarheid vertoont dan met α- en β-mannitol, wordt het niet vaak toegepast aangezien grootschalige productie van δ-mannitol moeilijk is. Daarom werd in

Hoofdstuk 3 de ontwikkeling van een methode voor continue productie van δ-mannitol via sproeidrogen beschreven. Sproeidrogen van een mannitol/PVP oplossing (ratio 4/1) in water resulteerde in de vorming van δ-mannitol. De tableteerbaarheid van een fysisch mengsel van gesproeidroogd δ-mannitol (20%) met PVP (5%) en paracetamol (75%) was superieur aan de tableteerbaarheid van fysische mengsels bestaande uit α- en β-mannitol met PVP (5%) en paracetamol (75%), wat de excellente tableteerbaarheid van de δ-polymorf van mannitol bevestigde. Bovendien werd de aangepaste sproeidroogmethode ontwikkeld in Hoofdstuk 1 toegepast om paracetamol kristallen (75%) te coaten met δ-mannitol (20%) en PVP (5%). De tableteerbaarheid en friabiliteit van deze stalen was beter dan deze van de fysische mengsels met een identieke samenstelling. Dit werd toegeschreven aan de coating van paracetamol kristallen met δ-mannitol en PVP tijdens het process en illustreerde de meerwaarde van de aangepaste sproeidroogmethode ontwikkeld in Hoofdstuk 1.

Alhoewel mannitol als excipiënt vaak de voorkeur geniet tijdens formulatie van tabletten, werd in de meeste studies op dubbeleschroefgranulatie lactose of microkristallijne cellulose gebruikt als excipiënt. Daarom werd het potentieel van δ-mannitol als excipiënt voor dubbeleschroefgranulatie geëvalueerd in **Hoofdstuk 4**. De invloed van procesparameters op de kwaliteitskenmerken van granules (vochtgehalte, kristalvorm, morfologie, deeltjesgroottedistributie, specifieke granule-oppervlakte, friabiliteit, vloei-eigenschappen, hygroscopiciteit) en tabletten (hardheid en friabiliteit) werd geëvalueerd na dubbleschroefgranulatie van δ-mannitol. De δ-polymorf van mannitol werd geselecteerd omdat een vocht gemedieerde transformatie naar β-mannitol met een unieke morfologie, groot specifiek oppervlak en verbeterde tableteerbaarheid werd waargenomen tijdens batchgewijze granulatie. Een full factorial experimenteel design werd uitgevoerd bij verschillende schroefsnelheden (400 – 900 rpm), granulatietemperaturen (25 – 40 °C), aantal kneedelementen (6 of 12) en liquid-to-solid (L/S) ratio's (0,08 – 0,16). De resultaten toonden aan dat de polymorfe transitie van δ- naar β-mannitol zich ook voordeed tijdens dubbeleschroefgranulatie, al zijn de residentietijden en L/S ratio's tijdens dubbeleschroefgranulatie lager in vergelijking met batchgewijze granulatie. De polymorfe transitie was echter niet in alle experimenten compleet en was afhankelijk van de L/S ratio, schroefsnelheid en het aantal kneedelementen. Desondanks vertoonden alle granules de unieke morfologie die verbonden is aan de polymorfe transitie en een superieure tableteerbaarheid in vergelijking met granules geproduceerd met β-mannitol als start-materiaal. Dit werd toegeschreven aan de verhoogde plastische deformatie van granules geproduceerd met δ-mannitol als startmateriaal. Bovendien werd geconcludeerd dat mannitol gegranuleerd werd volgens een ander mechanisme dan andere, minder oplosbare excipiëntia (bijvoorbeeld lactose en microkristallijne cellulose) omwille van zijn hoge

oplosbaarheid en oplossnelheid, aangezien de invloed van procesparameters op de kenmerken van mannitolgranules verschillend was.

In **Hoofdstuk 5** werd het potentieel van dubbeleschroefgranulatie voor continue productie van een formulatie met vertraagde geneesmiddelvrijstelling met hydroxypropylmethylcellulose (HPMC) als hydrofiele matrixvormer geëvalueerd. Metoprolol tartraat werd in de formulatie opgenomen als sterk wateroplosbaar geneesmiddel. Een mengsel van metoprolol tartraat, HPMC en vulstof (ratio 20/20/60) werd gegranuleerd met gedemineraliseerd water via dubbeleschroefgranulatie. Na drogen in de oven en malen, werden tabletten aangemaakt op een rotatieve tabletpers. Een D-optimal design (29 experimenten) werd toegepast om de invloed van procesparameters (schroefsnelheid, toevoersnelheid van het poeder, temperatuur van de schroefkamer, schroefconfiguratie) en formulatieparameters (percentage zetmeel in de vulstof) op het granulatieproces (torque) en kwaliteitskenmerken van granules (deeltjesgroottedistributie, vorm, friabiliteit, densiteit) en tabletten (hardheid, friabiliteit, dissolutie) na te gaan. De torque werd gedomineerd door het aantal kneedelementen en de toevoersnelheid van poeder, terwijl de schroefsnelheid en vullingsgraad van de schroefkamer slechts een beperkte invloed op de torque vertoonden. Toevoeging van screw mixing elementen na een zone van kneedelementen verbeterde de opbrengst van het proces voor en na malen. De temperatuur van de schroefkamer was ook een belangrijke parameters aangezien minder ongegranuleerd materiaal en meer sferische granules gevormd werden bij hogere temperaturen. De vorm van de granules met HPMC was vergelijkbaar met deze van formulaties met onmiddellijke geneesmiddelvrijstelling. De hardheid en friabiliteit van de tabletten was enkel afhankelijk van het percentage zetmeel in de granules. Volledige geneesmiddelvrijstelling werd bekomen na 16 - 20 h en was onafhankelijk van de onderzochte parameters.

In **Hoofdstuk 6** werd de invloed van formulatieparameters tijdens dubbeleschroefgranulatie van een formulatie met vertraagde geneesmiddelvrijstelling met HPMC bestudeerd. De invloed van viscositeit, substitutiegraad van HPMC en de deeltjesgrootte van theofylline op de kwaliteitskenmerken van op continue wijze geproduceerde granules (deeltjesgroottedistributie, vorm, vloei-eigenschappen, friabiliteit, densiteit) en tabletten (hardheid, friabiliteit, dissolutie) werd onderzocht. Formulaties met 20 of 40% HPMC, 20% theofylline en lactose als vulstof werden gegranuleerd met water bij constante procesparameters. De torque werd beïnvloed door de viscositeit en substitutiegraad van HPMC maar was geen beperkende factor voor het granulatieproces. Een optimale L/S ratio werd geselecteerd voor elke formulatie, gebaseerd op de granulegroottedistributie. De granulegroottedistributie werd beïnvloed door de substitutiegraad en concentratie HPMC en

de deeltjesgrootte van theofylline. Een ongelijke verdeling van theofylline over zeeffracties van de granules werd aangetoond na Raman- en UV spectroscopie. Dit fenomeen was echter niet gecorreleerd aan de snelheid van zwellen of viscositeit van HPMC. Gecontrolleerde vrijstelling van theophylline kan bekomen worden gedurende 24 h met vrijstellingsprofielen dicht bij nulde orde. De vrijstelling van theofylline kon aangepast worden door selectie van de viscositeit en substitutiegraad van HPMC.

CURRICULUM VITAE

PERSONAL INFORMATION

Name:	VANHOORNE Valérie
Date of birth:	February 12th, 1988
Place of birth:	Oostende, Belgium
Private Address:	Gestichtstraat 21, 9000 Gent
Professional Address:	Ghent University
	Faculty of Pharmaceutical Sciences
	Laboratory of Pharmaceutical Technology
	Ottergemsesteenweg 460
	9000 Ghent
	Phone: +32(0)92648039
	Mobile: +32(0)496079236
	Valerie.Vanhoorne@Ugent.be

RESEARCH EXPERIENCE

Sep 2011 – present	PhD research: "Towards continuous pharmaceutical tablet manufacturing: implementation of continuous agglomeration techniques" Laboratory of Pharmaceutical Technology, Ghent University Promotors: Em. Prof. dr. J.P. Remon, Prof. dr. C. Vervaet
Feb – Jun 2010	Master thesis: "SPME analysis of different populations of Ephedra *Nebrodensis* Tineo ex Guss subspecies *Nebrodensis* growing in Italy" Department of Chemical Sciences, University of Camerino, Italy (Erasmus Program) – Laboratory for Medicinal Chemistry, Ghent University Promotors: Prof. dr. S. Vittori, Prof. dr. S. Van Calenbergh

WORK EXPERIENCE

Sep 2011- present — Assisting academic personnel Laboratory of Pharmaceutical Technology, Ghent University

- Mentoring master students during laboratory internships
- Organizing, planning and teaching practical courses "Artsenijbereidkunde" (3rd Bachelor Pharmaceutical Sciences) and "Farmaceutische Technologie" (2nd Master Pharmaceutical Sciences)

Jul 2010 – May 2011 — Internship Pharmacist
Apotheek Centra, Koksijde

Aug 2008, 2009 — Pharmacist Assistant
Apotheek Centra, Koksijde

EDUCATION

2011 – present — PhD candidate in Pharmaceutical Technology
Laboratory of Pharmaceutical Technology, Ghent University
Promoters: Em. Prof. dr. J.P. Remon, Prof. dr. C. Vervaet

2009 – 2011 — Master of Science in Drug Development
Ghent University
Graduated with great distinction

2006 – 2009 — Bachelor of Science in Pharmaceutical Sciences
Ghent University

2000 – 2006 — Latin – Mathematics
Onze-lieve-vrouwe-college, Oostende

SKILLS

Languages

- Dutch: native speaker
- English: very well in speaking, writing, listening and reading
- French: very well in speaking, writing, listening and reading
- German: good in speaking, writing, listening and reading
- Italian: notions

Language courses

- Italian (1 level), University Centre of Languages, Ghent University, Belgium, 2009
- German (3 levels, CEFR B2), University Centre of Languages, Ghent University, Belgium, 2011-2012
- Academic English writing skills, University Centre of Languages, Ghent University, Belgium, 2013

Computer skills

- MS Office
- Gathering information in multiple scientific databases
- Various scientific statistical programs (Modde, Simca)

Scientific courses

- Differential scanning calorimetry, 3 day training at TA Instruments, Zellik, Belgium, 2012
- Design of experiments and multivariate data analysis course, 6 day course organized by Laboratory of pharmaceutical process analytical technology, Ghent University, Belgium, 2012
- Efficient powder characterization and processing of pharmaceutical particulate solids, 7 days specialist course at Otto Von Guericke Universität Magdeburg, Germany, 2013
- Spray drying and fluid prilling based lyophilization, workshop by APV, Mainz, Germany, 2013
- Particle Characterization Course, 2 day course organized by BePCIS and UGent Doctoral Schools, Ghent University, Belgium, 2013

- Granulation and Tableting workshop, 3 day course at Technology training centre, Binzen, Germany, 2014
- Continuous granulation workshop, 3 day course at Technology training center, Weimar, Germany, 2014
- ShinEtsu Technical Seminar, novel applications using cellulose derivatives in solid dosage, Wiesbaden, Germany, 2015
- Registration of medicines, optional course in Master of Science in drug development, Ghent University, Belgium, 2015

INTERNATIONAL PUBLICATIONS

- **V. Vanhoorne**, E. Peeters, B. Van Snick, J.P. Remon, C. Vervaet, *Crystal coating via spray drying to improve powder tabletability*, Eur. J. Pharm. Biopharm. 88 (2014) 939-944.

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- A. Kumar, M. Alakarjula, **V. Vanhoorne**, M. Toiviainen, F. De Leersnyder, J. Vercruysse, M. Juuti, J. Ketolainen, C. Vervaet, J.P. Remon, K.V. Gernaey, T. De Beer, I. Nopens, *Linking granulation performance with residence time and granulation liquid distributions in twin-screw granulation: an experimental investigation*, Eur. J. Pharm. Sci., (2015) available online December 18th 2015.

- E. Peeters, **V. Vanhoorne**, J.P. Remon, C. Vervaet, *Effect of the paddle movement in the forced feeder on lubricant sensitivity*, Drug Dev. Ind. Pharm., accepted for publication, DOI: 10.1080/03639045.2016.1200067

ORAL PRESENTATIONS

- Development of a controlled release formulation by continuous twin screw granulation
  V. Vanhoorne, J. Vercruysse, C. Vervaet, J.P. Remon
  Forum of pharmaceutical sciences, Spa, Belgium, October 17-18th, 2013.

- Development of a controlled release formulation by continuous twin screw granulation
  V. Vanhoorne, J. Vercruysse, F. De Leersnyder, T. De Beer, C. Vervaet, J.P. Remon
  Kuopio-Ghent Summerschool in Continuous Manufacturing, Kuopio, Finland, August 27-29, 2014.

- Development of a controlled release formulation by continuous twin screw granulation
  V. Vanhoorne, J. Vercruysse, C. Vervaet, J.P. Remon
  PSSRC Symposium, Ljubljana, Slovenia, September 16-18th, 2014.

- Development of a slow release formulation with HPMC as hydrophilic matrix former by twin screw granulation
  ShinEtsu Technical Seminar on novel applications using cellulose derivatives in solid dosage, Wiesbaden, Germany, June 10-11th, 2015.

- Continuous production of δ-mannitol via spray drying
  V. Vanhoorne, P.J. Van bockstal, B. Van Snick, E. Peeters, P. Gomes, T. De Beer, J.P. Remon, C. Vervaet
  PSSRC Symposium, Gent, Belgium, September 16-17th, 2015.

- Improved tabletability after a polymorphic transition from δ- to β-mannitol during twin screw granulation
  V. Vanhoorne, B. Bekaert, E. Peeters, T. De Beer, J.P. Remon, C. Vervaet,
  PSSRC Symposium, Copenhagen, Denmark, July 5-8th, 2016.

POSTER PRESENTATIONS

- Development of a controlled release formulation of metoprolol tartrate produced by continuous twin screw granulation
  V. Vanhoorne, J. Vercruysse, C. Vervaet, J.P. Remon
  9th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Lisbon, Portugal, March 31st – April 3rd, 2014.

- Development of a controlled release formulation by continuous twin screw granulation.
  V. Vanhoorne, B. Vanbillemont, J. Vercruysse, F. De Leersnyder, P. Gomes, T. De Beer, J.P. Remon, C. Vervaet
  50th Arden Conference: continuous manufacturing of oral solid drug products, Baltimore, US, March 16-18th, 2015.

- Continuous manufacturing of δ-mannitol via spray dying
  V. Vanhoorne, P.J. Van Bockstal, B. Van Snick, E. Peeters, P. Gomes, T. De Beer, J.P. Remon, C. Vervaet
  1st European Conference, Reims, France, April 13-14th, 2015.

- Development of a controlled release formulation by continuous twin screw granulation
  V. Vanhoorne, J. Vercruysse, F. De Leersnyder, T. De Beer, J.P. Remon, C. Vervaet
  7th International Granulation Workshop, Sheffield, UK, June 28-30th, 2015.

- Development of a controlled release formulation of metoprolol tartrate produced by continuous twin screw granulation
  V. Vanhoorne, B. Vanbillemont, J. Vercruysse, F. De Leersnyder, P. Gomes, T. De Beer, J.P. Remon, C. Vervaet
  AAPS Annual meeting and exposition, Orlando, US, October 25-29th, 2015.

- Continuous manufacturing of delta-mannitol via spray drying
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- Development of a controlled release formulation of metoprolol tartrate produced by continuous twin screw granulation
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  Compaction Simulation Forum, Copenhagen, Denmark, June 16-17th, 2015.

- Continuous manufacturing of delta-mannitol via spray drying
  V. Vanhoorne, P.J. Van Bockstal, B. Van Snick, E. Peeters, P. Gomes, W. Grymonpré, T. De Beer, J.P. Remon, C. Vervaet
  10th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Glasgow, UK, April 4-7th, 2016.