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Systematic investigations for the development and manufacturing of pharmaceutical mini-tablets

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-For my family-

Table of contents

List of abbreviations

API	Active pharmaceutical ingredient
AR	Aspect ratio
CMA	Critical material attributes
CPE	Co-processed excipient
CPP	Critical process parameter
CQA	Critical quality attribute
CRM	Confocal raman microscopy
DC	Direct compression
DCPA	Dibasic calcium phosphate anhydrous
EM	Enalapril maleate
EMA	European medicines agency
EU	European union
FDA	Food and drug administration
FE	Functionalized excipient
GPM	1-O-α-D-glucopyranosyl D-mannitol
GPS	6-O-α-D-glucopyranosyl sorbitol
HCT	Hydrochlorothiazide
LENA	Labelling enalapril from neonates to adolescents
MCC	Microcrystalline cellulose
NCE	New chemical entities
ODF	Orodispersible film
ODMT	Orodispersible mini-tablet
ODT	Orodispersible tablet
OOS	Out of specification
PDCO	Paediatric committee
Ph. Eur.	European pharmacopeia
PIP	Paediatric investigation plan
PUMA	Paediatric use-marketing authorisation

PVA	Polyvinyl acetate
QbD	Quality by design
QTPP	Quality target product profile
RCDG	Roll compaction and dry granulation
SF	Solid fraction
SPE	Specific plastic energy
SVR	Surface to volume ratio
SWT	Simulated wetting test
TS	Tensile strength
WHO	World health organisation

Chapter I

Introduction

1. Introduction

1.1. Mini-tablets

1.1.1. General aspects

Classification

Tablets are the most used solid dosage forms and oral drug delivery systems. For industrial purposes they are usually produced on rotary tablet presses. According to the European Pharmacopeia (Ph. Eur.) tablets are defined as *solid dosage forms manufactured by compression of a definite volume of powder or granule or another suitable method*. In Ph. Eur. tablets are classified into different groups according to their technological or biopharmaceutical properties into coated, uncoated tablets, gastro-resistant tablets, modified release tablets, effervescent tablets, tablets for preparation of a solution or suspension for oral use, orodispersible tablets, chewing tablets and oral lyophilisates (Ph. Eur., 2019). Unfortunately, the tablet size is neglected in current classification. A further classification for tablets can be done into mini-tablets and conventionally sized tablets. Mini-tablets have been described as a spherical solid dosage form with a diameter of 1 to 3 mm (Flemming and Mielck, 1995; Lennartz and Mielck, 1998). Due to their small dimensions they represent a suitable dosage form for the paediatric population either as a single or a multiparticulate dosage form (Klingmann et al., 2018; Klingmann et al., 2015; Klingmann et al., 2013). Their smaller dimensions might however, also be a limiting factor with respect to a limited maximum drug load and might therefore impair therapeutic use. As a single-dose application only diseases, which require a low dose regime and a high potent drug are eligible. For example, prolonged release melatonin mini-tablets with a diameter of 3 mm were clinically approved in two strengths (1 and 5 mg) to treat insomnia with autism spectrum disorder (Gringras et al., 2017; Malow et al., 2021; Schroder et al., 2019) and most recently authorized and marketed in Germany (Slenyto, InfectoPharm, Germany). A further example for a single-dose regime of mini-tablets is a combination of 3 mm mini-tablets containing 5 mg levodopa and 1.25 mg carbidopa for the treatment of Parkinson's disease by using an automatic dispenser (Aquilonius and Nyholm, 2017). Additionally, mini-tablets can be administered as a multiparticulate dosage form encapsulated or packed in sachets as in the marketed product Orfiril® long (Desitin Arzneimittel, Germany) with multiple sodium valproate coated mini-tablets for the treatment of epilepsies. An overview of further market products is given in the subchapter *Market products*.

Due to their small size and thus their ability for multiparticulate dosing mini-tablets compete with pellets. Pellets are allocated as a special type of granules. They are defined as agglomerates of 0.1 to 2 mm with a spherical shape, a narrow particle size distribution and smooth surface. They are frequently manufactured by wet granulation followed by a spheronisation and finally a drying process (Kleinebudde, 1997). Nevertheless, mini-tablets show major advantages compared to pellets. As a result of the manufacturing process, mini-tablets are highly reproducible in size and weight. Furthermore, a smoother surface can be reached and thus a more homogenous coating can be applied. These benefits result in lower production costs, higher product stability and less coating time in total (Gaber et al., 2015; Munday, 1994). Therefore, mini-tablets may also be used as drug free dosage forms for a downstream API coating process for a multiparticulate dosage form and may replace pellets in novel drug development.

Dosing devices

In contrast to conventionally sized tablets, the correct dosing of mini-tablets is a more challenging approach. Due to their small size and spherical shape the handling requires training and/or suitable dosing devices. Conventionally sized tablets are either administered unscored or scored for individual therapy regimes. However, tablet splitting is considered as a critical step in regards of uniformity of dosing and of functional coatings for example (Quinzler et al., 2006; Teng et al., 2002). For paediatric patients mini-tablets can be dosed as single dose or multiparticulates (Klingmann et al., 2018; Klingmann et al., 2015; Klingmann et al., 2013). Most recently the dose flexibility of mini-tablets with different sizes from 1.2 to 2.5 mm was shown (Mitra et al., 2020). In order to ensure a correct dosing and thus a successful therapy spoons or counting devices are used (Wening and Breitkreutz, 2011). A first approach for dosing 2 mm mini-tablets by a spoon was patented by Knoll (1999). The development and patent of several counting devices started early and continued over the past years (Bredenberg et al., 2003; Breitkreutz and Wazlawik, 2004; Hansen, 1993; Heimlich, 1984; Warren, 1940). The latest approaches aim to develop dosing devices for specific mini-tablet products and to evaluate them under technological but also clinical aspects (Fabio et al., 2019; Ringold et al., 2015; Senek et al., 2017).

Market products

Since mini-tablets have a high potential as solid dosage forms for paediatric population (European Union (EU), 2006; Strickley, 2019; World Health Organisation (WHO), 2008), there are already some market products available. In literature, summarized lists containing market products can already be found (Strickley, 2019; Tumuluri, 2020), table 1 also gives an overview of current market products. However, it is difficult to provide a comprehensive list of all available market products, because in many cases the actual size of mini-tablets or even the declaration of the dosage form as mini-tablets cannot be verified from the packaging and labelling. Some pharmaceutical companies do label their products for example as oral granules (e.g. Kalydeco® oral granules, Vertex Pharmaceuticals, Ireland). This could be attributed to the fact that the term mini-tablet does not appear in a monograph of any pharmacopeia, as there is still a lack of a scientifically based definition. Another advantage of the approach of labeling the mini-tablets as oral granules may be that the Ph. Eur. requirements for tablets do not have to be met such as disintegration time or breaking force. An example for the lack of information regarding the size of mini-tablets is the market product Ozym® (Trommsdorff, Germany), which obviously contains mini-tablets in capsules, but no tablet size can be found in accessible documents. Furthermore, the dosage form is declared scientifically false as micro-tablets indicating a tablet size below 1 mm. In products like ferro sanol® gyn (UCB Pharma, Germany) against iron and folic acid deficiency, the labeling and application instructions declare that pellets and one mini-tablet are encapsulated. However, the size of the described mini tablet is about 5 mm and larger than the scientifically cited common definition of 2-3 mm (Lennartz and Mielck, 1998). Therefore, these kind of products are not included in table 1. Additionally, most recently 2 mm ODMTs with EM were developed and completed the clinical evaluation following a PIP procedure (Bajcetic et al., 2019; Faisal et al., 2019; van Hecken et al., 2020; Walsh, 2017) Thus, it can be expected that a further commercially available mini-tablet may appear soon.

Table 1: Overview of exemplary market products of mini-tablets

Market product and company	**Drug and dosage strength**	**Size**	**Packaging**	**Indication**
Kalydeco® oral granules *Vertex Pharmaceuticals, Ireland*	Ivacaftor 25, 50, 75 mg	2 mm	Sachets	Cystic fibrosis
Lamisil® Oral Granules *Novartis, Switzerland*	Terbinafine 125, 187.5 mg	2.1 mm	Sachets	Tinea capitis
Levetiracetam Desitin® *Desitin, Germany*	Levetiracetam 250, 500, 1000 mg	2 mm	Sachets	Epileptic seizures
Orfiril® long *Desitin, Germany*	Sodium valproate 150, 300, 500, 1000 mg	2 mm	Capsule (150 and 300 mg) Sachets (500 and 1000 mg)	Epileptic seizures
Rhythmol SR *Glaxo Smith Kline, England*	Propafenone 225, 325, 425 mg	2 mm	Capsule	Cardiac arrhythmias
Slenyto® *InfectoPharm, Germany*	Melatonin 1, 5 mg	3 mm	Blistered as single dose	Insomnia with autism spectrum disorder
Zalviso® *AcelRx Pharmaceuticals, USA*	Sufentanil 15 µg	3 mm	Single dosed automatic dosing device	Acute moderate to severe pain after surgery.

1.1.2. Principles of manufacturing

Manufacturing routes

Conventionally sized tablets and mini-tablets can be manufactured using different types of tablet presses like rotary tablet presses, eccentric presses or compaction simulators, depending on the purpose and the targeted batch size. The main difference in the manufacturing equipment is the required tooling system for mini-tablets. The first multi-tip tooling system for mini-tableting was patented by Hershberg (1965). The motivation behind this invention was that physicians complained about inappropriate therapeutical success with encapsulated pellets. The manufactured pellets were not reproducible in their properties and a uniform coating could not be applied. Thus, differences in individualized therapy regimes occurred. Therefore, Hershberg (1965) patented a 2.4-2.5 mm four-tip tooling system, so that uniform tablets could be produced and encapsulated. The development of new tooling systems has increased so that punch manufacturers do offer a variety of tailor-made multi-tip tooling systems for the industrial manufacturing of mini-tablets. Regardless of the tooling system, there are three main production routes for the manufacturing of tablets and mini-tablets, which are shown in figure 1.

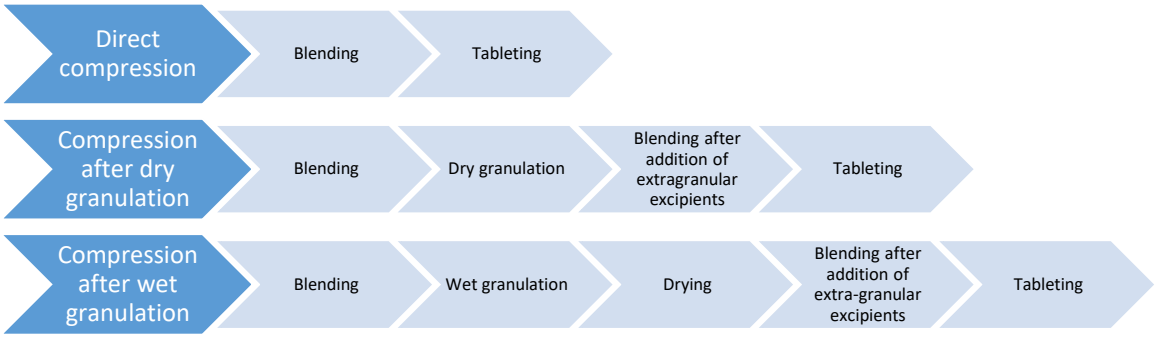

Figure 1: Overview of most common production routes for tablets

Direct compression is performed by a blending step of the excipients followed by a tableting process. Compression after dry granulation requires an intermediate dry granulation process. For pharmaceutical applications roll compaction/dry granulation (RCDG) and slugging are two possible dry granulation approaches (Miller, 2005). In RCDG, the powder is transported continuously between two rollers and finally compacted and densified to a targeted solid fraction in dependency of the used rolls, specific compaction force and gap width between the rolls. In a connected downstream process the obtained ribbons can be further processed into dry granules by a milling procedure (Kleinebudde, 2004).

Slugging is a method to manufacture dry granules by a tableting process in advance. The powders are compressed into lager tablets or so called slugs. These are milled afterwards into dry granules (Miller, 2005). For pharmaceutical approaches RCDG has prevailed over the slugging method. Less lubrication is required and furthermore a continuous process is feasible with better process control. Consequently, this results in higher yields and a more reproducible product (Kleinebudde, 2004). A second blending step before compression is often required after dry granulation, where usually a lubricant or further extra-granular components may be added. Wet granulation as an upstream process is performed for industrial purposes by either fluid bed granulation or high shear granulation (Kristensen and Schaefer, 1987). The principle of both methods is to achieve particle size enlargement and homogenisation by using liquid binders and a subsequent drying process. Granules are formed by combined interactions of the powder particles and liquid binders in agglomeration (and desegregation) processes, such as nucleation, coalescence and breakage. Depending on the type of liquid binder either crusty granules or glue granules are obtained after the drying process (Iveson et al., 2001). During a fluid bed granulation all steps (mixing, granulation, drying) can be performed and monitored in consecutive processes within the same fluid bed apparatus. In high shear mixers the mixing and granulation step can be performed, whereas the drying step has to be outsourced in either drying chambers or fluid bed devices (Kristensen and Schaefer, 1987; Miller, 2005). However, it is also possible to implement the mixing, wet granulation and the drying step in a one-pot system (Cooper et al., 1961). After drying the granules to a desired loss of drying a further blending step is implemented by adding extra-granular excipients before tableting.

Each production route offers several benefits and drawbacks. Direct compression is time and cost saving compared to dry and wet granulation. However, this production route is dependent on suitable flowability and tableting properties (compactibility, compressibility, tabletability) of the formulation. Especially for mini-tableting, the flowability of the formulation is a critical quality attribute (CQA), as the powder has to flow into dies with a diameter ≤ 3 mm (Flemming and Mielck, 1995). If direct compression cannot be performed, an intermediate granulation process has to be implemented. The decision which type of granulation to be performed is linked to the formulation. As wet granulation is allied to higher costs and potentially more critical process parameters (CPPs) and among other things a further drying process has to be implemented, dry granulation should be preferred if possible (Leane et al., 2015). However, a dry granulation process can be connected to a change of tableting properties such a reduction of compactibility and tabletability due to work hardening phenomena The resistance against deformation (yield pressure) is increased after the mechanical input. The particles are already densified to a certain extent and thus the solid fraction is reduced and cannot be further reduced during

tableting to form a more solid tablet (Herting and Kleinebudde, 2008; Malkowska et al., 1983). In literature mini-tablets were manufactured after both types of granulation processes (Colombo et al., 1985; Gupta et al., 2020; Rouge et al., 1998; Tissen et al., 2011; Weyenberg et al., 2005). As a granulation step is linked to an increase in particle size, it might lead to unproccessable granules for mini-tableting, as the die orifice is the limiting factor for the use of larger particle sizes, but on the other hand flow properties are linked to die fill accuracy (Flemming and Mielck, 1995; Goh et al., 2017; Zhao et al., 2018). Therefore, a balance between adequate flow properties and particle/granule sizes has to be found.

Tableting

The principle of tableting is independent from the used tableting machines and tablet sizes. In all cases there is a filling phase, where the powder or granule is filled into the die either by a feeding system or manually. Afterwards, the powder is compressed into tablets by the punches. The effect of the punches on the compression depends on whether a rotary tablet press (lower and upper punch are directly involved in compression process) or an eccentric tablet press (only upper punch movement is directly involved during compression, whereas the lower punch is not moving) is used. In the last phase, the tablet is ejected by the lower punch (Ritschel and Bauer-Brandl, 2002).

During tableting the powder undergoes several phases. Throughout the first contact with the punch the particles complete a rearrangement phase within the die and start volume reduction. In general, a material initially shows elastic behaviour with increasing pressure. After passing a material dependent yield pressure plastic deformation may occur, possibly showing final ductile fracture with increasing pressure. Depending on the material, brittle fracture can also result. The different stages of deformation do not follow a strict order, but can occur simultaneously and highly depend on the composition of the formulation. When the punch displacement gets larger the tablet undergoes a decompression phase with mainly elastic recovery processes. Lastly, the tablet is ejected out of the die by the lower punch (Amidon et al., 2014; Çelik and Driscoll, 1993; Hiestand et al., 1977; Train, 1956; York, 1978).

The resulting mechanical strengths depend on the used tooling system, its geometry and resulting pressure distribution, but are not so far concretely linked to the tablet size (Amidon et al., 2014; Çelik and Driscoll, 1993; Eiliazadeh et al., 2004; Hiestand et al., 1977; Osamura et al., 2017; Sixsmith and McCluskey, 1981; Train, 1956; York, 1978). For smaller sized tablets it is observed that higher mechanical strengths were obtained with non-pharmaceutical materials (Duckworth, 1953; Ryshkewitch, 1953). The higher mechanical strengths were explained by an increase of activation energy resulting in higher mechanical strengths for smaller tablets and more plastic deformation (Hüttenrauch et al., 1985; Jacob and Huettenrauch, 1982). Nevertheless, all these observations were made with conventional tablets, which cannot be translated into mini-tablets. The first industrial experience with mini-tablets were made by the company Nordmark, as a formulation with 99.5 % pankreatin failed to be compressed into 10 mm tablets, but succeeded when reducing the tablet size to 2.25 mm (Pich and Moest, 1984). Lennartz and Mielck (1998) observed a lower capping tendency and higher mechanical strengths of paracetamol lactose mixtures with decreasing tablet size from 5 to 1.5 mm at higher drug load.

Tissen et al. (2011) were also able to compress up to 90 % high drug loaded 1 and 2 mm mini-tablets of quinine hydrochloride, dried gentian extract and ibuprofen without visible sticking or capping tendency. A hypothesis to explain these deviations from larger tablets was introduced by Lennartz and Mielck (1998). As the ratio between outer surface and volume of the tablet increases with reducing tablet size a higher relative amount of material is exposed to punches and die. The authors claim that the resulting shear stress during tableting and die-wall friction leads to a wider distribution of density over the volume of the tablet and therefore to more binding sites and subsequently better compactibility. Furthermore, a higher transfer of energy (due to the small multi-tip tooling) and thus more plastic deformation was proposed but could not be validly proven (Lennartz, 1998; Mittwollen, 2002; Stoltenberg, 2012).

1.2 Orodispersible mini-tablets

Some tablets and mini-tablets can be categorized according to criteria of pharmacopeias into orodispersible solid dosage forms. The importance of orodispersible solid dosage forms for paediatric patients was further emphasized in the *Report of Informal Expert Meeting on Dosage Forms* by the WHO (2008). The main quality attribute of orodispersible tablets is the disintegration time of maximum 180 s (Ph. Eur., 2019) or 30 s according to the Food and Drug Administration (FDA, 2008). The aim is a rapid disintegration of the ODMT in the oral cavity, in order to improve compliance of the patient and increase, depending on resorption pathways and properties, the bioavailability of the drug (Slavkova and Breitkreutz, 2015). The very first ODMTs for paediatric patients were developed and characterized by Stoltenberg and Breitkreutz (2011). In comparison to other dosage forms with a rapid disintegration like oral lyophilisates and orodispersible films (ODFs), ODMTs display the benefit of higher mechanical and chemical stability and a more convenient manufacturing and packaging process. ODFs are typically manufactured by solvent casting method or hot-melt extrusion and need costly packing material due to moisture sensitivity. In many cases, an organic solvent is required in the formulation, which may remain as residuals in the ODFs and has to be critically evaluated for the use in paediatric patients (Hoffmann et al., 2011). Lyophilisates, which are also categorized as tablets according to Ph. Eur., show compared to a tablet manufacturing a more complicated production process including time and energy consuming freeze drying steps. The resulting product displays fast disintegration due to the distinct pore structure, but also show very low mechanical and physicochemical stability (Seager, 1998).

The most common techniques for manufacturing orodispersible tablets (ODTs) are direct compression (DC), sublimation or moulding (Slavkova and Breitkreutz, 2015). In this work, direct compression will be the chosen manufacturing route. For DC of ODTs, mainly mannitol based formulations are used, as mannitol is designated by good tableting properties, a sweet taste and high water solubility, which positively affects the disintegration process (Slavkova and Breitkreutz, 2015). To improve the tableting performance of mannitol, it is often designed as a co-processed excipient (CPE), which can be regarded as a starting material. CPEs are discussed in more detail in chapter 1.4.3.

As mini-tablets can be considered as a special form of tablets, they require advanced characterization methods. Particularly, the determination of the disintegration time is a crucial factor for the development, evaluation and comparison of (orodispersible) mini-tablets.

The described method in the Ph. Eur. is not applicable for mini-tablets of sizes below 3 mm, as the specification for the mesh sieve of apparatus A is given by 2.0 ± 0.2 mm (Ph. Eur., 2019). Consequently, all mini-tablets ≤ 2 mm would show per definition an immediate disintegration as they would immediately pass the sieve. This would even happen for functionally coated mini-tablets with delayed or prolonged release properties. In literature, several approaches have been made to develop suitable disintegration methods for ODTs and were classified by Stoltenberg (2012) into three groups (table 2). The motivation of her study was to test some of the methods and media conditions for ODMTs in order to find a method that has the greatest correspondence with biorelevant conditions. Therefore, the disintegration time of ODMTs was tested in 20 human volunteers. The endpoint was determined when the volunteers could not sense any particles in their oral cavity. The in vivo data were then correlated to the in-vitro data. According to her data, the Electro Force® and rotating punch methods showed the best correlation to the in-vivo data (Stoltenberg, 2012).

Table 2: Classification and examples of disintegration methods. Adapted and modified from Stoltenberg (2012)

Simple tests	
Wetting time	Bi et al., 1996
Simulated wetting test (SWT)	Park et al., 2008
Modified Ph. Eur. methods	
Modified basket method	Kleinebudde, 1997
Modified Ph. Eur. test	Schiermeier and Schmidt, 2002
Modified Ph. Eur. dissolution apparatus	Sunada and Bi, 2002
Methods with mechanical stress	
Texture analyser	Bohnacker et al., 2005
Rotating punch	Harada et al., 2006
Electro Force®	Bose, 2006
Hermes tester	Hermes, 2012
OD-mate	Sieber et al., 2017

The SWT test is further proposed for ODMTs by Stoltenberg and Breitkreutz (2011). The SWT should mimic the physiological conditions of the human tongue, without the mechanical stress. During this test an ODMT is placed on wet filter paper, which is embossed with a blue solution. The time which is required to wet the ODMT with a blue solution is defined as the SWT time. The endpoint is determined visually. The advantage of this method is its simplicity but a major disadvantage is the fact that SWT does not give a valid statement about the actual disintegration time. The determination of the disintegration time for mini-tablets remains a challenge. In the doctoral thesis of Hermes (2012) an apparatus was constructed for the determination of the disintegration time of mini-tablets. The construction consists of a lower and upper contact plate. An electrical resistance is measured between both contact plates. A mini-tablet is placed between the contact plates and a small volume of disintegration medium (< 1 ml) is added with a syringe. At the moment, when the medium leads to the disintegration of the mini-tablet both contacts touch, the electrical resistance decreases to a certain threshold and the time measurements stops automatically (Hermes, 2012). A study by Sieber et al. (2017) compared the Hermes-tester with the modified baskets from Kleinebudde (1997) and the OD-mate (Higuchi Inc, Japan). The OD-mate is an automatic device for orodispersible dosage forms like the Hermes tester. The (mini-) tablet is placed on a mesh and lowered into a beaker filled with the disintegration medium and a stirrer. A piston should mimic the human tongue and is placed on the tested tablet. The measurements start automatically and stop, when the piston moves downwards and passes a user defined limit. Both methods are exclusive and very comparable in their measurement technique. Nevertheless, the Hermes tester is self-constructed and not standardized for commercial production. Therefore, a commercial production line has to be implemented, which is qualified and validated to implement those systems in a GMP environment. However, for all devices suitable results could be obtained for larger ODTs but also for ODMTs (Sieber et al., 2017). In this work the modified disintegration apparatus for pellets of Kleinebudde (1997) is used for the determination of the disintegration time. A mini-tablet is placed into a cylinder and locked on the top and bottom with mesh sieves of 710 µm. The locked cylinder can be placed into a Ph. Eur. conventional disintegration apparatus and weighted using a metal cover. The endpoint is determined visually, which is a disadvantage of this method, as it requires training to observe the mini-tablet. Therefore, Stoltenberg rated this method as not suitable for mini-tablets (Stoltenberg, 2012). The main advantage is on the other side that these modified baskets can be reproduced easily, modified regarding the mesh sieves and fit in the required apparatuses of Ph. Eur.10. (2019).

1.3 Transfer and scale-up of mini-tablets

1.3.1 Principles of transfer and scale-up

In early stages of formulation development usually only small quantities of material or resources are available. Consequently, it is desirable to obtain as much information as possible, with only little experimental effort and small quantities of starting materials, in order to transfer the manufacturing process and perform scale-up studies. FDA defines a scale-up process as change of batch size by factor 10, where the equipment to produce the batch follows the same operating principles. The European medicines agency (EMA) recommends a pilot batch to be 10 % of production scale, whereas laboratory scale shall be conducted with a batch size 100-1000 times less than production scale (EMA, 2016; FDA, 1995). Both definitions are coherent for the production of immediate release solid dosage forms, which are present in this study. However, scale-up is not necessarily linked to an increase of process volume by processing the material on different sized equipment. Scale-up and consequently batch size enlargement can also be reached by increasing the throughput on the same equipment and prolonging the process.

For tablet formulations, the success of a scale-up is highly linked to the robustness of the formulation towards different process conditions (Levin, 2001). Tableting problems such as lamination, sticking or capping could occur during transfer or scale-up from one tableting machine to another, as the formulation is exposed to different compaction profiles, tableting and ejection speeds, temperature development, densification in the feeding unit etc. Therefore, a formulation should be designed and optimized for critical material attributes (CMAs), which can have a significant impact during tableting like flow property, morphology, particle size distribution, bulk and tapped density etc. These material data can support a transfer and scale-up process to succeed with less problems (Levin, 2005). In order to estimate the effect of the external impact, the use of compaction simulators can be beneficial, especially in early stage of formulation development (Çelik and Marshall, 1989) .This approach was also utilized in the present study. The working principle of the used compaction simulator is described in more detail in chapter 1.3.2.

A mathematical approach for scale-up is the use of dimension analysis. The main concept behind this approach is the assumption that a process can be described by a mathematical equation using dimensionless numbers and is therefore valid in any dimension or scale (Levin, 2005). The first pharmaceutical scale-up in literature based on dimensional analysis was applied by Leuenberger (1983) for granulation processes.
In general, a process can be scaled, when the process takes places in similar geometric environment and the significant process parameters can be described as dimensionless

numbers with the same numeric value (Leuenberger, 1983; Levin, 2005). However, in the present study dimensional analysis was not applied to perform transfer and scale-up studies. In this work, for the first time to the best of our knowledge a transfer from compaction simulator Styl'One Evo (Medelpharm, France) to the industrial rotary tablet press XM 12 (Korsch, Germany) should be performed for ODMTs following FDA and EMA regulatories for immediate release solid dosage forms.

1.3.2 Introduction to compaction simulator Styl'One Evo

The compaction simulator Styl'One Evo developed by Medelpharm (France) represents a fully instrumented press, particularly for research and development purposes, scale-up and production support. Contrary to compaction simulators with a hydraulic system (Bateman et al., 1989; Çelik and Marshall, 1989; Hunter et al., 1976), Styl'One Evo is a mechanically driven compaction simulator and works with the software Analis (Medelpharm, France). The Styl'One Evo used for our work is equipped with a dual scale, which means that two piezoelectric force sensors are installed on lower and upper piston, ranging from measurements from 0.5 N up to 50 kN. One sensor allows highly precise measurements up to 5 kN. Above 5 kN a seamless switch to the second sensor allows precise measurements up to 50 kN. Dual scale is especially suitable for basic research of powders using very low compression forces such as mini-tableting with a single tip or low force tamping operations for multi-layer (mini-)tablets. The software Analis controls and monitors all processes during tableting. In-process data acquisition and analysis but also post evaluation of data and reporting is possible. Styl'One Evo can be equipped with conventional single station EU-B and EU-D tooling but also shaped tooling systems like multi-tip tooling. Furthermore, external lubrication can be used with a micro-dosing unit with a pulsed air blow cabinet. In this work Styl'One Evo was used for research and development studies, but also to perform the transfer and scale-up study for ODMTs to Korsch XM 12, which represents an industrial rotary tablet press. As described in chapter 1.3.1, the formulation is exposed to different tableting profiles and velocities and different ejection speeds, when it is transferred to different tableting machines. With Styl'One Evo the tableting profile of Korsch XM 12 can be simulated in order to test the tableting behavior of the formulation with respect to pre-defined quality attributes of the final formulation. Styl'One Evo can mimic the kinetic of rotary tablet presses by simulating the punch and ejection speed, the compression symmetry (symmetrical or non-symmetrical) and the dwell time during compression. Nevertheless, further sub-processes such as segregation or densification processes in the hopper, (in-)homogenous die-filling or heat transfer during production are until now hardly investigable and have to be challenged in future studies.

1.4 Formulation development of ODMTs for paediatric patients

1.4.1 Background and general aspects

Drug formulation development can be either based on empirical or systematic approaches or by combinations of both (EMA, 2017). The EMA recommends to perform a systematic approach including novel tools like Quality by Design (QbD) for new development projects. In all cases, the aim is to design a pharmaceutical product, where the quality, efficacy and safety is provided for the patient. Six key elements to be considered for a systematic formulation development are defined by EMA (figure 2). In a quality target product profile (QTPP), essential elements of the final product are defined such as dosage form, dosing strength, route of administration, the container closure system and others. CQAs should define the properties of the final or intermediate dosage form, in case of tablets it would include mass, disintegration time, friability, dissolution profile and others. In a risk assessment further aspects are elaborated that influence the quality of the product. For example, CMAs are defined, which have a significant impact on the (intermediate) product quality. But not only CMAs do affect the product quality. The manufacturing process itself impacts CQAs of the (intermediate) products. For each manufacturing step CPPs are defined before starting the development. Furthermore, a design space should be established to assess the interactions of process inputs (e.g. materials, process parameters) and CQAs, typically with statistical tools like Design of Experiments (DoEs). In order to monitor and asses the quality of the product, it is necessary to implement suitable control strategies. The control strategies are not only linked to in-process controls or monitoring during and in the end of production, it is also recommended to implement strategies to control the quality of starting materials. Another elementary tool is the life-cycle management. The aim is to verify the quality of the product in all stages from development to commercial manufacturing. This can be done by monitoring the process and product performance, implementing on-going process verification and elaborate novel and innovative tools to control and steer the quality within the design space (EMA, 2017).

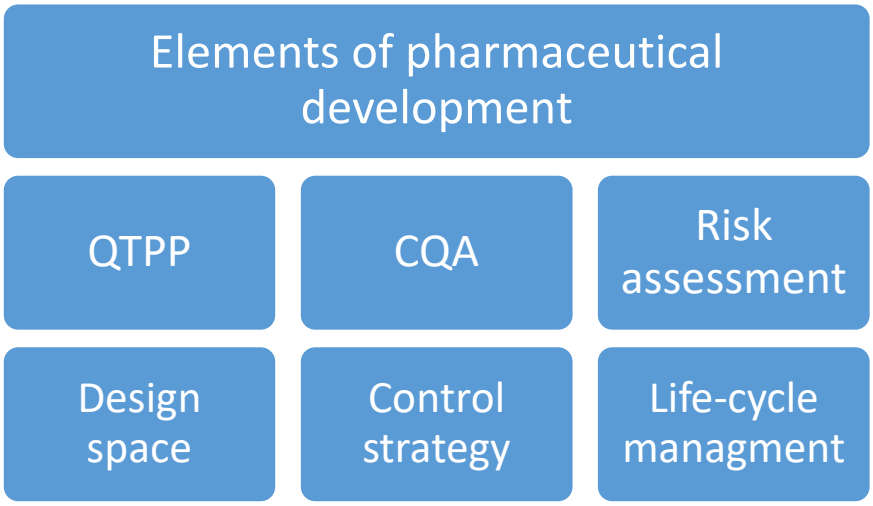

Figure 2: Elements of pharmaceutical development according to EMA ICH Q8 (R2)

In order to encourage and assist formulation scientists, the WHO publishes and updates a list of essential medicine for children. In this list, drugs are listed for the treatment of various diseases for children, but where no suitable dosage form is available (WHO, 2019). In many cases, a dosage form is administered as an off-label use for the treatment of paediatric patients, because suitable dosage forms are not available. The effect of an off-label use in different countries and age groups has been summarized by Pandolfini and Bonati, indicating that up to 80 % of patients were treated with off-label or unlicensed medicine (Pandolfini and Bonati, 2005). A lack of appropriate medicines for these patient groups is linked with an inadequate therapy and avoidable side effects (Aagaard and Hansen, 2011; Horen et al., 2002; Turner et al., 1998).

In order to overcome these challenges of lacking medicine for children, the EU filed the 1901/2006 regulation (EU, 2006). The aim of this EU regulation is to encourage pharmaceutical companies to implement a paediatric investigation plan (PIP) for new chemical entities (NCE). The PIP has to be implemented in the drug development phases and clinical phases to ensure the safety, quality and efficiency of the drug for the paediatric patients. However, a PIP can be waived by the paediatric committee of the European council (PDCO), if for example the pharmaceutical company claims for a waiver or a deferral due to a lack of use of the drug for paediatric patients or due to security concerns. Additionally, companies are encouraged to develop suitable paediatric dosage forms to avoid off-label medicine. If they succeed, they can benefit from a paediatric marketing authorization (PUMA) and are rewarded with a 10-year marketing authorization (Breitkreutz, 2008; EU, 2006). Since then, several PIPs have entered clinical studies or completed a PIP procedure (Thabet et al., 2018).

The motivation to develop suitable dosage forms for children has been also discussed at an expert meeting organized by WHO in 2008. A shift from the development of liquid dosage forms to (orodispersible) solid dosage forms was proposed (WHO, 2008) and was later certified by scientific experts. In addition, mini-tablets and ODMTs (described in chapter 1.1 and 1.2) were considered as most promising dosage forms for paediatric patients (Hoppu, 2016; Strickley, 2019). Most recently, the LENA project funded by EU has gone through a PIP procedure targeting the appropriate treatment of paediatrics and children with ODMTs containing enalapril maleate (EM). (Bajcetic et al., 2019; Faisal et al., 2019; van Hecken et al., 2020; Walsh, 2017).

1.4.2 Selection of API in the present study

1.4.2.1 Enalapril maleate

Enalapril maleate (EM) is listed in the WHO list of essential medicine (WHO, 2019) and represents a drug from the group of angiotensin converting enzyme inhibitors for the treatment of hypertonia, heart failure and chronic kidney disease. It is administered for the treatment of hypertension of children and infants weighting below 20 kg with doses of 0.2-2.5 mg (Smeets et al., 2020; Wells et al., 2001). EM is of high clinical importance, which resulted in a EU funded project (LENA) to address the challenges of developing child appropriate medicine for children with heart failure (Walsh, 2017; Thabet et al., 2018).

EM is defined by Ph. Eur. as a white or almost white crystalline powder with free solubility in organic solvents like methanol or diluted solutions of alkali hydroxides. It is stated to be sparingly soluble in water (Ph. Eur., 2019).

1.4.2.2 Hydrochlorothiazide

Hydrochlorothiazide (HCT) is considered as an essential drug for children by WHO (2019). It belongs to the group of diuretic drugs and is used for paediatric patients for different indications such as renal failure, hypertension, congestive heart failure and many more. Depending on the indication age and body weight 2-3.3 mg/kg are recommended for patients younger than 6 months, whereas above 6 months 2 mg/kg is recommended (van der Vorst et al., 2006). HCT was chosen as well as a model drug in studies by Stoltenberg and Breitkreutz (2011) to develop the very first ODMTs.

HCT is defined as a white or almost white crystalline powder by Ph. Eur. It is slightly soluble in water, but soluble in acetone and sparingly soluble in ethanol (96 %). It dissolves in diluted solutions of alkali hydroxides (Ph. Eur., 2019).

1.4.3 Ready-to-use excipients for the development of ODMTs

1.4.3.1 General aspects

Ready-to-use excipients are designed in order to improve the tableting performance on different levels. First of all, the number of different excipients should be reduced within a tablet aiming to assure the simplicity of the formulation. In the simplest formulation only a blending step of the ready-to-use excipient with the API (and lubricant) is necessary to perform direct compression, which should save time and costs. There are two types of ready-to-use excipients. Co-processed excipients (CPEs) are designed by at least two individual excipients and represent a multi-component system in order to obtain a synergy of different functionalities in one CPE mixture (Chow et al., 2008; Saha and Shahiwala, 2009). As mentioned in chapter 1.2, mannitol based CPEs are often used for the development of ODT/ODMTs and are available in several commercial market products (table 3), which were tested for manufacturability and acceptability by Bowles et al. (2018). CPEs for direct compression of orodispersible dosage forms aim for superior tableting properties, which result in ODTs with sufficient mechanical strengths and disintegration time in comparison with their physical mixtures (Bowles et al., 2018; Dziemidowicz et al., 2018).

Contrary to CPEs, functionalized excipients (FE) are based on single components. The effect of a FE on tableting performance and resulting CQAs of the tablet are highly linked to the processing of the raw material and the resulting particle design and morphology. Ilic et al. investigated different types of functionalized lactose grades. For example, spray dried lactose showed the best compressibility, whereas milled lactose the worst. On the other hand, milled lactose showed better compactibility in comparison to spray dried lactose (Ilić et al., 2009). Grote and Kleinebudde showed the effect of different types of dibasic calcium phosphate anhydrous (DCPA) on tabletability after roll compaction and dry granulation (RCDG). Functionalized DCPA (agglomerated type formed by small primary particles) showed superior tabletability profiles compared to milled grade and two further agglomerated grades (Grote and Kleinebudde, 2018). A similar conclusion was drawn for different mannitol grades after RCDG as functionalized spray-dried mannitol tablets showed better compactibility compared to unprocessed mannitol (Wagner et al., 2013). For both, CPEs and FEs, the tableting performance is improved via appropriate techniques such as spray drying, wet granulation, co-milling and co-crystallization, milling and sieving in comparison to the unprocessed excipient (Chow et al., 2008; Gohel and Jogani, 2005; Rojas et al., 2012; Saha and Shahiwala, 2009).

CPEs and FEs both may have advantages and disadvantages. With the use of ready-to-use excipients general aims like better flowability, improved tableting behavior, enhanced disintegration time and less segregation can be met. However, ready-to-use excipients also show several drawbacks. In the case of CPEs, the ratios of the components are final and cannot be modified anymore. In comparison the performance of a FE could be improved with additional excipients targeting for a specific quality attribute of the final dosage form. Another major disadvantage is the dependency from a specific supplier. For product development, as well for later production batches, the essential dependency from just one supplier might be very critical as no evasion to alternative suppliers is possible, when for example the main supplier cannot deliver the excipient or runs out of business.

For the development of ODMTs, the CPE Ludiflash® and FE galenIQ™721 have been used and are described below.

Table 3: Example of co-processed excipients (CPEs) based on D-mannitol for ODT manufacturing (adapted and modified from Bowles et al., 2018)

Marketed CPEs	Supplier	Ingredients
Compressol® SM	SPI Pharma, USA	80-90 % mannitol 10-15 % sorbitol < 2 % silicon dioxide
F-Melt® type C	Fuju Chemical Industry, Japan	55-70 % D-mannitol 10-25 % microcrystalline cellulose 2-9 % xylitol 5-13 % crospovidone 2-9 % dibasic calcium phosphate anhydrous
F-Melt® type M	Fuju Chemical Industry, Japan	55-70 % D-mannitol 10-25 % microcrystalline cellulose 2-9 % xylitol 5-13 % crospovidone 2-9 % magnesium aluminometasilicate
Ludiflash®	BASF, Germany	90 % D-mannitol 5 % crospovidone 5 % polyvinyl acetate dispersion
Pearlitol® Flash	Roquette, France	80-85 % mannitol 15-20 % maize starch
Pharmaburst® 500	SPI Pharma, USA	85 % mannitol < 10 % silicon dioxide < 10 % sorbitol 5 % crospovidone
ProSolv® ODT	JRS Pharma, Germany	60-70 % mannitol 15-30 % microcrystalline cellulose < 10 % fructose and silicon dioxide 5% crospovidone
SmartEx® QD 50	Shin-Etsu, Japan	D-mannitol polyvinyl alcohol low-substituted hydroxypropyl cellulose
SmartEx® QD 100	Shin-Etsu, Japan	D-mannitol polyvinyl alcohol low-substituted hydroxypropyl cellulose

1.4.3.2 Ludiflash®

Ludiflash® is a co-processed excipient for direct compression based on D-mannitol, crospovidone, a polymer dispersion of polyvinyl acetate (PVA) and povidone (BASF, 2017, 2013) Crospovidone as a super-disintegrant should enhance the disintegration process, whereas PVA in combination with povidone serves as a binder. It is further discussed that due to its hydrophobic properties disintegration is enhanced because of possible pore forming properties (BASF, 2017, 2013). Ludiflash® is characterized by a pleasant taste because of mannitol and shows a soft cake effect during disintegration (BASF, 2017). Ludiflash® was already used in several studies for the development of ODMTs with the API EM, which have gone most recently through a PIP procedure (Bajcetic et al., 2019; Faisal et al., 2019; Stoltenberg and Breitkreutz, 2011; van Hecken et al., 2020; Walsh, 2017).

1.4.3.3 galenIQ™721

Isomalt is a mixture of the two disaccharide sugar alcohols 6-O-α-D - glucopyranosyl sorbitol (GPS) and 1-O-α-D- glucopyranosyl D-mannitol (GPM) and is obtained after hydrogenation of isomaltulose. Different grades of galenIQ™ are designed for different manufacturing routes (Beneo-Palatinit, 2019). For direct compression there are two agglomerated type of isomalt galenIQ™720 and galenIQ™721. Functionalized isomalt for direct compression (galenIQ™721, Beneo-Palatinit, Germany) is designed via a fluid bed process of isomalt and subsequently a sieving operation. The ratio between GPS and GPM affects the water solubility of isomalt. In galenIQ™721 the ratio of GPS to GPM is 3:1, which results in a higher water solubility and faster disintegration and consequently benefits the development of ODMTs. Furthermore, this type of agglomerated isomalt showed a good compaction behavior in previous studies (Bolhuis et al., 2009; Bolhuis et al., 2009), which might lead to mechanical stable ODMTs at comparable lower tableting pressures. The sweet taste and non-cariogenic properties of isomalt enable isomalt as a potential single-component excipient for direct compression of ODMTs for paediatrics. To best of our knowledge, no ODMTs have been developed based on functionalized isomalt before.

1.5 Aim of the thesis

Aim of this thesis was to systematically investigate the development and manufacturing of mini-tablets using various excipients, tooling systems and tableting machines. Fundamental research using modern compaction simulators and rotary tablet presses should contribute to a better understanding of the tableting process, the impact of tooling systems and scale-up processes of mini-tablets as well as formulation development.

In the following, the aims are described in more detail:

- To perform systematical investigations of the tableting properties of mini-tablets in comparison with conventionally sized tablets, in order to gain knowledge about the tableting behavior of pharmaceutical excipients in dependence on the tablet size (Chapter II).

- To determine the effect of various tooling systems with different number of tips on CQAs and tableting properties of 2 and 3 mm mini-tablets (Chapter III).

- To evaluate a transfer from a compaction simulator to a rotary tablet press and to perform a scale-up process for 2 mm ODMTs using two ready-to-use excipients (Chapter IV).

- To develop and compare ODMTs based on EM and HCT for paediatric use comprising two different ready-to-use excipients (Chapter V).

1.6 Outline of the thesis

Chapter II accesses gaps of knowledge regarding the technological manufacturing process of mini-tablets in comparison with conventionally sized tablets. In previous studies, certain tablet formulations showed higher mechanical strengths, when being compressed into mini-tablets in comparison to conventionally sized tablets, but to best of our knowledge no systematic investigations have been made with a variety of pharmaceutically relevant excipients. Therefore, microcrystalline cellulose (MCC) and lactose as frequently used excipients and the novel ready-to-use excipients Ludiflash® and galenIQ™721 were tableted with compaction simulator Styl'One Evo at five different tableting pressures to 1, 2, 3, 8 and 11.28 mm tablets. Tableting properties like tabletability, compactibility and compressibility were evaluated with different approaches aiming to explain, whether mini-tablets show technological advantages over conventionally sized tablets. The hypothesis of a higher plastic energy transfer for smaller sized tablets has been investigated as well, in order to explain the proposed higher mechanical strengths of mini-tablets in comparison to conventionally sized tablets. Therefore, specific plastic energies (SPEs) were calculated and compared for mini-tablets and conventionally sized tablets.

Chapter III focuses on the impact of the tooling system for the manufacturing of 2 and 3 mm mini-tablets. The effect of number of used tips (single-tip vs. 7-tip vs. 19-tip tooling) on tableting properties (tabletability, compactibility and compressibility) is evaluated using Styl'One Evo. Furthermore, the hypothesis of a higher transfer of plastic energy reported in literature over the amount of tips is evaluated by comparing the obtained SPEs during compression for MCC, lactose, Ludiflash® and galenIQ™721. CQAs like mass and tensile strengths should be evaluated and interpreted in relation to the used tooling system. Lastly, the effect of die-wall friction expressed as the ejection force resulting from the different tooling system on tensile strength as a CQA is assessed.

In chapter IV, a transfer and scale-up process for 2 mm ODMTs from a compaction simulator to an industrial rotary tablet press should be conducted following EMA and FDA guidelines. ODMTs based on Ludiflash® and galenIQ™721 should be produced and CQAs like tensile strengths, mass and disintegration time need to be evaluated. Furthermore, the development of product temperature during production on the rotary tablet press and its impact on disintegration time as a major CQA of ODMTs should be monitored.

The effect of the product temperature and tableting duration on the mini-tablets is further evaluated using confocal Raman microscopy. Additionally, the properties of residual powder from the feeding shoe of the rotary tablet press are assessed by comparing tabletability and disintegration time to ODMTs produced from fresh powder.

Chapter V deals with the development of 2 mm ODMTs based on galenIQ™721 and Ludiflash® with EM and HCT as model drugs urgently needed for paediatric patients. In this chapter, galenIQ™721 will be introduced as a novel functionalized excipient for the development of ODMTs as either a single-component excipient or in combination with further components and compared to established ODMT formulations based on Ludiflash®. Furthermore, stability studies should evaluate the effect of ambient and stress conditions during storage on CQAs such as disintegration time and tensile strengths of HCT and EM ODMTs.

In chapter VI the thesis is concluded and future perspectives are discussed.

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Chapter II

Tableting of mini-tablets in comparison with conventionally sized tablets- A comparison of tableting properties and tablet dimensions

Chapter II: Tableting of mini-tablets in comparison with conventionally sized tablets: A comparison of tableting properties and tablet dimensions

2.1 Pretext

In literature, the effect of the tablet size on general tableting properties is often compared and evaluated. In most cases, tablet dimensions are compared, which are not in the size of mini-tablets or the differences in tablet sizes are not great enough. The aim of this study was to systematically evaluate, whether mini-tableting has benefits in comparison to conventionally sized tablets and really improves tableting properties, as it was described in literature by various researchers, and to gain more knowledge in the general tableting process. Therefore, mini-tablets (1-3 mm) were compared to conventionally sized tablets (8 and 11.28 mm) by tableting frequently used excipients like MCC and lactose and also modern ready-to-use excipients like functionalized isomalt (galenIQ™721) or co-processed mannitol (Ludiflash®). Tableting was conducted using compaction simulator Styl'One Evo, allowing highly precise measurements and data evaluation with Analis Software (Medelpharm, France).

The following research has been published in International Journal of Pharmaceutics in 2020. The first author Ard Lura was responsible for Methodology, Investigation, Formal Analysis, Data curation, Writing-Original draft preparation. Guillaume Tardy was responsible for the Software Analis and Evaluation of the modified Weibull function. Peter Kleinebudde and Jörg Breitkreutz as senior authors were responsible for Conceptualization, Writing, Reviewing and Editing.

Tableting of mini-tablets in comparison with conventionally sized tablets: A comparison of tableting properties and tablet dimensions

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Abstract

Mini-tablets are solid dosage forms with increasing interest for pharmaceutical industry due to clinical and biopharmaceutical benefits. But technological aspects on mini-tableting are not fully investigated. Therefore, the impact of punch size and tableting pressure for industrially relevant excipients like microcrystalline cellulose, lactose, isomalt and Ludiflash® are investigated using 8 and 11.28 mm punches for conventionally sized tablets and 1, 2 and 3 mm punches for mini-tablets. For evaluation of the effect of tablet size on deformation behaviour and mechanical properties, compressibility, compactibility and tabletability plots are created and evaluated. Deformation behaviour is analysed by In-Die Heckel plot and modified Weibull function. Further, specific plastic energy (SPE) profiles are generated out of force-displacement plots. The effect of the adjustment of the aspect ratio towards 1 in conventionally sized tablets on deformation behaviour and tabletability is analysed. The effect of tablet size on deformation behaviour mainly showed lower yield pressures for conventionally sized tablets, whereas comparable SPEs were obtained with all tablet sizes. Furthermore, mini-tablets indicate better compactibility, as (depending on the excipient) higher tensile strengths were obtained at lower solid fractions. However, no superior tabletability properties are obtained for mini-tablets compared to conventionally sized tablets.

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Chapter III

Production of mini-tablets.
Focus and impact of the tooling system

Chapter III: Production of mini-tablets. Focus and impact of the tooling system

Pretext

In chapter II it was shown that besides of an improvement on compactibility no superior tableting properties were observed for mini-tablets in comparison to conventionally sized tablets. This paper aims to investigate the impact of different tooling systems for mini-tableting on tablet properties like tabletability, compactibility and compressibility by using a 2 and 3 mm single-tip, 7-tip and 19-tip tooling system. Furthermore, the effect of the different zones of a 7 and 19-tip tooling on CQAs like mass or tensile strengths have been evaluated. Additionally, the effect of the resulting ejection force in dependency of the used tooling system by targeting a specific tensile strength is discussed also under a research and development but also industrial point of view.

The following research paper has been submitted Journal of Drug Delivery Science and Technology in 2021. The first author Ard Lura was responsible for Methodology, Investigation, Formal Analysis, Data curation, Writing-Original draft preparation. Jörg Breitkreutz as a senior author was responsible for Conceptualization, Writing-Reviewing and Editing.

Production of mini-tablets. Focus and impact of the tooling systems

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Abstract

Mini-tablets are gaining importance for the pharmaceutical industry as several clinical studies and organizations emphasize the benefits for special patient groups such as paediatrics. Mini- tablets can be manufactured on tablet presses using special tooling systems. For industrial purposes often multi-tips are used, in order to achieve a high yield during production time. However, the effect of the used tooling system on quality attributes is not fully investigated yet. Therefore, 2 and 3 mm mini-tablets have been manufactured on a compaction simulator using single-tip, 7-tip and 19-tip punches and industrial relevant excipients. Mass variation and tensile strengths of the mini-tablets were evaluated as critical quality attributes. Additionally, the deformation behavior and specific plastic energy (SPE) were analyzed. For evaluating the tableting performance tabletability and compactibility plots were created. With all used tooling systems significant differences in mass were observed for all excipients, despite of identical tableting conditions. In-die Heckel plot revealed that the lowest yield pressures and in most cases the highest SPE were obtained using a single-tip. No major differences were found regarding tabletability but in most cases compactibility was improved using a 19-tip tooling. On the other hand, with a 19-tip the highest ejection forces were measured and targeted tensile strengths could not be achieved.

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Chapter IV

Transfer and scale-up of the manufacturing of orodispersible mini-tablets from a compaction simulator to an industrial rotary tablet press

Chapter IV: Transfer and scale-up of the manufacturing of orodispersible mini-tablets from a compaction simulator to an industrial rotary tablet press

Pretext

After evaluation of the basic research of mini-tableting and the impact of the tooling system in chapter II and III a more practical and industrial approach should be demonstrated in this chapter. The feasibility of Styl'One Evo (Medelpharm, France) is assessed to predict the tabletability and compactibility profiles of galenIQ™721 and Ludiflash® by using the simulation profile of rotary tablet press Korsch XM 12 Eu-D and small quantities of powder. Furthermore, a scale-up process with both excipients is conducted following FDA and EU guidelines by increasing batch sizes at factor 10 on the rotary tablet press. Therefore, first 570 mini-tablets are produced on compaction simulator using the mentioned simulation profile. Subsequently the batch size is increased on XM 12 (Korsch, Germany) from 570, to 5.700 and finally to 57.000 mini-tablets. As CQAs mass variation, disintegration time and tensile strengths were selected and evaluated for both isomalt and Ludiflash®. Additionally, over 100.000 mini-tablets were manufactured with both excipients to monitor the process, the impact of product temperature and the effects on pre-defined CQAs.

The following research paper has been published in International Journal of Pharmaceutics. The first author Ard Lura was responsible for Methodology, Investigation, Formal Analysis, Data curation, Writing-Original draft preparation. Valentinë Elezaj was responsible for Investigation, Formal Analysis and Data Curation. Marcel Kokott was responsible for Investigation, Formal Analysis and Data Curation. Jörg Breitkreutz as a senior author was responsible for Conceptualization, Writing-Reviewing and Editing.

Transfer and scale-up of the manufacturing of orodispersible mini-tablets from a compaction simulator to an industrial rotary tablet press

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Abstract

Orodispersible mini-tablets (ODMTs) are a promising dosage form for the paediatric use showing increasing interest from pharmaceutical industry. However, a scale-up process for ODMTs from a compaction simulator to a rotary tablet press following FDA and EMA guidelines has not been performed and investigated yet. Isomalt (galenIQ™721) and Ludiflash® both excipients with proven suitability for the development of ODMTs have been investigated in transfer and scale-up from a compaction simulator to a rotary tablet press. ODMTs with Isomalt were produced on the rotary tablet press monitoring the product temperature over time and assessing the properties of the residual powder in the feed shoe. Critical quality attributes like tensile strength, mass and disintegration time are evaluated. The transfer from compaction simulator to rotary tablet press succeeded as for both excipients similar disintegration times, tabletability and compactibility profiles were obtained. However, during scale-up, disintegration time increases over time, while tensile strength decreases for both excipients. Monitoring of the product temperature revealed that with increasing batch size the product temperature increases as well having a significant impact on disintegration time. The properties of ODMTs produced with the residual powder are comparable in tabletability and disintegration time compared to ODMTs produced from fresh powder.

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Chapter V

New orodispersible mini-tablets for paediatric use - A comparison of isomalt with a mannitol based co-processed excipient

Chapter V: New orodispersible mini-tablets for paediatric use- A comparison of isomalt with a mannitol based co-processed excipient

Pretext

This chapter deals with formulation development of orodispersible mini-tablets (ODMTs). The ODMTs are developed and manufactured based on the ready-to-use excipients Ludiflash® and for the first time galenIQ™721 as a functionalized isomalt for direct compression. The focus of this paper is the comparison of novel isomalt formulations with already established Ludiflash® based ODMT formulations. As active pharmaceutical ingredients (APIs) hydrochlorothiazide (HCT) and enalapril maletate (EM) were chosen. Both APIs are listed in the WHO List of Essential medicine for children. So far the EM formulation with Ludiflash® is the only ODMT which finished clinical studies in paediatric patients following a PIP procedure and serves therefore as a suitable bench mark formulation for comparison regarding CQAs of the ODMTs such as content uniformity, disintegration time and dissolution profile, tensile strengths and stability.

The following research paper has been published in International Journal of Pharmaceutics in 2019. The first author Ard Lura was responsible for Methodology, Investigation, Formal Analysis, Data curation, Writing-Original draft preparation. Oliver Luhn was responsible for Conceptualization, Writing-Reviewing and Editing. Javier Suarez Gonzales was responsible for investigation, formal analysis and data curation. Jörg Breitkreutz as a senior author was responsible for Conceptualization, Writing-Reviewing and Editing.

New orodispersible mini-tablets for paediatric use- A comparison of isomalt with a mannitol based co-processed excipient

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Abstract

The development of orodispersible mini-tablets (ODMTs) for paediatric use has gained importance within recent years as European authorities set up regulations for developing suitable and palatable dosage forms for paediatric patients. Polyols like mannitol and isomalt are frequently used in the manufacture of tablets where sensory properties have to be taken into account. In literature, ODTMs based on a commercialized co-processed excipient based on mannitol (Ludiflash®) have been already described. Isomalt is known for its pleasant sensory properties and therefore appears to be a good candidate for ODMTs. The feasibility of the direct compression grade of isomalt for the manufacture of ODMTs was assessed and compared to Ludiflash®. Hydrochlorothiazide and enalapril maleate were chosen as model drugs and compressed to 2 mm mini-tablets. ODMTs could be obtained fulfilling the criteria of Ph. Eur. with disintegration times of 180 s or even the FDA limit of 30 s. Dissolution studies and mass variation were fulfilled for all mini-tablets. Acceptance values (AV) ≤ 15 were achieved for formulations based on both isomalt and Ludiflash®. Stability data showed the change of disintegration time and tensile strength as a function of storing time, condition and excipient. Both excipients showed their potential for ODMTs for paediatric use.

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Chapter VI

Conclusion and future perspectives

Chapter VI: Conclusion and future perspectives

This thesis systematically evaluated the manufacturing and development of mini-tablets in different perspectives. Basic research studies on tableting properties of mini-tablets in comparison to conventionally sized tablets indicate that tabletability and compressibility are not systematically impacted by the tablet size. Mini-tableting improved compactibility, as lower solid fractions were calculated at comparable tensile strengths compared to conventionally sized tablets. This is coherent with observations from literature, but the hypothesis of a higher plastic deformation during tableting could not be supported according to the obtained data. The reason why certain formulations or materials succeed only as mini-tablets and not as conventionally sized tablets might be an interaction of different factors and cannot be attributed to a single factor. These factors might be the surface to volume ratio (SVR) of mini-tablets, the used tableting equipment, such as tooling and tableting machine and finally the physicochemical properties of the formulation itself. What supports this hypothesis is the fact that an adjustment of the aspect ratio (AR) of conventionally sized tablet did not lead to an adjustment of the SVR compared to mini-tablets. This might support the result of better compactibility as relatively more material is exposed to the punches during tableting. The surface of the mini-tablet could be densified more compared to the inner structure resulting in a higher compactibility. In many cases compactibility was improved as well when using a 19-tip tooling in comparison to a 7- or single-tip. On the other hand, a higher number of tips led to higher die-wall friction resulting in too high ejection forces. Consequently, targeted tensile strengths could not be achieved, so the number of tips had to be reduced. In development stage, a formulation might form a solid compact when decreasing the tablet diameter or increasing the number of tips. This hypothesis has to be further evaluated with API loaded formulations. For the industrial manufacturing a balance should be found between aiming for higher yields and the consequence of higher die-wall frictions and possibly higher variations in tablet quality with increasing number of tips. From the practical point of view also the maintenance of the tooling should not be neglected. For industrial purpose, we could show that a transfer with the ready-to-use excipients galenIQ™721 (Beneo-Palatinit, Germany) and Ludiflash® (BASF, Germany) from a compaction simulator to an industrial rotary tablet press is feasible. Tabletability, compactibility and further CQAs for ODMTs like tensile strengths and disintegration time were comparable. A further scale-up by factor 10 revealed significant changes in CQAs.

Especially the disintegration time increased with increasing batch size and longer process time until both formulations could neither met FDA nor Ph. Eur. specifications for orodispersible tablets. Over-lubrication and changes in porosity could be obliterated as the main raison. Due to longer process time and consequently increasing temperatures of the tableting machine followed by higher heat transfer to the mini-tablets, structural changes such as sintering and higher roughness of the surfaces could be elaborated. This observation represents a warning for manufacturing and development of ODMTs as during scale-up and/or longer process time CQAs could be impacted significantly. In the worst case, the manufacturer will produce a product, which will be out of specification (OOS). Therefore, proper process and in-process controls are mandatory.

Formulation development studies were introduced with direct compression grade of isomalt (galenIQ™721), a novel functionalized excipient for the manufacturing and development of ODMTs of 2 mm. Manufacturing and development of various formulations succeeded with low dose enalapril maleate and high dose hydrochlorothiazide. Furthermore, they could be compared to existing ODMT formulations based on Ludiflash® as a comparator. Ludiflash® is an established CPE, which is designed to simplify formulation development. In most cases, only the API and a lubricant are additionally required to develop orodispersible solid dosage forms. However, galenIQ™721 represents a more classical approach for formulation development, as in development stage a formulation scientist has more possibilities to add design and change further excipients to fulfill targeted quality attributes. ODMTs with both excipients and APIs showed that depending on the storage conditions and chosen container closure system CQAs of the ODMTs such as tensile strengths and disintegration time can be affected significantly. In the worst case this will lead to an OOS product. CPEs offer many advantages but a main downside of CPEs will always be the dependency from a specific supplier. From the regulatory point of view, a closure of the source might lead to heavy variations and in the worst case to a sunset clause of the product.

Mini-tablets may gain even more importance as a suitable dosage form for especially the paediatric population in future. Recommendations of the WHO, PIPs and PUMA initiative of the EU are a guidance for the pharmaceutical industry to enhance investigations for child appropriate medicine. The clinical and biopharmaceutical benefit of mini-tablets were proven in several studies. Nevertheless, there is a lack from authorities and pharmacopeias to define and officially accept mini-tablets as a stand-alone dosage form.

The technological challenge in development and manufacturing and more important the lack of standardized analytical methods impede the development process of commercial mini-tablets. So far, mini-tablets are claimed in most cases as granules in pharmaceutical companies and by legal authorities.

The research and development of mini-tablets is promoted, as the performance of compaction simulators is being continuously improved and thus highly precise trials with various compaction profiles are feasible. With only few quantities of material, conclusions can be drawn on tableting properties and further scale-up processes can be verified on industrial tablet presses. However, the flowability of the powder is one of the major challenges on performing mini-tableting on compaction simulators. Therefore, suitable feeding systems have to be developed to mimic the die filling as good as possible in order to avoid manual die filling or inappropriate die filling by non-suitable feeding systems.

In future investigations, different API loaded formulations by either direct compression or an intermediate granulation process should be performed. An assessment of the influence of the properties of API in low and high drug loaded formulations on mini-tableting has to be evaluated to verify or reject the impact of mini-tableting and the tooling system on compactibility and other tableting properties and CQAs. Besides, the focus should move towards a more industrially relevant direction. CMAs and CPPs have to be defined and their effect on CQAs should be investigated for upstream processes like granulation or blending, and for downstream processes like coating and packaging. Additionally, suitable methods for the characterization of mini-tablets need to be investigated and standardized. Otherwise the comparison of data will be strongly impacted by the used method. For industry as well as for academia mini-tablets will be a challenging task to take, but also give a great opportunity to develop and manufacture medicine for special patients and try to improve the quality of life.

Summary

Since the change of paradigm from liquid dosage forms to solid dosage forms for paediatric patients mini-tablets became a promising dosage form, but also a challenge for pharmaceutical scientists as especially the basic research on the manufacturing and development is not fully understood, yet. This work deals with the systematic approach to understand the manufacturing and development of mini-tablets. The focus has been set on basic research regarding the tableting process in comparison with conventionally sized tablets, as well as the impact of the used tooling equipment on critical quality attributes (CQAs) for mini-tablets. Furthermore, a transfer and scale-up process for orodispersible mini-tablets (ODMTs) was conducted. Finally, formulation development of ODMTs with two co-processed excipients and further stability studies were performed.

In literature, manufacturing of different formulations is described to fail, when being compressed to conventionally sized tablets, but succeed when being compressed to mini-tablets. Several hypotheses were established trying to describe higher mechanical strengths of small tablets in comparison to bigger tablets, but these could not be fully adapted to mini-tablets. Mini-tablets show, depending on the composition of the formulation, a different tableting performance in comparison to conventionally sized tablets. In a systematic study, using a modern compaction simulator, the tableting performance of 1, 2 and 3 mm mini-tablets was compared to 8 and 11.28 mm conventionally sized tablets. Tableting attributes like tabletability, compactibility and compressibility were evaluated using four pharmaceutically relevant excipients like frequently used MCC and lactose as well as novel ready-to-use excipients like direct compression grade of isomalt (galenIQ™721) or co-processed mannitol (Ludiflash®). No systematic behavior was found regarding a better tabletability or different deformation behavior which would result in higher mechanical strengths with decreasing tablet dimension. Nevertheless, mini-tablets showed better compactibility and could be further characterized by their surface to volume ratio (SVR) of minimum 2 mm^{-1}.

The effect of the tooling system on mini-tableting revealed that despite or because of manual die filling significant differences were observed in mass and tensile strengths at low and high tableting pressure within the different zones of a 19-tip, 7-tip and a single-tip. The scattering in mass and tensile strengths emphasizes that variations among mini-tablets could impact these CQAs. However, only a trend but no significant effect was found for tabletability or compressibility in dependence of the used tooling.

Better compactibility was obtained for almost all excipients by using a 19-tip tooling. From an industrial point of view, a higher number of tips would be beneficial to obtain higher yield in shorter manufacturing time. Nevertheless, with increasing number of tips, the possibility of higher deviations impacting CQAs gets higher and also higher ejection forces occur. For formulations, which might tend to capping or lamination, a reduction of the number of tips might be beneficial for manufacturing mini-tablets targeting a specific tensile strength.

A more industrially relevant approach of this work was a transfer and scale-up study of ODMTs driven by FDA and EU guidelines. Tensile strengths, mass and disintegration time were selected as CQAs of ODMTs. For the transfer and scale-up a compaction simulator and an industrial rotary tablet press were used. It was proven that a transfer is feasible but with increasing batch sizes and consequently longer process times the disintegration time of the ODMT increased until neither FDA nor Ph. Eur. specifications for orodispersible solid dosage forms were fulfilled. The main reason was found to be the higher heat transfer with increasing process time, which led to partial sintering processes and other structural changes of the mini-tablets such as change in surface structure. Consequently, these changes did obviously prevent water penetration and disintegration processes. However, other processes, such as over-lubrication or densification during process time should not be neglected. Therefore, proper process understanding including the definition of critical process parameters (CPPs) and critical material attributes (CMAs) is required. Furthermore, suitable in-process controls should be implemented to assure the quality of ODMTs.

Formulation development of 2 mm ODMTs was successful using enalapril maleate and hydrochlorothiazide as model drugs with galenIQ™721 and Ludiflash®. Direct compression grade of isomalt was introduced as a novel excipient for development of ODMTs. Both, galenIQ™721 and Ludiflash® formulations fulfilled disintegration specification of Ph. Eur. and FDA. Acceptance values of ≤ 15 were achieved for various formulations based on galenIQ™721 and Ludiflash®. Stability studies of ODMTs based on both excipients, stored under ambient or stress conditions, showed that the CQAs tensile strength and disintegration time of ODMTs are impacted by the storage and packaging conditions. This emphasizes that, besides formulation development and manufacturing, packaging materials and storage conditions require proper consideration as well.

This work systematically carried out the manufacturing and development of mini-tablets based on basic research and industrially related topics. Differences between mini-tablets and conventionally sized tablets could be worked out as well as the impact of the tooling system on mini-tableting and CQAs. For the first time a transfer and scale-up study of ODMTs was conducted and identified CPPs and CMAs and their effect on CQAs. The suitability of functionalized isomalt (galenIQ™721) for the development and manufacturing of ODTMs for paediatric patients was proven and compared to an established Ludiflash® formulation.

Zusammenfassung

Seit dem Paradigmenwechsel von flüssigen zu festen Darreichungsformen für pädiatrische Patienten stellen Mini-Tabletten eine Herausforderung für die Wissenschaft dar, da insbesondere die Grundlagenforschung zur Herstellung und Entwicklung nicht vollständig untersucht wurde. Diese Arbeit befasst sich mit dem systematischen Ansatz zum Verständnis der Herstellung und Entwicklung von Mini-Tabletten. Der Fokus lag dabei auf der Grundlagenforschung bezüglich der Tablettierung von Mini-Tabletten im Vergleich zu konventionell großen Tabletten, sowie dem Einfluss der verwendeten Stempelwerkzeuge auf Qualitätsmerkmale von Mini-Tabletten. Weiterhin wurde ein Transfer und Scale-up für orodispersible Mini-Tabletten (ODMTs) durchgeführt. Schließlich wurde die Formulierungsentwicklung von ODMTs mit zwei gebrauchsfertigen Hilfsstoffen mit Stabilitätsstudien durchgeführt.

In der Literatur wurden Formulierungen beschrieben, die sich bei der Tablettierung zu größeren Tabletten nicht verpressen ließen, bei der Tablettierung zu Mini-Tabletten jedoch schon. Es wurden Hypothesen zur Untersuchung der höheren mechanischen Festigkeiten von kleinen Tabletten im Vergleich zu größeren Tabletten aufgestellt. Mini-Tabletten zeigen in Abhängigkeit von der Formulierung ein unterschiedliches Tablettierverhalten Verglichen mit konventionell großen Tabletten. In einer systematischen Studie unter Verwendung eines modernen Kompaktionssimulators wurde das Tablettierverhalten von 1, 2 und 3 mm großen Mini-Tabletten mit 8 und 11,28 mm großen konventionellen Tabletten verglichen. Tablettierattribute wie Tablettierbarkeit, Kompaktibilität und Kompressibilität wurden mit vier pharmazeutisch relevanten Hilfsstoffen MCC und Lactose sowie neuartigen gebrauchsfertigen Hilfsstoffen wie galenIQ™721 oder Ludiflash® bewertet. Es wurde kein systematisches Verhalten in Bezug auf eine bessere Tablettierbarkeit oder ein anderes Verformungsverhalten gefunden, das zu höheren mechanischen Festigkeiten mit abnehmender Tablettendimension führt. Nichtsdestotrotz zeigten Mini-Tabletten eine bessere Kompaktibilität und konnten durch ihr Oberflächen-Volumen-Verhältnis (SVR) von mindestens 2 mm^{-1} weiter spezifiziert werden.

Die Auswirkung des Stempelwerkzeuges auf die Mini-Tabletten zeigte, dass selbst oder gerade wegen der manuellen Matrizenfüllung signifikante Unterschiede in der Masse und den Druckfestigkeiten bei niedrigem und hohem Tablettierdruck innerhalb der verschiedenen Zonen einer 19er-, 7er- und Einzelstempels beobachtet wurden.

Die Streuung in Masse und Druckfestigkeiten unterstreichen, dass Variationen innerhalb der Mini-Tabletten kritische Qualitätsattribute (CQAs) beeinflussen könnten. Für die Tablettierbarkeit und die Kompressibilität wurde jedoch nur ein Trend, aber kein signifikanter Effekt in Abhängigkeit vom verwendeten Werkzeug festgestellt. Eine bessere Kompaktibilität wurde für fast alle Hilfsstoffe durch die Verwendung eines Werkzeugs mit 19 Stempeln erzielt. Aus industrieller Sicht wäre eine höhere Anzahl von Stempel vorteilhaft, um eine höhere Ausbeute in kürzerer Herstellungszeit zu erzielen. Nichtsdestotrotz steigt mit zunehmender Anzahl der Stempel die Möglichkeit höherer Abweichungen, die sich auf CQAs auswirken können. Zudem treten auch höhere Ausstoßkräfte auf. Für Formulierungen, die zum Deckeln oder Laminieren neigen, könnte eine Reduzierung der Anzahl der Stempel von Vorteil sein, um eine angestrebte Druckfestigkeit zu erreichen. Nicht nur für industrielle Zwecke scheint ein 19er Stempel vorteilhaft zu sein, da einerseits eine höhere Ausbeute erzielt wird und andererseits wurde auch abhängig von der Formulierung ein Trend zu besserer Tablettierbarkeit und Kompaktibilität festgestellt.

Ein industriell relevanter Ansatz dieser Arbeit war der Transfer und Scale-up von ODMTs, auf Basis von FDA- und EU-Richtlinien. Druckfestigkeit, Masse und Zerfallszeit wurden als CQAs der ODMTs ausgewählt. Für den Transfer und den Scale-up wurde ein Kompaktionssimulator und eine industrielle Rundläufertablettenpresse verwendet. Es konnte nachgewiesen werden, dass ein Transfer machbar ist, jedoch mit zunehmender Chargengröße und damit längerer Prozesszeit die Zerfallszeit der ODMTs anstieg, bis weder FDA- noch Ph. Eur.-Spezifikationen für orodispersible feste Darreichungsformen erfüllt wurden. Der Hauptgrund dafür war der mit zunehmender Prozessdauer steigende Wärmeübergang, der zu partiellen Sinterungsprozessen und anderen strukturellen Veränderungen der Minitabletten führte. Diese Veränderungen verhinderten das Eindringen von Wasser und Zerfallsprozessen. Andere Prozesse, wie z.B. Überschmierung oder Verdichtung während der Prozesszeit, sollten jedoch nicht vernachlässigt werden. Daher ist ein angemessenes Prozessverständnis einschließlich der Definition kritischer Prozessparameter (CPPs) und kritischer Materialeigenschaften (CMAs) erforderlich. Darüber hinaus sollten geeignete prozessbegleitende Kontrollen durchgeführt werden, um die Qualität von ODMTs zu gewährleisten.

Die Formulierungsentwicklung von 2 mm ODMTs unter Verwendung von Enalaprilmaleat und Hydrochlorothiazid als Modellarzneistoffe mit galenIQ™721 und Ludiflash® war erfolgreich. Isomalt für die Direkttablettierung (galenIQ™721) wurde als neuer Hilfsstoff für die Entwicklung von orodispersiblen Mini-Tabletten etabliert. Sowohl galenIQ™721- als auch Ludiflash®-Formulierungen erfüllten die Spezifikationen für die Zerfallszeit der Mini-Tabletten von Ph. Eur. und FDA. Für verschiedene Formulierungen auf Basis von galenIQ™721 und Ludiflash® wurden Akzeptanzwerte von ≤ 15 erreicht. Stabilitätsstudien mit ODMTs auf Basis beider Hilfsstoffe, die unter Umgebungs- oder Stressbedingungen gelagert wurden, zeigten, dass Druckfestigkeiten und Zerfallszeiten als CQAs von ODMTs von den Lagerungs- und Verpackungsbedingungen beeinflusst werden. Dies unterstreicht, dass neben der Formulierungsentwicklung und der Herstellung auch die Verpackungs- und Lagerbedingungen untersucht werden müssen.

In dieser Arbeit wurde die Herstellung und Entwicklung von Mini-Tabletten auf Basis von Grundlagenforschung und industrienahen Themen systematisch durchgeführt. Unterschiede zwischen Mini-Tabletten und konventionell großen Tabletten konnten ebenso herausgearbeitet werden wie der Einfluss des Tablettierwerkzeugs auf Mini-Tabletten und CQAs. Zum ersten Mal wurde eine Transfer- und Scale-up-Studie von ODMTs durchgeführt, in der CPPs und CMAs und ihre Auswirkungen auf CQAs herausgearbeitet wurden. Die Eignung von funktionalisiertem Isomalt (galenIQ™721) für die Entwicklung und Herstellung von ODTMs für pädiatrische Patienten wurde nachgewiesen und mit einer etablierten Ludiflash® -Formulierung verglichen.

List of original publications

1. Lura, A., Tardy, G., Kleinebudde, P., Breitkreutz, J., 2020
   Tableting of mini-tablets in comparison with conventionally sized tablets:
   A comparison of tableting properties and tablet dimensions.
   Int. J. Pharm. X (2); doi.org/10.1016/j.ijpx.2020.100061
2. Lura, A., Breitkreutz J., 2021
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3. Lura, A., Elezaj, V., Kokott, M., Breitkreutz J., 2021
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   Eur. J. Pharm. Biopharm.168 (2021), pp 122-130;
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7. Elezaj, V., Lura, A., Klingmann, V., Bosse, H.B., Breitkreutz, J.
   Revival of Mini-tablets: Recent Advancements and Future Perspectives
   To be submitted in Eur. J. Pharm. Biopharm. *(invited Review)*
8. Elezaj, V., Lura, A., Canha, L., Breitkreutz, J., 2022
   Pharmaceutical Development of Film-coated Mini-tablets with Losartan Potassium for Epidermolysis Bullosa
   Article submitted as revised manuscript to Pharmaceutics

Contribution to meetings

1. **Oral presentations**

   R&D of Mini-tablets with Styl'One Evo; *Medelpharm Webinar, 2020 online*

   Production of mini-tablets for the paediatric population; *UBT Summer Acadamey, 2020*.

   Drug Development for Children, *UBT Summer Academy, 2018. Prishtinë, Kosovo*

2. **Poster presentations**

   A. Lura, J. Breitkreutz
   Does Tabletability Really Improve With Decreased Diameters of Tablet Punches?
   12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2021, online

   V. Elezaj, A. Lura, L. Canha, S. Saaler-Reinhardt, J. Breitkreutz
   Development of mini-tablets with SSR-25
   12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2021, online, oral presentation by Valentinë Elezaj

   M. Kokott, A. Lura, T. Okabayashi, J. Breitkreutz, R.Wiedey
   Granfiller D® as a new co-processed excipient for orally disintegrating tablets produced by direct compression
   12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2021, online

   P. Bawuah, M. Evan, A. Lura, D. Farrell, P. J. Barrie, P. Kleinebudde, D. Markl, J. A. Zeitler
   Insight into the impact of compaction process variations on tablet disintegration by non-destructive at-line terahertz porosity sensing
   12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2021, online, oral presentation by Prince Bawuah

   A. Lura, J. Breitkreutz
   Impact of different tooling systems on mini-tableting
   12th European Paediatric Formulation Initiative, 2020 online

A. Lura, O. Luhn, J. Breitkreutz
Orodispersible mini-tablets based on galenIQ™721
CPHI Worldwide, 2019 Frankfurt

A. Lura, F. Siebel, A. Siepen, J. Breitkreutz
Development of bilayer mini-tablets for paediatric use
11th European Paediatric Formulation Initiative, 2019 Malmö

A. Lura, J. Breitkreutz
Production of orodispersible mini-tablets for paediatric use made from two commercialized functionalized excipients
3rd European Conference on Pharmaceutics, 2019 Bologna

B. Hahn, A. Lura, J. Breitkreutz
Matrix mini-tablets containing high loads of sodium benzoate made from natural waxes
3rd European Conference on Pharmaceutics, 2019 Bologna

A. Lura, J. Suarez Gonzales, J. Breitkreutz
Comparison of orodispersible minitablets based on galenIQ™721 for paediatric use
12th Central European Symposium on Pharmaceutical Technology and Regulatory affairs, 2018 Szeged

A. Lura, O. Luhn, J. Breitkreutz
galenIQ™721-A Novel Excipient for Orodispersible Minitablets
10th European Paediatric Formulation Initiative, 2018 London

D. Kottke, A. Lura, J. Breitkreutz
Formulation development of a composite drug dosage form with lidocaine hydrochloride for paediatric use
11th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2018 Granada

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Eidesstattliche Erklärung

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

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Ard Lura