Pharmaceutical development of losartan mini-tablets for Epidermolysis Bullosa and investigations on the technological transfer into industrial scale

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Für meine geliebte Familie

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List of abbreviations

API	Active Pharmaceutical Ingredient
CCD	Central Composite Design
CMA	Critical Material Attribute
COL7	Collagen, Type VII
CPE	Co-processed excipient
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
GMP	Good Manufacturing Practice
GRAS	Generally Recognized As Safe
HPLC	High Performance Liquid Chromatography
HPMC	Hydroxypropyl methylcellulose, hypromellose
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MCS	Manufacturing Classification System
ODMT	Orodispersible mini-tablet
PAT	Process Analytical Technology
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
PUMA	Paediatric Use Marketing Authorisation
QbD	Quality by Design
QTPP	Quality Target Product Profile
SMCC	Silicified microcrystalline cellulose
WHO	World Health Organization

1 Introduction

1.1 Mini-tablets

Mini-tablets are becoming increasingly important and prove to be beneficial especially in the field of paediatric medicine [L1]. There have been global initiatives to encourage the availability of child-appropriate medicine. The EU regulation of 2006 introduced a Paediatric Investigation Plan (PIP) with details on the development and clinical evaluation for the drug administration to the paediatric population. The regulation also enables to obtain a Paediatric Use Marketing Authorization (PUMA) for already approved drug substances for adults, when a child-appropriate formulation is developed [1,2]. In 2008, the World Health Organization (WHO) released a report [3], followed by subsequent publications promoting a shift from liquids to oral solid dosage forms [4,5]. Multiparticulate dosage forms, like granules, pellets or mini-tablets, are considered to exhibit an advantage regarding swallowability and dose flexibility compared to monolithic solid dosage forms [3,4]. Particularly single-dose or multiparticulate mini-tablets seem to represent a promising solid dosage form [6]. Mini-tablets can be described as tablets with a diameter of < 4 mm and a surface-to-volume ratio of at least 2 mm^{-1} [7,8]; [L1]. However, mini-tablets are not specifically monographed in the European Pharmacopeia (Ph. Eur.) regarding their size, yet. Analytical test methods have still to be adapted and implemented by the authorities, too. Mini-tablets may be manufactured on rotary presses, eccentric presses or compaction simulators similar to conventionally sized tablets, while the use of multi-tip toolings is common. Manufacturing routes can similarly range from direct compression to intermediate dry or wet granulation processes and subsequent compression [L1]. Further technological and clinical evaluation of mini-tablets, as well as information on market products and dosing devices, are outlined in an extensive structured review paper in chapter 2.

1.2 Epidermolysis Bullosa and losartan potassium

Epidermolysis Bullosa is a rare disease and comprises a group of inherited skin fragility disorders which might be diagnosed already in newborn children [9]. Patients are affected by defective epithelial cell adhesion which finally manifests in fragile and blistering skin [10]. Different subtypes of Epidermolysis Bullosa exist, with the following prevalent types: dystrophic, simplex, junctional and Kindler [9,11]. Dystrophic Epidermolysis Bullosa (including the dominant and recessive subtype) is characterized by mutations of the gene for type VII collagen (COL7), a structure protein responsible for stability of the epidermis to the dermis as the main element of the anchoring fibrils. Different degrees of severity are distinguished between localized to generalized blistering, appearance in mucosal areas, nail dystrophy, alopecia [9,12]. Infections and inflammations as well as scarring of the wounds, fibrosis and

ulcerations can result from frequent epidermal injuries. Related manifestations like esophageal stenosis following nutritional intake issues, pseudosyndactyly or squamous cell carcinomas can emerge over time. As a result those patients face reduced life expectancy and a high risk of skin cancer [9,10,12].

Certain progress has been achieved for developing medicines to treat Epidermolysis Bullosa. A topical gel with birch triterpenes (Filsuvez®) has been approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for dystrophic Epidermolysis Bullosa for patients aged 6 months and older. The gel is applied to the wound surface and covered by a wound dressing. The full mechanism of action is unknown, but it is presumed that the birch bark extract supports wound healing by supporting keratinocytes in growing [13,14]. Beremagene geperpavec-svdt (VYJUVEK™) is an FDA approved herpes-simplex virus type 1 (HSV-1) vector-based gene therapy for the treatment of dystrophic Epidermolysis Bullosa in patients aged 6 months and older. The genetically modified herpes-simplex virus provides copies of the COL7A1 gene (encoding for type VII collagen/COL7) to the wounds region but not in normal cells. The produced COL7 protein can support the outer and middle skin layers. The suspension is mixed into a gel before topical use [13,15]. Additionally, there are further therapies under current investigation in several clinical trials [13].

In this work, losartan was chosen as the active pharmaceutical ingredient (API) to address the rare disease. According to Ph. Eur. losartan potassium is a white to off-white crystalline powder, freely soluble in water and methanol [16]. The chemical structure can be found in Figure 1.

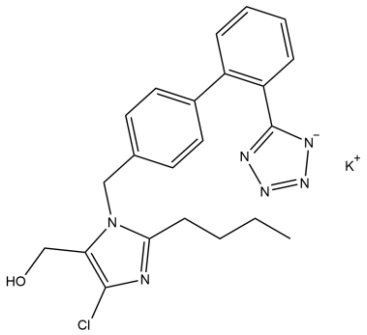

Figure 1 Chemical structure of losartan potassium

This drug substance is a non-peptide angiotensin II receptor blocker and widely administered for the treatment of the following diseases: hypertension, heart failure, ischemic peripheral circulatory disorder, myocardial ischemia, diabetic neuropathy, glaucoma and prevention of progression of post-myocardial infarction heart failure [10]. This drug substance proved to also show beneficial effects in Epidermolysis Bullosa, when given systemically, improving the life quality of patients. It can be administered for this treatment without negatively affecting the blood pressure, even though a higher dosing scheme than for therapy of hypertension is administered [10]. High TGF-ß activity has been observed in inflammatory events in dystrophic

Epidermolysis Bullosa, losartan may reduce TGF-ß expression and slow down fibrosis [10,17]. In physiological conditions, the TGF-ß pathway is involved in e.g. tissue regeneration and regulation of immune responses. However, in pathological conditions, dysfunctional activation is observed in cancer or fibroproliferative diseases. The REFLECT phase I/II clinical study (symptom-RElieF with Losartan - EB Clinical Trial) investigated safety, tolerability and efficacy of losartan in children with recessive dystrophic Epidermolysis Bullosa [18]. Dosing scheme included an escalation interval, target dose application of about 1.4 mg/kg daily and a potential tapering phase, as reported in the European patent [10].

In general, losartan potassium is commercially available as tablets in doses from 12.5 to 100 mg for adults. In 2009, Cozaar® 2.5 mg/mL suspension was licensed in different European Union (EU) countries, but for several years limited availability and/or discontinuation of this product has been observed. As a result, hospitals turn to extemporaneous oral suspensions, e.g. to treat paediatric hypertension [19]. This approach, however, bears the risk of restricted information on stability and shelf-life [20]. This issue of the limited availability of a child-friendly dosage form also applies to the treatment of Epidermolysis Bullosa. Hence, a dosage form is strongly required that offers dose flexibility incorporating the dosing regimen described above, and easy swallowability, especially in cases of concomitant esophageal stenosis. In line with the paradigm shift from liquid to solid dosage forms (see chapter 1.1), losartan potassium containing mini-tablets have been developed, with more information available in chapter 3.

1.3 Formulation development of taste-masked losartan mini-tablets

The objective of pharmaceutical development according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline Q8 (R2) of EMA is to design a drug product fulfilling patients' requirements and the criteria of quality, safety and efficacy. The formulation scientist can follow an empirical strategy, a more systematic strategy in terms of Quality by Design (QbD) or a combination of both [21].

The following elements should be addressed as part of the development [21]:

- Definition of the Quality Target Product Profile (QTPP): The QTPP defines the key points of the product: dosage form, route of administration, delivery systems, planned application in the clinical environment, dosage strength, container closure system, release and further characteristics that may have an effect on pharmacokinetic attributes, quality requirements for the drug product.
- Identification of CQAs: CQAs entail any properties of the drug product, intermediates or materials that should remain within predefined limits to provide the target drug product quality.

- Risk Assessment: Relationship between critical material attributes (CMAs) and critical process parameters (CPPs) with drug product CQAs
- Creation of a design space based on the aforementioned connection between CMAs and CPPs with CQAs
- Definition of a control strategy to provide steady quality of the product
- Conduction of product lifecycle management and continuous improvement

There are different processing routes to produce mini-tablets or conventionally sized tablets depending on API characteristics and the formulation. According to the proposed Manufacturing Classification System (MCS) four classes are distinguished [22,23]:

I. Direct Compression
II. Dry Granulation
III. Wet Granulation
IV. Other Technologies

Along the classes, the number of operating steps and thus the costs of production increase. On the other hand, the capability to compensate for disadvantageous physical properties of the API also rises in this ranking order, but the stress exposed on the API might increase, as well. Class IV additionally involves more complex manufacturing, such as active coating, spray-drying and melt granulation [22]. The larger the drug loading, the higher the chance of the API characteristics to influence the processability of the formulation, especially at or above the percolation threshold [22]. In chapter 3 the development of 2 mm mini-tablets containing losartan potassium at a high drug load (approx. 40 %) based on QTPP associated requirements is addressed. The strategy regarding the selection of the processing routes based on MCS and the formulation composition are subject of discussion to overcome several challenges as flowability issues and related compaction behaviour in the hopper as well as sticking to the multi-tip punches.

For a suitable paediatric dosage form the expectations of swallowability and dose flexibility as described in chapter 1.1, safety of the components [24,25], and palatability are intended. Palatability is a major factor for the patient acceptability and comprises the valuation of appearance, smell, taste and mouth feel of the respective dosage from. Particularly the taste plays a major role for the children’s compliance [26,27]. Taste perception occurs via interactions of chemical substances, APIs and other ingredients with taste receptors, which are predominantly located on the tongue. Human taste perception can differentiate between sweet, sour, umami, salty and bitter; it is further influenced by subjective factors, however. Children show greater taste sensitivity towards bitter compounds than adults. Therefore, oral drug products should not produce an uncomfortable taste, but also should not be too much appealing as it could elevate the intoxication risk among the paediatric population [24]. As a consequence, various approaches have been subject of development to mask the taste of

bitter drugs, aiming at e.g. physical barriers, alteration of drug solubility or of taste perception [26]. Selection of the taste masking strategy may be influenced by the choice of final dosage form, API load and a taste threshold of the API [26,27]. Addition of sweeteners may for example be sufficient for a lower API load, combined with the benefits of not requiring additional equipment or manufacturing steps and the improbable influence on API release rates. However, at higher doses it might be ineffective in covering the unpleasant taste. Bitter blockers aim to inhibit the respective receptor signaling so that the API cannot be sensed. This approach is only successful, if the same taste receptor is targeted, hence the respective bitter receptor has to be identified and the interaction with the bitter blocker has to be sufficiently understood, which represents a challenging undertaking. As a consequence, commonly a "trial-and-error" strategy is applied to choose the bitter blocker [26,27]. Another strategy refers to film coating of solid dosage forms or single API particles as a physical barrier. Coated tablets would be protected from disintegration in the mouth and generation of the bitter taste before being swallowed. The coating polymer should be insoluble at the pH of the saliva and should not interfere with the API release [24,26,27]. Lipid matrices (fats, waxes) minimize API diffusion, so that less API is available in the saliva [24,26,27]. Other techniques focus on complexing agents like cyclodextrins or ion exchangers to reduce the amount of freely available API in the saliva that can interact with the taste receptors, both in solid and liquid dosage forms. Hereby, excipient toxicity becomes relevant, as e.g. for some materials there are no safety thresholds for neonates available [24]. As the API solubility is a significantly influential factor, considering that the dissolved compound interacts with the respective taste receptors in taste buds, this may also be modified by using e.g. a different counterion or non-ionic form of the API (in case of ionisable API with pH-dependent solubility). The application of the non-ionic form, by using e.g. pH modifiers, may reduce the solubility in the formulation and potentially the dissolution rate in the saliva. One emerging challenge for modification of API solubility includes reconsideration of effects on pharmacokinetic properties and bioavailability [26–28]. Viscosity modifiers that elevate viscosity in a liquid formulation may reduce the diffusion of the drug and thus the contact time with the receptors [26].

If we consider taste measurements or evaluations in early stage drug development, trials with human taste panels may be a challenge due to the still unknown toxicity of the drug substance *in-vivo*. These trials in humans are generally also related to safety and ethical concerns and therefore restrictions for the paediatric population. As the taste alters over age, a transfer of results from adults to children may be incorrect. Nevertheless, it is helpful to gather some data available before the PIP submission. Alternative evaluation methods can be applied here, e.g. the application of electronic tongues or animal models [24,26,29].

Losartan potassium displays a bitter and hence unpleasant taste, which could compromise the acceptability of the developed mini-tablets by the paediatric population [30]. Taste masking

was accordingly one of the key topics that was addressed alongside the other technological challenges during development (see chapter 3). The implementation of a physical barrier has already been applied for child-friendly dosage forms to enhance the taste, among suitable materials Hypromellose (HPMC) was named as one example for a widely used material not impeding the API release profile by Walsh et al. [27]. This approach was selected as method of choice for the losartan potassium mini-tablets by using a fluid bed device and HPMC as coating polymer.

1.4 Transfer and scale-up

A major challenge in the early research and development stage of drug products is the limited availability and the high costs of API necessitating a material-saving strategy in this phase. Compaction simulators are therefore often used in formulation development and scientific research. They can consist of hydraulic systems [31–33] or roller screws for driving the upper and lower punch as in case of STYL'One Evo [34]. They can simulate punch movement of different presses [34]. Manufacturing on compaction simulators typically represents lab scale. For a subsequent scale-up to pilot or production scale, rotary tablet presses are certainly the most industrially relevant tablet machine type for high-volume tablet manufacturing.

According to the FDA the principles of scale-up comprise an increase in batch size by factor 10 while retaining the equipment with same design and operating principles, as well as the same formulation and manufacturing process [35]. Similarly, the EMA states that the pilot batch size should amount to at least 10 % of the production scale batch size and the factor should not exceed 10 [36]. There are different strategies of accomplishing a scale-up and hence enlarging the batch size, e.g. by switching to a differently sized equipment with a high-volume capability or by elevating the throughput on the same equipment e.g. by extending production time. EMA recommends a commercial batch size of at least 100,000 units, unless there is a rationale for a smaller batch size, e.g. in the field of orphan diseases [37]. In our studies, the focus was primarily laid on the transfer and scale-up of the tableting process of 2 mm mini-tablets.

It is recommended to not only consider the scale-up of a tableting process at the end as a separate phase but during the entire development process [38]. During development, data gathering of process data, e.g. by using tablet press instrumentation, and characteristics like material properties (e.g. deformation behaviour) or physical properties of the dry blend or granules (particle size distribution, density, flowability etc.), lubrication, compressibility, compactibility and tabletability as well as dissolution behaviour in dependence of process parameters can give helpful hints for scaling up the tableting process [39]. Some effects of scale-up may be attributed to upstream processes before tableting, e.g. milling, blending and granulation, because they can influence the attributes of the final blend to be tableted [39].

Still, there are scale-up effects that may correlate directly with the tableting process and that may not be immediately visible on lab scale. Firstly, the tableting speed and its potential effects related to die filling, dwell time in dependence of the deformation behaviour of the formulation or further tablet issues (capping, lamination etc.) are to be mentioned, as usually an increase of the speed during scale-up is pursued to elevate the throughput. Secondly, over-lubrication might be observed in the forced feeder of the production scale tablet press with potential impact on tablet hardness and dissolution. Temperature increase over process time might also adversely impact the process and also tablet properties or API stability [39]. Temperature rise over process time and potential effects on the properties of orodispersible mini-tablets (ODMTs) are discussed in chapter 4. Additionally, speed variation and over-lubrication issues are further investigated in chapter 5 as part of the transfer and scale-up study of 2 mm mini-tablets containing losartan potassium.

In literature, a further approach for scaling up is described and refers to dimensional analysis on the basis of dimensionless numbers to describe a process, which correspond at different scales. In a dimensionless space you do not encounter scale-up issues as there is no scale prevalent. Two processes may be defined as similar provided they run in a comparable geometrical area (geometrical similarity) and the same numerical value of all dimensionless numbers for the particular process is given [40].

In this work, the scale-up approach was based on the principles of FDA/EMA using the compaction simulator STYL'One Evo by Medelpharm and the rotary tablet press XM 12 by Korsch (see chapter 4 and 5).

1.5 External lubrication

Lubricants are an integral part of a tablet formulation with the purpose to reduce friction and hence facilitating a successful tableting process. A high ejection force usually implies high friction at the interface between tablet and die wall. High friction in turn can lead to tablet defects and also to demolition of the tools over time. The addition of a small amount of lubricant to the formulation usually between 0.25 and 5 % depending on the type of lubricant, formulation and process parameters, also known as internal lubrication, may also alleviate issues associated with sticking to punches [41–44]. Among the different lubricants available, magnesium stearate is one of the most commonly used lubricant. Alternative lubricants, amongst others sodium stearyl fumarate, stearic acid, glycerol dibehenate and polyethylene glycol, have also been investigated [45–47].

However, internal lubrication can also be accompanied by adverse changes of tablet properties. Reduced tensile strengths are observed, and also prolongation of disintegration and dissolution times may occur in case of hydrophobic lubricants like magnesium stearate.

Susceptibility to the lubricant can be ascribed to various factors like particle size and related surface area, texture and surface roughness, flowability as well as deformation behaviour. Materials exhibiting mainly plastic deformation are more susceptible to lubricant film formation on particle surfaces. This may in turn weaken interparticle bonding with the final result of reduced tensile strengths of tablets. Brittle materials, in comparison, may create new surfaces through fragmentation, maintaining the binding properties [44,48–50]. There are comprehensive studies with the focus on the impact of blender type, mixing intensity and mixing time on tablet characteristics of formulations containing e.g. magnesium stearate [51–53]. Studies have also exhibited that the selection of the paddle speed in the forced feeder of a tablet press may effect the tensile strength of tablets. Additional mixing prior die filling takes place considering the shear forces and can lead to over-lubrication [46,54,55]. A recent study by Brands et al. investigates another type of lubrication method, referred to as feed frame lubrication. Here, the lubricant is added into the feed frame without previous mixing using the blending ability of the feed frame instead. This type of lubrication yielded similar or enhanced tablet properties in comparison to internal lubrication and the authors concluded that this approach lowered the risk of over-lubrication [56].

Hence, lubricant properties and concentration should be thoroughly selected as part of a tablet formulation to reduce die wall friction whereas the tablet properties are ideally not adversely impacted [45]. Ejection forces can increase with elevation of tableting speed. One explanation for this observation may include that due to higher speeds there is less time for lubricant migration to the interface between tablet and die wall which leads to a higher coefficient of friction. Therefore upon scale-up, an eye has to be kept on this phenomenon to ensure sufficient lubrication efficiency during full production scale and avoid occurrence of sticking issues over time [43]. To sum up, consideration of the following factors are recommended due to their interdependence: type and amount of lubricant, formulation properties, process parameters and equipment used [41,43–45].

External lubrication, where the lubricant is sprayed onto the tablet punches and die walls, has received increasing attention as an alternative to internal lubrication with regards to the mitigation of the above mentioned detrimental impact on tablet properties when lubricating internally. Numerous research studies have been carried out on this topic [57–65]. De Backere et al. investigated external lubrication systems in a compaction simulator and rotary tablet press. Three different lubricants (magnesium stearate, sodium stearyl fumarate and glyceryl dibehenate) were used and the process parameters of the tablet press and the lubrication system were varied. The drug-free formulation exhibited low and comparable ejection forces for all lubricants on both presses. Furthermore, no detrimental impact on the tensile strength was detected independent of the setting of the external lubrication systems and lubricant type. Main compaction pressure represented the only significant factor, tableting speed and lubricant

feed rate did not effect the tensile strength. Disintegration times were a little higher with sodium stearyl fumarate on the rotary tablet press, which was ascribed to the higher concentrations of the lubricant found on the tablets; on the compaction simulator disintegration times were similar for the three lubricants. Long runs on the rotary tablet press verified the stability of the system in terms of ejection forces and tablet properties [57]. Jahn and Steffens report a reduction of magnesium stearate concentration to around 0.04 % per tablet with the external lubrication technique. A relation between spray rate and amount of magnesium stearate per tablet was found and optimized spray rates were pursued by checking the ejection forces. Different spray rates did not exert an adverse impact on tensile strength [58]. In another study the magnesium stearate amount was minimized to 1/13th of what was observed with internal lubrication. Application of external lubrication also led to an increase of 40 % in tensile strength not impeding the disintegration time [59]. Kamiya et al. observed higher tensile strengths and shorter disintegration times of externally lubricated tablets compared to the internal lubrication technique. Among the externally lubricated tablets comparable tablet properties were obtained at different process parameters. The parameters tableting speed, spray rate and flow air volume of the dust collector impacted the amount of magnesium stearate on the tablets [60]. Usually, compressed air is utilized to spray the lubricant onto the tablet tooling via a nozzle. Zimmermann et al., however, applied a modified external lubrication system using electrostatic forces. Ejection forces could be reduced and tensile strengths proved to be higher than for internal lubrication, aligning with the results of the previously mentioned studies [61].

All the aforementioned studies were conducted on conventionally sized tablets. So far, scarcely any systematic studies have been conducted on the impact of external lubrication on the tableting process and properties of mini-tablets. Uzondu et al. reported that amongst others tablet diameter and thickness influence the ejection force. However, the study was carried out with 10 mm tablets [42]. Kuck and Breitkreutz investigated the impact of internal lubrication with magnesium stearate and sodium stearyl fumarate on orodispersible tablets and ODMTs (diameter of 11.28 and 2 mm) containing various co-processed excipients [66]. Tableting was performed on the STYL'One Evo compaction simulator. In general, higher quantity of lubricant was required for mini-tablets compared to the larger tablets to adequately reduce the ejection force, based on the higher surface-to-volume ratio and associated higher die-wall friction. Sodium stearyl fumarate containing mini-tablets disintegrated faster than the equivalents with the same amount of magnesium stearate. External lubrication (magnesium stearate) was also applied and showed adequate lubrication efficiency. This technique yielded mini-tablets with high tensile strengths but disintegration times were shown to be retarded for most excipients. Authors indicate that with a higher specific area of ODMTs where the lubricant can form a hydrophobic film, an elevation of disintegration time might be a consequence. The spray nozzle was mounted in the middle of the multi-tip die, so that lubricant spraying may not have been

done homogenously, which in turn might explain the high deviations in the disintegration times [66].

According to the author's best knowledge, to date, we are lacking systematic studies on external lubrication of mini-tablets on rotary tablet presses. Therefore, chapter 6 is dedicated to this topic with a special focus on the tensile strengths of mini-tablets.

1.6 Aim of the thesis

As can be deduced from the previous sub-chapters, mini-tablets represent a promising dosage form, especially for paediatric patients. Aim of this work was to investigate the development and manufacturing of mini-tablets using the API losartan for the treatment of Epidermolysis Bullosa. Additionally, a general understanding of transfer and scale-up processes and implementation of external lubrication of mini-tablets on rotary tablet presses was pursued.

The aim of this thesis can be structured into five objectives:

- A detailed systematic review of existing publications was performed to find out the current state of research on mini-tablets in terms of technological and clinical aspects and addressing the gap of harmonized definition and classifications of mini-tablets.
- Losartan potassium mini-tablets were developed meeting the challenge of high drug loading and the demand for taste masking to treat the rare disease Epidermolysis Bullosa.
- A first transfer and scale-up process of drug-free ODMTs was conducted with focus on CQAs using the compaction simulator STYL'One Evo by Medelpharm and the rotary tablet press XM 12 by Korsch.
- Subsequently, a transfer and scale-up process was performed with losartan potassium containing mini-tablets.
- Based on the observations regarding over-lubrication during internal lubrication with magnesium stearate and its detrimental effect especially on tensile strength, both in the development of the high-dose mini-tablets and in the transfer and scale-up study of the lower-dose mini-tablets, external lubrication was tested systematically for the first time to the best of our knowledge on a rotary tablet press for mini-tablets, using placebo formulation.

1.7 Outline of the thesis

This work comprises five peer-reviewed publications in scientific journals. Chapter 2 represents a systematic review article providing the current state of research on technological and clinical advancements of mini-tablets. The systematic research was based on the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) scheme for the screening of different databases [67]. After thorough literature review, tablets with a diameter of < 4 mm were defined as mini-tablets and included in the review paper. An overview of different types of mini-tablets were given amongst others orodispersible, immediate release or modified release mini-tablets, but also an enhanced insight into technological processes like

tableting and film-coating as well as characterization of mini-tablets is provided. An analysis of exemplary available market products and a summary of clinical studies are included.

Chapter 3 deals with the pharmaceutical development of losartan potassium mini-tablets. Several challenges had to be addressed during development. Due to the high drug load of around 40 % limited flowability and sticking issues were found during tableting on a compaction simulator. Sticking to punches could be tackled by using the excipient silicified microcrystalline cellulose (SMCC 50) and a combination of lubricants, however, direct compression on a rotary tablet press at higher batch sizes was not successful owing to compaction phenomena in the hopper. In line with the MCS, an intermediate dry granulation step was included mitigating the observed issues. Final film-coating to mask the bitter taste of losartan potassium was successful. Promising stability results were obtained.

Chapter 4 focuses on a transfer and scale-up process for 2 mm ODMTs from the compaction simulator STYL'One Evo by Medelpharm to the rotary tablet press XM 12 by Korsch in line with EMA and FDA guidelines to get first insights into this process. The excipients Ludiflash® and isomalt with the lubricant sodium stearyl fumarate were used. Tensile strength, mass and disintegration time were monitored as CQAs. Product temperature was also closely observed and the impact on the disintegration time was evaluated during scale-up.

While in chapter 4 product temperature rise was assumed to show a potential adverse impact on the quality of the drug-free tablets over time, in chapter 5 transfer and scale-up processes of losartan potassium containing mini-tablets were conducted. The aim was to apply this process to an API containing formulation and to further investigate speed variation and over-lubrication issues, that may not emerge distinctly during lab scale compaction simulator experiments but primarily when transferring to an industrial rotary tablet press. A lower drug load of around 22 % compared to the study in chapter 3 was selected enabling direct compression. Tensile strength, mass variation, disintegration as well as content uniformity were investigated as CQAs.

In chapter 6 the observed over-lubrication issues experienced in chapter 3 and 5 with internal lubrication, adversely impacting the tensile strength, are taken as a driver to perform a feasibility study of mini-tableting via external lubrication on a rotary tablet press. Until now, to the author's best knowledge, there are hardly any published studies systematically investigating this process on a rotary press with focus on tensile strength of mini-tablets. The study was conducted with the two co-processed excipients (CPEs) SMCC 90 and SMCC 50, while different process parameters and their impact on the tensile strength were investigated.

Chapter 7 compiles all findings from the previous chapters in a holistic discussion, chapter 9 and 10 provide an executive summary of the present work in English and German language.

2 The revival of the mini-tablets: Recent advancements, classifications and expectations for the future

Pretext

Particularly in the last decade the number of publications about mini-tablets has been increasing impressively. Consistent with the shift of paradigm from liquid to solid dosage forms in paediatric therapy and the availability of acceptability studies, industrial interest has increased as well. A systematic research based on the PRISMA scheme screening four scientific databases was conducted. The review highlights technological and clinical advancements as well as challenges. It also provides an overview of market products, used drug substances in publications and the current status of administration options of mini-tablets.

The following review article has been published in European Journal of Pharmaceutics and Biopharmaceutics. Valentinë Lura was responsible for Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing – Original Draft and Writing – Review & Editing. Ard Lura was responsible for Conceptualization, Methodology, Formal analysis, Investigation, Data curation, Visualization, Writing – Original Draft and Writing – Review & Editing. Jörg Breitkreutz was responsible for Conceptualization, Methodology, Writing – Original Draft, Writing – Review & Editing, Supervision and Project Administration. Viviane Klingmann was responsible for Conceptualization, Methodology, Visualization, Writing – Original Draft, Writing – Review & Editing and Supervision.

The revival of the mini-tablets: Recent advancements, classifications and expectations for the future

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Abstract

Mini-tablets have recently raised huge interest in pharmaceutical industry. The present review aims to identify the rational, the opportunities and challenges of this emerging small solid drug dosage form by a structured literature review following the PRISMA algorithm. In total, more than 5,000 literature and patent sources have been found starting with the very first in the 60s of the past century, followed by the first multiparticular products using mini-tablets with pancreatin (Panzytrat® by the former BASF subsidiary Knoll/Nordmark) authorized in 1985. There seems to be a second boost of common interest in the 2000s when clinical studies demonstrated that one or more mini-tablets could enable superior drug administration even in very young patients including neonates over the former gold standard, a liquid drug preparation. Several pharmaceutical companies immediately started clinical development programs using the mini-tablet concept and the first products have been recently authorized by the competent authorities. Superiority was given as the mini-tablets ease the swallowing procedure compared to conventional tablets, enable various modified drug release opportunities including taste-masking by film-coating technology and provide excellent drug stability compared to liquid oral dosage forms. Due to these product attributes they are particularly beneficial to children and their caregivers. Furthermore, there is potential for precise individual drug dosing by counting adequate amounts of the multiple drug carriers. Most recently, two novel products with different concepts were authorized by the EMA and entered the market which are highlighted in this review: the first orodispersible mini-tablet with enalapril maleate for congenital heart failure (Aqumeldi® from Proveca Pharma) and the first single unit mini-tablet with matrix-type controlled melatonin release for insomnia (Slenyto® from Neurim Pharmaceuticals).

Our review reveals, that the majority of the published scientific papers use co-processed, ready-to-use excipients for the orodispersible mini-tablet formulations. However, traditional fillers such as microcrystalline cellulose or lactose have also been used for immediate release

mini-tablets after adding a (super)disintegrant and a lubricant. The manufacturing of mini-tablets is conducted on conventional rotary tablet presses, predominantly equipped with multi-tip toolings to improve the yield or production speed. Scaling-up has been successfully realized from compaction simulators to pilot and production scale. Film-coatings enabling gastric resistance, taste masking or sustained-release properties have been realized in both fluid-bed and drum coaters using the same polymers as for conventional tablets. There is still a significant lack in regulatory guidance despite the recent success of the mini-tablet concept, starting from suitable characterization methods in the pharmacopoeias up to the design and conduct of clinical studies on mini-tablets.

3 Pharmaceutical development of mini-tablets with losartan potassium for Epidermolysis Bullosa

Pretext

This section deals with the pharmaceutical development of losartan potassium mini-tablets for the treatment of Epidermolysis Bullosa, a rare inherited skin fragility disorder already appearing in newborns. Several challenges and identified solutions in connection with the high drug load are outlined, including limited flowability and sticking as well as the bitter taste of the API.

The following research paper has been published in Pharmaceutics. Valentinë Lura (born Elezaj) was responsible for the conceptualization, methodology, investigation, data curation and writing – original draft preparation. Ard Lura was responsible for conceptualization, methodology, investigation and writing – review and editing. Luis Canha was responsible for conceptualization, methodology, writing – review and editing and project administration. Jörg Breitkreutz was responsible for conceptualization, methodology, writing – review and editing and project administration.

Pharmaceutical development of film-coated mini-tablets with losartan potassium for Epidermolysis Bullosa

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Abstract

Epidermolysis bullosa is a genetically heterogenous skin fragility disorder with multiorgan involvement appearing already in newborn children. Severe progressive fibrosis follows skin blistering, mucosa lesions, and wound healing, favouring development of highly aggressive squamous cell carcinomas. Losartan potassium (LP) has been described to show positive effects; therefore, it was of clinical interest to develop 2 mm mini-tablets with LP for treatment of the affected children. Several challenges emerged during development: limited flowability and sticking to punches were observed in the first tableting experiments due to a high drug load, and a bitter taste of the LP was reported. Sticking to punches was reduced by using SMCC 50 and a combination of different lubricants; however, direct compression trials on a Korsch XM 12 rotary press were not successful due to compaction phenomena in the hopper. Thus, an intermediate dry granulation was successfully introduced. Two final formulations of the mini-tablets complied with the requirements of the European Pharmacopoeia regarding disintegration times (<15 min) and friability (<1.0%); mean tensile strengths amounted to about 1 MPa as a compromise between manufacturability and sufficient mechanical strength for further coating studies. The subsequent coating step succeeded delaying the initial drug release for more than 2 min. An acceptance value ≤15 was matched for the coated mini-tablets, and stability studies showed a promising shelf life.

4 Transfer and scale-up of the manufacturing of ODMTs from a compaction simulator to an industrial rotary tablet press

Pretext

A deeper understanding of transfer and scale-up processes of mini-tablets should be obtained moving towards a more industrial approach. In this study, this is realized using examples of placebo formulations for targeting orodispersible properties of mini-tablets.

The following research paper has been published in International Journal of Pharmaceutics. Ard Lura was responsible for Methodology, Investigation, Formal Analysis, Data curation, Writing – Original draft preparation. Valentinë Lura (born Elezaj) was responsible for Investigation, Formal Analysis and Data Curation. Marcel Kokott was responsible for Investigation, Formal Analysis and Data Curation. Jörg Breitkreutz 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 pediatric 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 and Ludiflash® 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 were 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 significantly increases over time 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 with ODMTs produced from fresh powder.

5 Challenges in the transfer and scale-up of mini-tableting: Case Study with losartan potassium

Pretext

As in chapter 4 transfer and scale-up of mini-tablets were investigated with orodispersible placebo formulations, in this study the focus should be placed on the industrial approach using a losartan potassium containing formulation. Speed variation and potential over-lubrication issues should be investigated, they represent scale-up effects that may not be immediately detectable on lab scale, e.g. when using a compaction simulator. In comparison, in chapter 4, the emphasis was rather placed on the temperature rise, a phenomenon that may also become prevalent during scale-up activities.

The following research paper has been published in European Journal of Pharmaceutics and Biopharmaceutics. Valentinë Lura was responsible for Conceptualization, Methodology, Investigation, Data curation, Formal analysis and Writing – original draft. Stefan Klinken was responsible for Formal analysis and Writing – review & editing. Jörg Breitkreutz was responsible for Conceptualization, Writing – review & editing and Supervision.

Challenges in the transfer and scale-up of mini-tableting: Case study with losartan potassium

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Abstract

Mini-tablets (MTs) with losartan potassium were developed to treat the rare disease Epidermolysis Bullosa. The focus was placed on transfer and scale-up of a direct compressible formulation from the compaction simulator STYL'One Evo (CS) to the rotary tablet press Korsch XM 12 (RP). Transfer of tabletability and compactibility profiles from CS to RP did not show good agreement, e.g. at a tableting pressure of 125 MPa mean tensile strengths (TS) of 4 MPa on CS and 1–1.5 MPa on RP were reached. These results highlight the impact of the feed frame on final product qualities depending on process and material factors. In the scale-up studies the critical quality attributes (CQAs) mass variation, content uniformity, TS and disintegration time were investigated. After an appropriate run-up time, most CQAs reached a plateau, after reaching a balance between influx, efflux and distribution of lubricant in the feed frame. TS values of 1–2 MPa, disintegration times of max. 50 s, mass variation of 0.9–2.2 % (CV) and acceptance values below 15.0 were reached depending on chosen process parameters.

6 A systematic investigation of external lubrication of mini-tablets on a rotary tablet press with focus on the tensile strength

Pretext

In chapter 3 and 5 over-lubrication issues on the rotary tablet press were observed with a detrimental impact on tensile strength of mini-tablets. To date, there is still a huge gap in the existing literature with respect to the external lubrication of mini-tablets on rotary tablet presses, a topic that may also be of industrial relevance. Therefore, this should be addressed with the following feasibility study: external lubrication should be systematically investigated with drug-free preparations, with a special focus on the response tensile strength.

The following research paper has been published in European Journal of Pharmaceutics and Biopharmaceutics. Valentinë Lura was responsible for Conceptualization, Methodology, Investigation, Data curation, Formal analysis and Writing – original draft. Stefan Klinken was responsible for Methodology, Investigation, Data curation, Formal analysis and Writing – review & editing. Jörg Breitkreutz was responsible for Conceptualization, Writing – review & editing and Supervision.

A systematic investigation of external lubrication of mini-tablets on a rotary tablet press with focus on the tensile strength

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Abstract

External lubrication is an alternative to internal lubrication and its related detrimental effects on properties of tablets like tensile strength (TS). However, to date there are hardly any systematic investigations on external lubrication of mini-tablets on rotary tablet presses. Aim of this study was the systematic investigation of the impact of parameters tableting pressure, tableting speed, dosing rate and air pressure on the TS of mini-tablets. Both studies, the Central Composite Design (CCD) with SMCC 90 and the subsequently executed D-optimal design with SMCC 50, exhibited that tableting pressure had the highest positive effect on TS. Tableting speed and dosing rate in the CCD presumably did not seem to influence the TS, air pressure represented a positive coefficient. An additional temporal factor seemed to impact the results, deduced from the negative effect of the experimental order on TS in the CCD and from the negative correlation along the execution order in the residual plots. Additional long runs support findings of a non-linear decrease of TS over time. An interplay between dosing rate level and performance of the dust extraction collector is assumed, making more magnesium stearate available in the tablet press and potentially causing gradual contamination of the powder over time.

7 Discussion and future perspectives

The systematic review article in chapter 2 reveals that publications on mini-tablets have been published since the 1960s. An impressive increase in the number of publications over time can be observed, especially in the last decade. A correlation with the introduction of the Paediatric Regulation in the European Union, the increasingly recommended shift from liquid to solid dosage forms, as well as the execution of clinical acceptability studies building a platform for clinical evidence for the paediatrics can be assumed for this exponential growth. This increase in relevance of mini-tablets culminated with the market launches of Slenyto® (containing melatonin) in a sustained release formulation and Aqumeldi® (containing enalapril maleate) which represent the first commercially available single-unit mini-tablets compared to already available multiparticulate products. These two products represent an example for PUMA medicinal products to counteract the use of off-label medicine in the paediatric population. Aqumeldi® is also the first ODMT on the market [68]. A great amount of knowledge has already been generated from many systematic studies with regard to tableting and film-coating processes but also different types of mini-tablets, e.g. orodispersible, immediate-release, modified-release, colon-targeting and ophthalmic mini-tablets. Despite these striking advancements in technological and clinical terms over the years, the review also points out to challenges. The missing harmonization of compendial methods remains a major obstacle in conjunction with regulatory acceptance, particularly for the pharmaceutical industry clarification in this context is required. Many characterization methods commonly used for conventionally sized tablets are not suitable for the small-sized mini-tablets and need to be modified. For comparability of data e.g. from different working groups standardized methods should be proposed. Also, no standard definition of mini-tablets can be found in pharmacopoeias, yet [68]. The systematic review paper proposes a definition of tablets smaller than 4 mm to be defined as mini-tablets, further guidance regarding classifications and characterization methods are also suggested by the authors. Besides the manufacturing, a closer look on the administration is required, as well. Dose flexibility poses a relevant advantage with respect to individualized therapy. Some inventions with respect to dosing devices are already described in literature, however further efforts have to be made for optimization. Hereby, the costs and hence related pricing could pose a risk [68,69].

Based on the insights gained from this review the thesis compiles further studies on the development and manufacturing of losartan potassium mini-tablets but also general investigations for technological transfer into industrial scale. The pharmaceutical development of highly loaded losartan potassium mini-tablets was based on a QTPP, as defined in the ICH guideline Q8 (R2) of EMA, in terms of the key points, such as dosage form, dosage strength, release and further quality requirements for the product [21]. The development was composed

of various steps where different challenges were targeted. The preference was to select the lowest MCS class for manufacturing. Therefore, initial experiments were carried out on STYL'One Evo with direct compression. The API properties represented a major issue with respect to the edgy and irregular particle shape and the broad particle size distribution ranging from mean D_{10} of 4 µm, D_{50} of 29 µm and D_{90} of 97 µm leading to very poor flowability. Additionally, a high drug load of approximately 40 % was required, which resulted in the attributes of the API taking on a more dominant role in pharmaceutical development and properties of the product. Sticking was experienced at this high drug load and was mitigated by adding silicified microcrystalline cellulose (SMCC) as the main excipient and a combination of the two lubricants magnesium stearate and talc. The optimized formulation was transferred to the rotary tablet press XM 12, but once the batch size was enlarged, production was no longer feasible due to compaction phenomena in the hopper. For this reason, the MCS class II was chosen and an intermediate dry granulation step was successfully implemented. Film-coating with HPMC to mask the bitter taste of the API was performed on a fluid bed device. Most studies found in the literature applied fluid bed technology considering similarities between pellets and mini-tablets and a considerable amount of knowledge about this technology has been already gained. Publications about pan coating of mini-tablets are still scarce, but in pharmaceutical industry the utilization of specialized pans with smaller perforations or addition of smaller mesh is known [68,70], [L1]. Besides the choice of technology, the selection of child-appropriate excipients is of importance. Exemplary, the coating polymer HPMC with GRAS status was chosen according to the suitability for use in children and non-interference with immediate release of a drug [27]. Final dissolution studies of the coated compared to the uncoated mini-tablets successfully displayed the suppression of initial burst in the first minutes. Stability studies over the observed time period of 6 months at 25 °C/60 % r.h. and 40 °C/75 % r.h. were promising, but also highlighted the importance of appropriate packaging, as at stress conditions a slight trend of decline in content as well as in dissolution for one formulation was observed when stored openly or in PE bags compared to sealed aluminium foil. Impurities stayed below the acceptance criteria from the USP 39 monograph on losartan potassium tablets, also after 6 months at both storage conditions.

For industrial purposes, chapter 4 focuses on a transfer and scale-up of 2 mm mini-tablets – firstly, with placebo formulations to produce ODMTs. Tableting was performed with the ready-to-use excipients isomalt and Ludiflash® and the lubricant sodium stearyl fumarate. A transfer from the compaction simulator to the rotary tablet press was feasible with both excipients as tabletability and compactibility profiles were comparable, as well as the CQAs tensile strength and disintegration. However, during scale-up by factor 10, an elevation of the disintegration time was observed to the point where FDA (30 s) or Ph. Eur. specifications (180 s) for orodispersible tablets were not met, anymore. In this case, the elevation of product temperature over time was concluded to have an impact on this CQA, as over-lubrication and

porosity changes could be ruled out as the underlying cause. Raman measurements indicated that potential sintering effects by heat transfer to the mini-tablets could have led to prolongation of disintegration times. Concluding, temperature increase during tableting, especially at production scale, should not be overlooked albeit not immediately visible on lab scale [39], as it can become relevant depending on the choice of formulation, potentially leading to out-of-specification results after a certain production time as in this example for ODMTs.

After these trials, a consecutive study was conducted with an API containing formulation, specifically losartan potassium. This time focus should be also placed on speed variation and detectable over-lubrication issues, as with magnesium stearate a different lubricant was chosen and overall a different formulation was used compared to chapter 4. In contrast to the pharmaceutical development of high-dose losartan mini-tablets in chapter 3, in this study a lower dose of 1.4 mg was selected based on the latest clinical study program [10]. Direct compression was feasible due to the lower drug load and no intermediate granulation step was required. Transfer of the tableting process from STYL'One Evo to the rotary tablet press XM 12 did not show good agreement in terms of tabletability and compactibility. Tabletability profiles were considerably higher on STYL'One Evo. This discrepancy could be traced back to over-lubrication phenomena in the feed frame of XM 12, because the removal of the residual volume from this feed frame and subsequent tableting of this powder on STYL'One provided similar profiles as tableting on XM 12. The paddles in the feed frame additionally stressed the blend before tableting, the residence time in such a forced feed frame can indicate a further mixing step [46,54]. Lubricant sensitivity has to be strongly monitored during formulation development and transfer. Disintegration times were also considerably longer for mini-tablets produced on STYL'One Evo which may be attributed to their generally considerably higher tensile strengths and hence higher forces to be mastered for disintegration [71]. The scale-up study indicated that steady state had to be awaited for the transition to the plateau phase for the CQAs. No noticeable trends of mass variation were detected at different tableting and paddle speeds. Mean content of ten (single) mini-tablets generally stabilized over time after reaching steady state. It is already described in literature, that satisfactory content uniformity is more demanding to achieve in case of single unit mini-tablets compared to multiparticulates forming a dose [72]. The acceptance values at different process settings (calculated both from contents expressed as percentage of label claim and also related to the mass of the individual mini-tablets) hint at lower values when increasing paddle speed or reducing tableting speed in comparison to the batch tableted at a tableting speed of 50 rpm at paddle speeds of 15 and 25 rpm. The residence time and the movement/shear stresses in the feed frame therefore appear to have a slight influence on the mean content and/or deviation considering the described trend. After steady state was reached during tableting, an equilibrium between influx, efflux and dispersion of the lubricant in the feed frame seemed to having been established, showing no trends of the tensile strength over time thereafter. In literature, adverse effects on

tensile strength, but also on disintegration have been described in connection with hydrophobic lubricants [44]. Some combinations of tableting speed and paddle speed exhibited a trend of prolongation of disintegration times over time, but could not be verified for each tested setting combination in this study. Also, maximum disintegration times amounted to 50 s in total, not jeopardizing out-of-specification results, as 15 min are allowed for immediate release tablets. However, chapter 4 with the example of the CQA disintegration times of ODMTs already clearly indicated, that depending on the targeted quality of the product changes over time can risk out-of-specification results and should be monitored.

In the studies of chapter 3 and 5, where losartan potassium was used as API to target the disease Epidermolysis Bullosa, the issue of over-lubrication, particularly when using magnesium stearate, emerged repeatedly. Therefore, external lubrication of mini-tablets on a rotary tablet press was systematically investigated as an alternative for the first time to the author's best knowledge, with the special focus on the response tensile strength. Feasibility studies were conducted with placebo formulations at first place; different grades of SMCC, known as an integral part of the losartan potassium formulations from the previous chapters, were used. Adequate ejection forces between 50 and 280 N were measured at all settings of the Central Composite Design (CCD) study with SMCC 90 and D-optimal design study with SMCC 50. In this regard tableting speed showed the highest effect on the response ejection force. The studies with SMCC 90 and 50 further focused on the impact of the parameters tableting pressure, tableting speed, dosing rate and air spray pressure on the tensile strength of mini-tablets. In chapter 1.5 numerous publications of external lubrication of conventionally sized tablets are summarized. In total, the parameters tableting speed, spray rate and flow air volume of the dust collector were found to influence the amount of magnesium stearate on the tablets, but did not show adverse effects on the tensile strength [57,58,60]. Only tableting pressure was reported to impact this attribute, and also in chapter 6, consistent with that observation, tableting pressure depicted the highest positive coefficient. However, in this statistical study an additional temporal factor was assumed which might have impacted the findings. In retrospect, it was discovered that the experimental order in the CCD had a negative effect on tensile strength if subsequently inserted into the model. The negative correlation coefficients of the residual plots of tensile strength along the execution order also underpin this hypothesis. As the tableting speed coincidentally also happened to be negatively correlated with the execution order, the first runs were excluded, so that the correlation of the tableting speed with the order became smaller (< -0.05). After mitigation of this confounding, tableting speed did not represent a major positive coefficient, anymore. Also, the dosing rate no longer indicated a relevant detrimental effect on the tensile strength. Air pressure seemed to show a slight positive effect underlying the hypothesis that inlet and outlet of the air volume might play a role. Long runs with SMCC 90 were performed that strengthened the hypothesis of an additional temporal factor. It was discovered, that the mean tensile strength declined

non-linearly over time. This effect appeared to additionally depend on the magnitude of the dosing rate. Any time the external lubrication system was stopped while tableting was continued, the mean tensile strength increased again to the starting values. Overall, these findings indicate an interplay between dosing rate and a (possibly insufficient) dust extraction power, that may provide more magnesium stearate within the tablet press to contaminate powder so that tensile strength is reduced over time. As an outlook, further studies are required to expand the knowledge of external lubrication of mini-tablets on rotary tablet presses. The temporal factor which was observed in our machine and experimental setup and hence the observed phenomenon have to be further investigated, e.g. also on different presses, in direct comparison with conventionally sized tablets. As the air flow rate of the used dust collector was not controllable, an exchange of the setup with controlled air flow rates should be tested. After this first feasibility study, further trials should follow with various (drug-containing) formulations to gain further insights and practical knowledge and to address the remaining technological gap between conventionally sized tablets and mini-tablets.

In order to provide a holistic view of the findings of this work, further conclusions can be drawn in the area of pharmaceutical development and production of mini-tablets using the example of losartan mini-tablets, an important undertaking to expand the treatment of Epidermolysis Bullosa for the paediatric population. In addition to the challenges involved in this development, this thesis also provided further insights into the transfer and scale-up processes and implementation of external lubrication of mini-tablets on rotary tablet presses. The comprehensive review of the current publication situation showed the progress made but also pointed out the challenges, starting with the lack of regulatory guidance on mini-tablets for the pharmaceutical industry.

Looking towards the future, there is still a lot of research to be continued in the field of mini-tablets. Industrial relevance should continue to be in the scope, so that higher scale-up ranges should also be in the focus in order to test the limits of mini-tableting by formulation. The interactions between CPPs, CMAs and CQAs should be closely monitored here. Consideration may be given to focusing further work on the continuous manufacturing of mini-tablets, e.g. with the general inclusion of PAT methods for in-line analysis. The first steps have now been taken in the area of external lubrication, but further test set-ups and further formulations are essential for a comprehensive overview. With further research in this direction and parallel adaption and implementation of standard methods for characterization, which simplify the establishment of such products as a guidance for the pharmaceutical industry, as well as further efforts in the area of dosing devices, mini-tablets represent a promising dosage form for the future, in particular for the paediatric population.

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9 Summary

Mini-tablets are increasingly growing in importance which is reflected in the rise of publication counts, particularly in the last decade, as illuminated by the systematic review paper. During this period the paradigm shift from liquid to solid dosage forms was deemed more preferable and beneficial supporting mini-tablets to be considered as a promising dosage form. Also, the clinical evidence of mini-tablet acceptability among the paediatric population was being gradually consolidated by numerous clinical studies. The enhanced attention to this dosage form is emphasized by the market launches of Slenyto® and Aqumeldi®, both medicinal products with Paediatric-Use Marketing Authorisation (PUMA), representing the first available single-unit mini-tablets on the market. The review paper sums up relevant advancements in the technological and clinical area, but also points out significant challenges that are currently being faced and have an impact on the development and manufacturing of mini-tablets in the pharmaceutical industry. Firstly, there is no standard definition of mini-tablets in pharmacopoeias. Secondly, compendial methods are not yet standardized which is required for better clarity among pharmaceutical industry with regard to regulatory acceptance. Therefore, the review paper proposes a definition of mini-tablets and a guidance regarding classifications and some suitable characterization methods. The development of dosing devices is also to be continued in terms of optimization, cost and related pricing could be a risk.

Mini-tablets present a valuable option to target paediatric patients, which is why this child-appropriate dosage form was chosen to make losartan potassium available for the treatment of Epidermolysis Bullosa. Dosing is based on body weight, hence mini-tablets would provide a great opportunity for dose flexibility. Also, good swallowability is a valuable benefit in case of this skin fragility disorder, as patients can suffer from oesophageal stenosis. Highly drug-loaded mini-tablets were successfully developed on the compaction simulator STYL'One Evo by Medelpharm and then on the rotary tablet press XM 12 by Korsch, while several challenges were encountered. The lowest feasible Manufacturing Classification System (MCS) class for the manufacturing process was attempted. Given the high drug load, the active pharmaceutical ingredient (API) properties dominated the formulation resulting in challenging flowability and sticking to the punches. These issues could be mitigated by the formulation and selection of the excipients, but the transfer to the rotary tablet press showed the additional problem of compaction in the hopper when increasing the batch size, so that an intermediate dry granulation (MCS class II) was successfully introduced to address this concern. Taste masking via fluid bed coating was carried out successfully on a laboratory scale and dissolution studies exhibited the delay of release in the first minutes, preventing the high initial burst. Stability studies showed promising results, but also highlighted the relevance of appropriate packaging.

Further insights were gained in the field of transfer and scale-up of mini-tablets with drug-free orodispersible formulations and consecutively with a losartan formulation. Tensile strength, mass variation, disintegration and in case of the losartan potassium studies also content were chosen as critical quality attributes (CQAs). Depending on the formulation and choice of excipients a transfer from compaction simulator to the rotary tablet press was feasible in terms of compactibility and tabletability. However the transfer and scale-up studies underlined certain effects that may show correlation with the tableting process directly but might not be instantly noticeable on laboratory scale. Temperature rise is one of these factors that became apparent with greater batch size and hence longer production time in case of the study with placebo orodispersible mini-tablets (ODMTs). Particularly, the disintegration time as a CQA, increased over time, which might be attributed to sintering effects owing to the temperature elevation. The studies conducted with the losartan potassium formulation, however, showed that with magnesium stearate instead of sodium stearyl fumarate from the ODMT formulation, over-lubrication occurred, with the result that the transfer did not show a good agreement of compactibility and tabletability. Residence time and shear stresses in the feed frame have a major influence depending on the formulation; lubricant sensitivity must be taken into account. In this scale-up study, any potential effects induced by speed variation were also tested. Scale-up investigations reflected that the steady state was required to be reached for the transition to the plateau phase of the CQAs. During steady state an equilibrium between influx, efflux and dispersion of lubricant in the feed frame could be recognized, so that mean tensile strengths would stay stable once this phase was obtained. Changes in speed of tableting and feed frame paddles showed a slight trend of impacting the acceptance value. Acceptance values below 15.0 were obtained at different settings. In total, adequate process understanding of the critical process parameters (CPPs) and the critical material attributes (CMAs) has to be established during development and scale-up of mini-tableting processes to ensure meeting required ranges of CQAs.

As over-lubrication issues were encountered during development of the high drug-loaded losartan potassium mini-tablets and also during the transfer and scale-up of the lower dosed mini-tablets in the direct compression trials, feasibility studies were conducted to investigate external lubrication on the rotary tablet press during mini-tableting as an alternative. A special focus was placed on the response tensile strength. The parameters investigated were tableting pressure, tableting speed, dosing rate and air spray pressure. A look at the literature shows a gap in this technology for mini-tablets, while there are already many studies for conventionally sized tablets. External lubrication proved to be feasible, as appropriate ejection forces were measured enabling mini-tableting. The systematic studies (Central Composite Design (CCD) and D-optimal study) were performed with silicified microcrystalline cellulose grades SMCC 90 and 50, respectively. Concluding, an additional temporal factor was recognized, amongst others mean tensile strengths were declining non-linearly over time in long runs with the degree

being dependent on the dosing rate, while also a dependency of the dust extraction power is assumed, so that more magnesium stearate would be available in the tablet press, potentially contaminating powder and hence deteriorating the tensile strength. In total, the parameters tableting speed and dosing rate did not seem to have an effect on the response tensile strength in the CCD study, while tableting pressure represented the highest positive coefficient, and the air spray pressure a slightly positive coefficient. Further studies are necessary to investigate this phenomenon that occurred at a specific machine and experimental setup, e.g. with further tablet presses and a setup with the possibility to control the air flow rate of the dust collector. Studies should also be also extended to further formulations in the future.

10 Zusammenfassung

Minitabletten gewinnen zunehmend an Bedeutung, was sich in der Zunahme der Zahl an Veröffentlichungen, insbesondere im letzten Jahrzehnt, widerspiegelt, wie der systematische Übersichtsartikel beleuchtet. In diesem Zeitraum wurde der Paradigmenwechsel von flüssigen zu festen Darreichungsformen als vorteilhaft und gewinnbringend erachtet, so dass Minitabletten in diesem Hinblick als vielversprechende Darreichungsform angesehen wurden. Auch die klinische Evidenz für die Akzeptanz von Minitabletten in der pädiatrischen Bevölkerung begann in dieser Zeit durch zahlreiche klinische Studien allmählich gefestigt zu werden. Die erhöhte Aufmerksamkeit für diese Darreichungsform wird durch die Markteinführung der PUMA-Arzneimittel Slenyto® und Aqumeldi® unterstrichen, die die ersten auf dem Markt verfügbaren einzeldosierten Minitabletten darstellen. Der Übersichtsartikel fasst relevante Fortschritte im technologischen und klinischen Bereich zusammen, weist aber auch auf bedeutende Herausforderungen hin, mit denen die pharmazeutische Industrie derzeit konfrontiert wird und die sich auf die Entwicklung und Herstellung von Minitabletten auswirken. Erstens gibt es keine einheitliche Definition von Minitabletten in den Arzneibüchern. Zweitens sind zum jetzigen Zeitpunkt noch keine standardisierten Methoden für die Charakterisierung von Minitabletten etabliert, welche hinsichtlich der regulatorischen Akzeptanz besonders für die pharmazeutische Industrie als Anhaltspunkt notwendig sind. Daher wird im Übersichtsartikel eine mögliche Definition von Minitabletten und ein Leitfaden für Klassifizierungen und einige geeignete Charakterisierungsmethoden vorgeschlagen. Auch im Hinblick auf Dosiervorrichtungen sind noch weitere Bestrebungen zu tätigen, die Kosten stellen dabei ebenfalls ein Risiko dar.

Minitabletten stellen eine wertvolle Option für die Behandlung pädiatrischer Patienten dar. Deshalb wurde diese kindgerechte Darreichungsform gewählt, um Losartan-Kalium für die Behandlung von Epidermolysis Bullosa verfügbar zu machen. Die Dosierung erfolgt bezogen auf das Körpergewicht, so dass die Dosierung durch die Anzahl der verabreichten Minitabletten flexibilisiert werden kann. Die gute Schluckbarkeit ist ein weiterer wertvoller Vorteil dieser Darreichungsform bei der Behandlung dieser Hauterkrankung, da die Patienten an einer Ösophagus-Stenose leiden können. Hochbeladene Minitabletten wurden erfolgreich auf dem Kompaktionssimulator STYL'One Evo von Medelpharm und anschließend auf der Rundläufer-Tablettenpresse XM 12 von Korsch entwickelt, wobei einige Herausforderungen zu bewältigen waren. Es wurde die niedrigst mögliche MCS-Klasse für den Herstellungsprozess angestrebt. Angesichts der hohen Arzneistoffbeladung dominierten die Eigenschaften des Wirkstoffs in der Formulierung, dies führte zur unzureichenden Fließfähigkeit und Kleben an den Stempeln. Diese Probleme konnten durch die Formulierung und die Auswahl der Hilfsstoffe verbessert werden. Dennoch zeigte der darauffolgende

Transfer der Direkttablettierung auf die Rundläufer-Tablettenpresse die zusätzliche Herausforderung der Verdichtung im Trichter bei Erhöhung der Chargengröße. Als Lösungsansatz wurde ein intermediärer Trockengranulationsschritt (MCS-Klasse II) erfolgreich eingeführt. Die Geschmacksmaskierung durch Befilmung mithilfe der Wirbelschichttechnologie wurde erfolgreich im Labormaßstab durchgeführt. Freisetzungsstudien zeigten, dass die Freisetzung in den ersten Minuten erfolgreich verzögert werden konnte. Stabilitätsstudien zeigten vielversprechende Ergebnisse, verdeutlichten aber auch die Relevanz einer geeigneten Verpackung.

Weitere Erkenntnisse wurden im Rahmen dieser Arbeit auf dem Gebiet des Transfers und des Scale-up von Minitabletten gewonnen. Druckfestigkeit, Massenvariation, Zerfall und im Falle der Losartan-Kalium Studien auch der Gehalt wurden als kritische Qualitätsattribute ausgewählt. Abhängig von der Formulierung und der Wahl der Hilfsstoffe war ein Transfer vom Kompaktionssimulator zur Rundläufer-Tablettenpresse in Bezug auf die Kompaktibilität und die Tablettierbarkeit möglich. Die Transfer- und Scale-up-Studien haben jedoch Effekte aufgezeigt, die zwar direkt mit dem Tablettierungsprozess korrelieren, aber im Labormaßstab möglicherweise nicht sofort erkennbar sind. Der Temperaturanstieg ist einer dieser Faktoren, der sich bei der Studie mit den Placebo orodispersiblen Minitabletten bei einer größeren Chargengröße und damit einer längeren Produktionszeit zeigte. Insbesondere die Zerfallszeit als kritisches Qualitätsattribut nahm mit der Zeit zu, was letztlich vermutlich auf Sinterungsprozesse aufgrund der Temperaturerhöhung zurückgeführt werden kann. Die mit der Losartan-Formulierung durchgeführten Untersuchungen zeigten jedoch, dass mit Magnesiumstearat anstelle von Natriumstearylfumarat aus der orodispersiblen Formulierung eine Überschmierung auftrat, so dass der Transfer keine gute Übereinstimmung von Kompaktibilität und Tablettierbarkeit zeigte. Verweilzeit und Scherbelastungen im Füllschuh haben je nach Formulierung einen großen Einfluss, folglich muss die Schmiermittelempfindlichkeit berücksichtigt werden. In dieser Scale-up-Studie wurden auch mögliche Auswirkungen von Variationen in den Geschwindigkeiten getestet. Die Scale-up-Untersuchungen ergaben, dass die kritischen Qualitätsattribute einer Einstellungszeit zum Prozessstart bedürfen. Es konnte ein Gleichgewicht zwischen Influx, Efflux und Dispersion des Schmiermittels im Füllschuh erkannt werden, so dass die mittleren Druckfestigkeiten nach Erreichen dieser Phase stabil blieben. Änderungen in der Tablettier- und Rührflügelgeschwindigkeit zeigten einen leichten Trend bezüglich der Auswirkung auf die Akzeptanzwerte (AV). Akzeptanzwerte unter 15,0 wurden bei verschiedenen Einstellungen erzielt. Insgesamt muss ein angemessenes Prozessverständnis der kritischen Prozessparameter und der kritischen Materialeigenschaften während der Entwicklung und des Scale-up der Minitablettierung etabliert werden, um die Einhaltung der kritischen Qualitätsattribute zu gewährleisten.

Da bei der Entwicklung von hochdosierten Losartan-haltigen Minitabletten sowie beim Transfer und Scale-up der niedriger dosierten Minitabletten während der Direkttablettierung eine Überschmierung beobachtet wurde, wurden Machbarkeitsstudien durchgeführt, um die externe Schmierung an der Rundläufer-Tablettenpresse als Alternative zu untersuchen. Ein besonderer Schwerpunkt lag auf der Druckfestigkeit als Zielgröße. Die untersuchten Parameter inkludierten den Tablettierdruck, die Tablettiergeschwindigkeit, die Dosierrate und den Sprühluftdruck. Die wissenschaftliche Literatur weist deutliche Lücken in der externen Schmierung bei Minitabletten auf, während die Datenlage für normalgroße Tabletten deutlich besser ist. Die externe Schmierung erwies sich als machbar, da entsprechende Ausstoßkräfte gemessen wurden, die die Herstellung von Minitabletten ermöglichten. Die systematischen Studien (Central Composite Design (CCD)- und D-Optimal-Studie) wurden mit silifizierter mikrokristalliner Cellulose SMCC 90 bzw. 50 durchgeführt. Zusammenfassend wurde ein zusätzlicher zeitlicher Faktor erkannt, da u.a. bei den langen Produktionsläufen die mittleren Druckfestigkeiten nichtlinear über die Zeit abnahmen. Dabei schien das Ausmaß von der Dosierrate abhängig zu sein, während auch eine Abhängigkeit von der Saugleistung des Staubsaugers angenommen wird. Folglich stand dadurch vermutlich mehr Magnesiumstearat in der Tablettenpresse zur Verfügung, das möglicherweise das Pulver kontaminierte und somit die Druckfestigkeit der Minitabletten reduzierte. Insgesamt schienen die Parameter Tablettiergeschwindigkeit und Dosierrate in der CCD-Studie keinen Einfluss auf die Druckfestigkeit zu haben, während der Tablettierdruck den höchsten positiven Koeffizienten und der Sprühluftdruck einen leicht positiven Koeffizienten darstellten. Weitere Studien sind erforderlich, um dieses Phänomen zu untersuchen, das bei diesem bestimmten Versuchsaufbau auftrat, z.B. mit weiteren Tablettenpressen und einem Aufbau mit der Möglichkeit, den Luftdurchsatz des Staubsaugers zu steuern und zu kontrollieren. Die Untersuchungen sollten in Zukunft auch auf weitere Formulierungen ausgeweitet werden.

List of original publications

[L1] V. Lura, A. Lura, J. Breitkreutz, V. Klingmann, The revival of the mini-tablets: Recent advancements, classifications and expectations for the future, Eur. J. Pharm. Biopharm. 210 (2025) 114655.

[L2] V. Elezaj, A. Lura, L. Canha, J. Breitkreutz, Pharmaceutical development of film-coated mini-tablets with losartan potassium for epidermolysis bullosa, Pharmaceutics 14 (2022) 570.

[L3] A. Lura, V. Elezaj, M. Kokott, B. Fischer, J. Breitkreutz, Transfer and scale-up of the manufacturing of orodispersible mini-tablets from a compaction simulator to an industrial rotary tablet press, Int. J. Pharm. 602 (2021) 120636.

[L4] V. Lura, S. Klinken, J. Breitkreutz, Challenges in the transfer and scale-up of mini-tableting: Case study with losartan potassium, Eur. J. Pharm. Biopharm. 192 (2023) 161–173.

[L5] V. Lura, S. Klinken, J. Breitkreutz, A systematic investigation of external lubrication of mini-tablets on a rotary tablet press with focus on the tensile strength, Eur. J. Pharm. Biopharm. 198 (2024) 114236.

Contributions to meetings

Oral presentations

Development of mini-tablets with losartan potassium, 12th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2021, online

Poster presentations

1. Valentinë Elezaj, Luis Canha, Jörg Breitkreutz, Pharmaceutical development of mini-tablets with losartan potassium for an inherited rare disease; 13th European Paediatric Formulation Initiative, 2021, online
2. Valentinë Elezaj and Jörg Breitkreutz, Transfer and scale-up of mini-tablets with losartan potassium, 13th World Meeting on Pharmaceutics and Biopharmaceutics Technology, 2022, Rotterdam
3. Valentinë Elezaj and Jörg Breitkreutz, Manufacturing of mini-tablets for epidermolysis bullosa, 14th European Paediatric Formulation Initiative, 2022, Rome

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Eidesstattliche Versicherung

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

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Valentinë Lura