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Rational development of orodispersible minitablets under particular consideration of the lubrication system

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It always seems impossible until it's done

- Nelson Mandela

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List of abbreviations

Abbreviation	Meaning
abbr.	Abbreviation
ACN	Acetonitrile
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
approx.	approximately
BCS	Biopharmaceutics Classification System
BET	Brunauer-Emmett-Teller
CA	Contact angle
CCD	Charged coupled device
CCS	Croscarmellose sodium
CMA	Critical material attribute
CPE	Co-processed excipient
CPP	Critical process parameter
CQA	Critical quality attribute
c_t	Concentration at the timepoint t
$d_{10/50/90}$	10/50/90 % percentile of the particle size distribution
DC	Direct compression
DCPA	Dibasic calcium phosphate anhydrous
DL	Drug load
DoE	Design of Experiments
ε	Porosity
EC	European Commission
EMA	European Medicines Agency
EuB	Euro norm Type B
EuD	Euro norm Type D
FDA	U.S. Food and Drug Administration
FDM	Fused deposition modeling
GSH	Galenical Development System Heidelberg
HAR	Haus
HCl	Hydrochloric acid
HLB	Hydrophilic-lipophilic balance
HPLC	High-performance liquid chromatography

HAR	Hausner ratio
IBU	Ibuprofen
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IQR	Interquartile range
k_B	Bonding capacity constant
k_C	Compressibility resistance constant
L-HPC	Low substituted hydroxypropyl cellulose
Lub conc	Lubricant concentration
Max.	Maximum
MCC	Microcrystalline cellulose
$MgCl_2$	Magnesium chloride
MgSt	Magnesium stearate
Min.	Minimum
MT	Minitablet
NPX	Naproxen
n.r.	Not recorded
ODMT	Orodispersible minitablet
ODT	Orodispersible tablet
ODx	Orodispersible dosage form
OFAT	One factor at a time
PA	Polyamide
PAT	Process Analytical Technology
PEG	Polyethylene glycol
Ph. Eur.	European Pharmacopeia
PIP	Pediatric Investigation Plan
PUMA	Pediatric Use Marketing Authorization
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone, povidone
P_x	Pressure at $\varepsilon = x$
QbD	Quality by Design
QTPP	Quality target product profile
ρ	Density
r.h.	Relative humidity

RMSEP	Root mean square error of prediction
rpm	revolutions per minute
RSD	Relative standard deviation
SA	Stearic acid
SD	Standard deviation
SEM	Scanning electron microscopy
SF	Solid fraction
SFW	Successful formulation window
SPE	Specific plastic energy
SSF	Sodium stearyl fumarate
SSG	Sodium starch glycolate
SVR	Surface-to-volume ratio
TBI	Tablet brittleness index
TS	Tensile strength
T_x	Tensile strength at $\varepsilon = x$
USP	United States Pharmacopeia
ZMT	Zolmitriptan

List of publications and contributions

Parts of this thesis were already published at conferences or peer-reviewed journals:

Original publications

Research paper

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Kuck, J., Fischer, B., Breitkreutz, J.: *Evaluation of external lubrication for orodispersible minitablets*, 14th Conference of European Paediatric Formulation Initiative, Rom 2022

Kuck, J., Breitkreutz, J.: *Influence of lubrication on orodispersible tablets and minitablets*, 13th World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Rotterdam 2022

1. Introduction

1.1. Orodispersible minitablets

1.1.1. Definition

After the introduction of tablets in the literature over 150 years ago [1], they are still the most popular dosage form on the pharmaceutical market. They show a lot of benefits such as good patient compliance or cost-effective production compared to other dosage forms [2, 3]. Tablets offer many different formulation possibilities depending on the desired effect in the body. In the Ph. Eur. monograph “Tablets” different types of tablets are distinguished: non-coated tablets, coated tablets, enteric-coated tablets, modified release tablets, effervescent tablets, tablets for the preparation of an oral solution, tablets for the preparation of an oral suspension, orodispersible tablets, chewable tablets and lyophilizates for oral use [4]. Further, additional types of tablets are monographed according to their administration mode such as vaginal, rectal, sublingual or buccal tablets [5-7].

Orodispersible tablets (ODTs) are defined as uncoated tablets which should be kept in the oral cavity and disintegrate within 3 min in the saliva [4] . In contrast, a FDA guidance for industry defines a stricter limit of 30 s for the disintegration of ODTs, referred to as “orally disintegrating tablets” [8]. Besides ODTs, orodispersible films are another prominent group of orodispersible dosage forms (ODx). In the last years, orodispersible dosage forms have gained greater interest due to their improved patient compliance and a possible increase in bioavailability [9, 10].

At the moment, no monograph for minitablets exists in either the European or US pharmacopeia. Therefore, they do not specify a maximum tablet size up to which tablets can be labelled as minitablets. In the scientific literature, the definition of minitablets can differ from author to author. Lennartz and Mielck [11] defined tablets less than or equal to 3 mm as minitablets, while other sources specified the maximum diameter as 4 mm [12-14]. In some cases, even tablets with a diameter up to 5 mm were classified as minitablets [15]. In a recent structured review paper by Lura et al. [16], a limit of less than 4 mm was proposed.

The smallest tablet size described in literature was 1 mm [17, 18]. A study by Lura et al. [18] compared the properties of 1, 2 and 3 mm minitablets with 8 and 11.28 mm tablets and showed superior compactability, but no improved tabletability for the tablets with a smaller diameter. The smaller the tablet, the more complicated the manufacturing process may get. Compared to conventional tablet formulations, minitablets have even more demanding requirements: A better flowability of the powder blend is needed to ensure mass uniformity and the particle size of the API and the excipients has to be chosen appropriately in order to guarantee content uniformity [19-21]. Due to the higher surface-to-volume ratio (SVR) they might require a higher lubricant amount and the quantitative

composition of the tablet might has to be adapted as e.g. the compactability can be altered for smaller tablet sizes [18].

Stoltenberg and Breitkreutz first presented the idea of orodispersible minitablets (ODMTs) in 2011 [22] as a child-appropriate dosage form because of their simple administration and dose flexibility. The disintegration of MTs in the oral cavity can be beneficial as the risk of aspiration and choking is decreased [23, 24]. However, the hypothesis that the use of ODMTs improves pediatric patient safety still has to be confirmed in clinical studies. To enable a flexible dosing, ODMTs can also be administered via a nasogastric tube after diluting the ODMT in a syringe, as described for enalapril ODMTs by Thabet et al. [25].

With the introduction of the Pediatric Investigation Plan (PIP) in the regulation of the European Commission (EC) No. 1901/2006, pharmaceutical companies are obliged to develop child-appropriate dosage forms for new medicinal products. Several publications [26, 27] elaborated the suitability of different dosage forms such as orodispersible films or multiparticulate dosage forms like pellets or minitablets beside liquid dosage forms for their use for children. The first product containing ODMTs (Aqumeldi®) was authorized by the European Medicines Agency (EMA) in 2023 and represents a child-appropriate dosage form of enalapril maleate for children up to 17 years suffering from heart failure [28]. It was developed for receiving a Pediatric Use Marketing Authorization (PUMA) by EMA and provides an alternative to liquid enalapril formulations e.g. Epaned® in the USA and is currently available in an adapted dose of 0.25 mg and 1 mg for children. Aqumeldi® now represents the first child-appropriate ODMT product.

However, the development of appropriate dosing devices is essential for the appropriate administration of numerous minitablets as a multiparticulate dosage form consisting of several minitablets. Hejduk and Lulek [29] provided a recent overview of the current possibilities for dosing of minitablets, ranging from sachets to specialized dosing devices for minitablets.

Although minitablets are known in literature for quite a long time, there are still many challenges and unanswered questions highlighting the importance of ongoing research in this field. As especially ODMTs present a promising dosage form for special patient groups, research in this field is of huge interest.

1.1.2. Manufacturing methods

Orodispersible (mini-)tablets can be produced with different manufacturing techniques:

One possibility is the production by lyophilization (e.g. Zydis® or Lyoc® technology [30, 31]) which results in tablets with a highly porous structure and a rapid disintegration in the oral cavity. On the other hand, freeze-drying is a very time- and energy-consuming process, and the resulting tablets are very brittle and have to be handled with care. Another method is the manufacturing by molding where either a solvent or heat is used for molding the components into pre-defined tablet geometries [32]. Comparable to lyophilized tablets, molded ODTs offer rapid disintegration but also show poor mechanical properties. Besides these methods, production by sublimation [33] can also be performed by using excipients with a high volatility to form a matrix with a high porosity.

The most common manufacturing technique is compression of solid particles into tablets, either as powder blends via direct compression (DC) or as granules. Direct compression offers several advantages: It is the easiest production method for ODTs as it only has a few processing steps (sieving, blending & tableting) and results in mechanically stable tablets. As no liquid is used in the entire process, no drying step has to be conducted leading to a fast, simple and cost-effective process. Packaging and storage are also less demanding as the mechanically stable tablets can be easily processed and do not need specific storage conditions. The requirements for direct compression are a good flowability of the powder mixture for a stable tableting process and sufficient compaction properties [34]. If the powder blend does not offer sufficient flowability or good compaction behavior, an intermediate granulation step should be performed [35].

In literature, some publications also evaluated the suitability of 3D printing for the manufacturing of minitablets. Therefore techniques like drop-on-demand printing [36, 37] or fused deposition modeling (FDM) [38-40] present a novel alternative for individualization of the dosage form especially for pediatric patients. Hu et al. [41] could also achieve orodispersible properties for their 3D-printed minitablets by the addition of 40% croscarmellose sodium in the formulation. Spritam® is currently the only 3D-printed ODT on the market and was introduced in 2015. It contains up to 500 mg levetiracetam and shows ODT properties with a mean disintegration time of 11 s [42]. The tablet is manufactured using the ZipDose® technology and has been developed and marketed by Aprecia Pharmaceuticals. This method employs a specific, proprietary 3D-inkjet-printing technique, where a binder solution is applied onto a powder bed and the process is executed several times to achieve the three-dimensional ODT [43].

Minitablets are manufactured with either single-tip or multi-tip toolings (Figure 1).

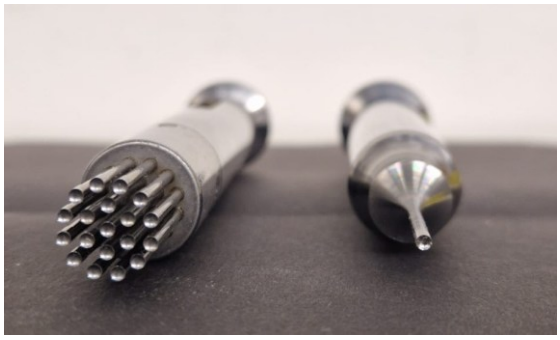


Figure 1: Picture of 2 mm minitablet punches, left: multi-tip with 19 tips, right: single tip

Multi-tip punches offer a higher throughput because more minitablets can be produced within the same compression step. In general, different numbers of tips can be mounted to the punch and up to 40 tips per punch were described in literature [44]. Lura and Breitkreutz [45] investigated the influence of single-tip, 7-tip and 19-tip punches for minitablets with a diameter of 2 and 3 mm . They figured out that ejection forces were the highest for the 19-tip and the compactability also increased by the number of tips. On the other hand, deviations in mass and content have to be expected for multi-tip punches. If deviations occur for a single minitablet within a multi-tip tool, detecting these variances becomes quite challenging and thereby complicates the validation of the process and monitoring of the critical quality attributes (CQAs) [46]. Loo et al. [47] elaborated the difference between different punches and observed increased mass variations (4 – 8 x higher), longer dwell times, resulting in higher tensile strengths and longer disintegration times for minitablets (MTs) manufactured with the multi-tip compared to the single-tip. Therefore, they proposed an adaptation of the compression speed in order to minimize the variations between the different types of punches.

Overall, specific challenges can arise during the development of ODMTs: The powder blend has to show sufficient flowability to ensure a smooth filling process of all dies of the multi-tip tooling and thereby, low deviations in mass and content. Furthermore, problems with sticking and insufficient lubrication may occur, as minitablets have a higher SVR and tend to show higher ejection forces [45]. Depending on the taste properties of the drug substance, taste masking strategies, for example film coating (e.g. with Eudragit® EPO [48]), the use of microparticles with taste-masked properties [49] or taste-masked lipid-based granules [50] can be applied to develop ODMTs with a high compliance in the targeted patient group.

1.1.3. Areas of application and acceptance studies

Minitablets and specifically ODMTs can be a suitable dosage form for several special target groups like children, elderly and people with swallowing difficulties [23].

Different clinical studies in different age groups of children were conducted using minitablets to prove their superior acceptance in comparison to alternative dosage forms:

Thomson et al. [51] conducted a clinical trial with minitablets for pediatric use where the majority of children successfully swallowed 3 mm minitablets. Thus, they proposed minitablets as a promising dosage form for children aged from 2 to 6 years. A study by van Riet-Nales et al. [52] pointed out that 4 mm minitablets were also a well-accepted dosage form and preferred over a suspension for children from 1 to 4 years. Contrary to their expectations, Spomer et al. [53] were the first to report that children up to 6 years accepted 2 mm minitablets not less or even better compared to 3 ml of syrup. In a prospective randomized clinical study Klingmann et al. [54] demonstrated the superior acceptance of 2 mm uncoated minitablets compared to syrup in a study involving over 300 children from 6 months up to 5 years of age. The administration of several coated minitablets revealed no significant difference between minitablets and a liquid formulation in a similar age group [55]. Regarding even younger patients, a study with 151 neonates in the age range of 2 – 28 days presented no inferiority of an uncoated minitablet compared to a syrup formulation [56]. A clinical trial by Mitsui et al. [57] confirmed the superiority of minitablets over liquids or fine granules in children aged 6-11 months and additionally showed a preference for minitablets of the caregivers in a survey.

Wargenau et al. [58] developed a composite endpoint as a new acceptability criterium for clinical studies, as acceptance in the target group cannot only be described by swallowability, but also has to consider the palatability. The authors could achieve a better differentiation of the different dosage forms using the composite endpoint method. A study by Münch et al. [59] evaluated the acceptance for children between one month and 6 years regarding swallowability and palatability by the composite endpoint method for 2 and 2.5 mm coated minitablets and found these to be a suitable dosage form.

Regarding the maximum possible number of minitablets, Klingmann et al. conducted a study [60] where up to 400 minitablets were administered to children older than 12 months and were accepted even better than syrup. A clinical trial by Kluk et al. [61] elaborated the acceptance for children between 24 – 48 months and showed that units of 5 or 10 minitablets could be administered successfully with a commercially available fruit gel. In a questionnaire-based study by Wargenau et al. [62], the maximum acceptable number of 2 and 3 mm minitablets was determined for children up to 18 years. Most of the participants included in the study had no prior experience with the intake of MTs. Treatment duration and the age of the children were considered in the evaluation of the data. For children aged 0 – 2 years, more than 10 minitablets (2 mm) were considered acceptable, with even higher numbers reported for older children.

A study by Münch et al. [63] compared small-sized oblong tablets (2.5 x 6 mm) with three round 2 mm minitablets and revealed their non-inferiority. This finding may present a suitable alternative, if normal minitablets are not capable to contain the required API single dose and can enable to reduce the number of administered tablets and hence increase the drug load, due to their higher volume.

The minitablets can be administered either with water or soft food which was shown to be a safe application method even for film-coated minitablets in another publication by Münch et al. [64] as no adverse events were reported.

A study by Hayakawa et al. [65] compared 3 mm MTs and ODMTs with 8 mm (orodispersible) tablets in healthy adults. ODMTs were found to be the easiest dosage form to take, requiring the least amount of water.

A recently published study by Lazic et al. [24] studied the acceptability and palatability of single and multiple enalapril ODMTs in children up to 6 years. No signs of aspiration (e.g. coughing or choking) were observed and ODMTs were well accepted in the studied patient group, demonstrating the safety and suitability of ODMTs as a child-appropriate dosage form. This is the first study addressing the acceptability of ODMTs in children, as all other available studies have been conducted with “normal” minitablets. Further trials should be conducted to elaborate the suitability of ODMTs for children, using different methods to assess acceptability. As the composite endpoint method considering swallowability and palatability was recently supported by the EMA [66], future studies with this method should be conducted.

1.1.4. Excipients for the production of orodispersible minitablets

1.1.4.1. Fillers

Fillers typically represent the largest proportion of the formulation and play a relevant role in determining the mechanical strength and the compressibility of the tablet. Orodispersible tablets manufactured by direct compression often contain highly soluble fillers as these may influence the disintegration and dissolution process [67]. The most frequently used filler is D-mannitol, a sugar alcohol with a sweet taste, which presents another benefit for the application in the oral cavity. Al-khattawi and Mohammed [68] summarized the preference of mannitol for the production of ODTs as it offers a cooling effect in the mouth due to its negative heat of solution, a good mouth feel and low hygroscopicity. On the downside, mannitol does not show good compactability and exhibits fragmentation during compression which may lead to mechanically less stable tablets.

In the past cellulose-based excipients like microcrystalline cellulose or L-HPC [69, 70] were used but gradually lost their relevance when the switch to advanced mannitol-based excipients (e.g. Ludiflash®)

happened [68]. Also, co-processed excipients (CPEs) based on MCC have been reported to function as a filler for orodispersible tablets such as Prosolv® EASYtab SP [71].

To overcome the poor compaction behavior of mannitol, α-lactose, commonly used in the production of tablets, can be used as an alternative filler for ODTs. StarLac®, a co-processed excipient (CPE) of 85% α-lactose monohydrate and 15% maize starch [72], was already used successfully for the production of OD(M)Ts [73-75]. Also pure α-lactose was used in ODT development together with a superdisintegrant [76].

Other sugar alcohols, in particular sorbitol or xylitol, could potentially also be used as a filler for ODTs, but their hygroscopicity must be considered in terms of stability. Therefore they are mostly used in smaller amounts in addition to mannitol to improve the sweetness and the compactability of the excipient [68]. Some publications describe the use of xylitol as a filler and were able to obtain ODTs within the pharmacopeial limits [77, 78].

Isomalt (galenIQ™ 721, abbr.: galenIQ™), a combination of the two disaccharide alcohols, was also utilized in literature for the production of OD(M)Ts [79, 80]. Lura et al. [79] compared ODMTs containing isomalt to formulations using other co-processed excipients and demonstrated its suitability for the manufacturing of ODMTs. Even without a disintegrant, the disintegration criterion according to Ph. Eur. was fulfilled and disintegration could be further improved by the addition of the disintegrant crospovidone.

In order to minimize the insufficient properties of single excipients and to avoid segregation tendencies, co-processed excipients were developed as an all-in-one solution and can save an enormous amount of time. They are defined as “a combination of two or more compendial or non-compendial excipients designed to physically modify their properties in a manner not achievable by simple physical mixing, and without significant chemical change” [81]. CPEs are manufactured by processes such as spray drying, co-crystallization, co-milling or wet granulation and offer a higher functionality than the physical mixture including improved flowability or disintegration time, spherical particle shape or better compressibility [82]. In Table 1, currently available CPEs for orodispersible tablets based on mannitol are summarized:

Brand name	Manufacturer	Composition
Compressol™ SM	SPI Pharma, USA	80 – 90 % D-mannitol 10 – 15 % sorbitol <2 % silicon dioxide
F-Melt® type C	Fuji Chemical Industries, Japan	55 – 70 % D-mannitol 10 – 25 % Microcrystalline cellulose (MCC) 5 – 13 % crospovidone 2 – 9% xylitol 2 – 9% Dibasic calcium phosphate anhydrous (DCPA)
F-Melt® type M	Fuji Chemical Industries, Japan	55 – 70 % D-mannitol 10 – 25 % MCC 5 – 13 % crospovidone 2 – 9 % xylitol 2 – 9 % Magnesium aluminium metasilicate
Granfiller-D® [83] [1]	Daicel, Japan	D-mannitol MCC crospovidone carmellose
Hisorad® [83] [1]	Daicel, Japan	D-mannitol MCC croscarmellose sodium
Ludiflash®	BASF, Germany	90 % D-mannitol 5 % crospovidone 5 % polyvinyl acetate dispersion
Parteck® ODT [84]	Merck, Germany	90 – 95 % D-mannitol 3 – 7 % croscarmellose sodium
Pearlitol® Flash	Roquette, France	80 – 85 % D-mannitol 15 – 20 % maize starch

Pharmaburst™ 500	SPI Pharma, USA	85 %	D-mannitol
		< 10 %	silicon dioxide
		< 10 %	sorbitol
		5 %	crospovidone
Prosolv® ODT G2 (abbr.: Prosolv® ODT)	JRS Pharma, Germany	60 – 70 %	D-mannitol
		15 – 30 %	MCC
		5 %	crospovidone
		< 10 %	fructose and silicon dioxide
Smart Ex® [1]	ShinEtsu, Japan		D-mannitol
			L-HPC
			polyvinyl alcohol

Table 1: List of mannitol-based CPEs for ODTs currently available on the market (adapted and modified from [85]), [1]: no information on the percentage composition available

Several studies compared CPEs with their respective physical mixtures of the individual components and verified their superiority. Woyna-Orlewicz et al. [86] investigated five different CPEs in comparison to the physical mixture and highlighted F-Melt® due to its very short disintegration time and good mechanical properties. Brniak et al. [87] found Pharmaburst™ to be the most suitable excipient for ibuprofen ODTs compared to two other CPEs (Ludiflash® and F-Melt®). Kokott et al. [83] studied two new CPEs named Granfiller-D® and Hisorad® in comparison to previously known CPEs for the production of ODTs as well as for ODMTs. The new CPEs performed well especially regarding the incorporation of a hydrophobic drug. Hejduk et al. [88] examined twelve different CPEs for ODMTs and classified them into three levels by morphological and rheological factors. The best excipient for the used model API melatonin was Granfiller-D® 215, which was chosen according to the previously determined parameters.

In general, all CPEs were found to be suitable for the production of ODTs with individual advantages. The choice for an excipient has to be made with regard to the properties of the API and the desired product profile.

1.1.4.2. Lubrication systems

Lubrication describes the overall effect which leads to a reduction of the ejection force by minimizing the friction between the die wall and the tablet [89-91]. This can be achieved by the addition of lubricating ingredients, the use of lubrication methods during the manufacturing process or lubricating properties of the API itself. The need for lubrication is even more pronounced for the production of minitablets than for conventionally sized tablets due to the higher SVR.

1.1.4.2.1. Types of lubricants

The most commonly used lubricant is magnesium stearate (MgSt), a magnesium salt of stearic acid, mainly consisting of magnesium stearate and magnesium palmitate [92]. Several studies in literature propose the formation of a thin lubricant film on the surface of the particles [90, 93-96]. A study by Gunawardana et al. [97] recently rejected this hypothesis by SEM-EDS mapping as they found agglomerates of the lubricant on the tablet surface instead of the expected lubricant film. Blanco et al. [98] confirmed these findings as they also found a discontinuous MgSt layer on the excipient particles. Obviously, no full coverage of the powder particles or the tablet surface is required for the lubrication effect.

Elevated ejection forces can lead to capping or lamination of the produced tablets, sticking of powder particles on the punches or abrasion of the tableting tools [94, 99, 100]. MgSt is cost-effective and shows good lubrication efficiency, but on the other hand, the negative effects of MgSt have to be considered. MgSt can lead to a decrease in tensile strength and prolonged disintegration and dissolution processes [90, 93, 101-107], which can be especially critical for orodispersible tablets. To avoid these effects, Martinez-Acevedo et al. [108] modified MgSt into solid lipid nanoparticles, but this technique has not been applied in the industrial practice yet. The modified MgSt achieved superior tabletability and lubrication efficiency together with a less pronounced delay in the disintegration time.

Many alternative lubricants have been studied in the literature and compared with magnesium stearate. Next to MgSt, sodium stearyl fumarate (SSF) is the most favorable lubricant, especially due to its lower hydrophobicity compared to MgSt. Hölzer and Sjörgen [109] found SSF to be at least as effective as MgSt with comparable effects on the disintegration time and hardness of the tablets. Shah et al. [110] also tested the influence of the lubricants on the dissolution rate and obtained the fastest dissolution with SSF. A study by Soulairol et al. [111] also confirmed the superiority of SSF for ODMTs with regard to the disintegration time.

Stearic acid (SA) can also act as a lubricant and was studied by Paul and Sun [112] in regard of the lubricant concentration and in combination with a material with either plastic or brittle deformation. They stated that MgSt is slightly more effective than SSF or SA due to its higher plasticity. However, this also leads to a more pronounced negative effect on the tensile strength.

Yu and Nie [113] evaluated sodium and calcium stearate besides MgSt for the use as lubricants in tablet formulations. While calcium stearate did not offer sufficient lubrication efficiency, sodium stearate showed a satisfactory performance and demonstrated comparable lubrication capability to MgSt, even at lower concentrations.

De Backere et al. [100] researched twelve alternative lubricants, including substances with varying hydrophobic and hydrophilic properties. They concluded that SSF and SA are the most promising alternatives to MgSt in regard to lubrication efficiency and the resulting CQAs of the tablets. The hydrophilic lubricants used in this study did not reveal a more favorable disintegration which was explained with the competition-for-water-hypothesis [114]. This theory states that soluble fillers require more water for the disintegration process. Also, hydrophobic APIs prolong the wetting of the tablet but on the other hand they do not interact with water molecules and so the water is available for the disintegration process. Originally this hypothesis was developed for fillers and filler-binder-mixtures, but de Backere et al. extended this to filler-lubricant interactions [100]. Deshmukh and Kapadia [115] investigated three different hydrophilic lubricants (SSF, PEG 6000 and behenoyl-polyoxyl-9 glycerides) in comparison to the non-lubricated form of the granules. They declared all lubricants as effective for their use in tablet formulations, considering their impact on mechanical properties, disintegration and dissolution rate. Sodium lauryl sulfate, which is usually used as a surfactant, also has lubricating properties, but is necessary in higher amounts than MgSt and shows longer disintegration [100, 116, 117] and dissolution behavior [118]. Glyceryl dibehenate also revealed good disintegration times [100, 110, 119] but requires higher concentrations to be effective as a lubricant. Poloxamers showed no superiority to MgSt in regard of lubrication efficiency but show less negative effects on the hardness of the resulting tablets [100, 120, 121]. Sucrose fatty acid esters can also be an alternative to MgSt [100, 122], but their performance is dependent on their HLB-value (hydrophilic-lipophilic balance) which should be relatively low [123]. Zheng et al. [124] examined the influence of four lubricants (MgSt, SA, SLS and hydrogenated castor oil) on orodispersible tablets. Only MgSt significantly reduced the TS of the ODTs, if it was used in a concentration of more than 1%, but also showed the best lubrication efficiency. The effect of MgSt on the disintegration time was also dependent on the used disintegrant, as tablets with crospovidone exhibited a greater sensitivity to MgSt than tablets with sodium starch glycolate (SSG). Another study [125] found that alternative lubricants like glyceryl behenate, talc, PEG 6000 and SA did not perform better in comparison to MgSt. Only hexagonal boron nitride revealed results comparable to MgSt, suggesting its potential as an alternative lubricant. Talc which is normally used as an anti-sticking agent, can also be utilized as a lubricant [126], but is needed with a small mean particle size in order to be effective as a lubricant [127].

All these alternative substances can be used as lubricants if negative effects of MgSt are quite pronounced or MgSt shows incompatibilities with other tablet excipients, whereby SSF is used most frequently besides MgSt.

1.1.4.2.2. Different lubrication methods

1.1.4.2.2.1. Internal lubrication

In the pharmaceutical industry, internal lubrication is still the standard. The lubricant is added to the remaining components in the last mixing step. The powder is only blended for a short time to avoid so-called “overlubrication”, as the mixing time of the lubricated blend is a critical factor. A longer blending time can reduce the tablet tensile strength and prolong the disintegration and dissolution of the tablet significantly [93, 128-133]. Barrocas et al. [134] studied the effect of overlubrication on powder blends for capsule filling. They found a correlation between the wettability of the powder, the blending mechanism (shear or diffusion mixing) and the dissolution profile whereas the disintegration testing was not sufficient to predict failures in the dissolution performance. Negative effects, in particular, decreased tablet hardness, prolonged disintegration and dissolution times, can result from an excessive amount of lubricant in the powder mixture [90, 100, 102, 135]. Paul and Sun [102] studied the effect of MgSt on the brittleness of tablets and found a decreased TS and increased tablet brittleness index (TBI) which was even more pronounced for longer blending times and higher concentrations of the lubricant, which confirmed older studies from the 1950s [101]. Bolhuis et al. [93] observed an interaction between the tablet disintegrant and the lubricant and compared SSG, a disintegrant with a strong swelling behavior, with potato starch with low swelling properties. Tablets with SSG showed less prolongation of the disintegration time by MgSt, which was explained by the stronger swelling behavior of SSG, which destroyed the MgSt film on the tablet. On the other hand, potato starch did not swell sufficiently to damage the lubricant film, therefore the impact of the lubricant on the disintegration time was more pronounced.

The impact of the lubrication system also depends on the tablet formulation and its deformation behavior. Jarosz and Parrott [107] studied the influence of different lubricants on four different substances. Materials with plastic deformation, for example microcrystalline cellulose were much more sensitive to the addition of lubricants. This can be explained by the areas available for bonding which are mostly covered by the lubricant for plastic materials and leads to a weakened bonding between the single particles. For brittle materials, this is not the case as fragmentation occurs during deformation and offers new areas on the powder particles, which are not covered with MgSt and thus can exhibit a stronger bond [104]. These findings were also confirmed by several other studies [94, 103, 136].

Besides the previously mentioned parameters, other factors can have an impact on the lubrication efficiency, as some studies suggest an influence of the crystal structure [137] and particle size [138-140] on the lubrication efficiency of MgSt.

1.1.4.2.2.2. External lubrication

In contrast to internal lubrication, external lubrication does not use a lubricant in the tableting blend but applies the lubricant onto the surface of the tooling system only (Figure 2).

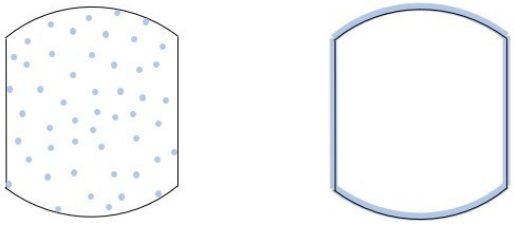


Figure 2: Schematic drawing of internal lubrication (left) and external lubrication (right) with full surface coverage, blue color presents MgSt particles

The external lubrication concept was intensively investigated on conventional tablets in several research papers [141-146]. Jahn and Steffens [141] used a press chamber coating system patented by Hinzpeter et al. [147] where the lubricant was transported by a double screw feeder and sprayed continuously onto the upper and lower punch with permanent removal of the excessive MgSt. The authors successfully produced tablets with the described system which had sufficient tensile strength and a much lower MgSt content of 0.032 – 0.046% compared to the need for internal lubrication. Another study by Kamiya et al. [142] investigated different process parameters and highlighted the spray rate, tableting speed and air flow volume of the dust collector as the most significant factors regarding the MgSt content. On the other hand, these parameters did not significantly affect the disintegration time of the produced tablets. Moreover, they could successfully predict the MgSt content from the above mentioned process parameters by multiple regression analysis. Otsuka et al. [146] demonstrated that tablets with external lubrication with MgSt showed a faster disintegration and dissolution behavior compared to internal lubrication.

Yamamura et al. [144] studied an external lubrication system with an API-containing formulation and examined the distribution of MgSt on the tablet surface by scanning electron microscopy. Additionally, they charged the lubricant powder electrically to improve the adhesion of MgSt on the punch and die surfaces.

A disadvantage of external lubrication can be the reduced wettability and therefore decreased adhesion of a coating layer which was studied by Kondo et al. [143]. The authors found no correlation between the sprayed amount of lubricant and adhesion force of the film coating and produced tablets with an evenly distributed lubricant layer. Externally lubricated tablets were superior to internally lubricated ones, as the latter showed agglomerates of the lubricant, resulting in peeling of the coating film.

Another disadvantage of the external lubrication of the punches with compressed air is the high need of the lubricant (100 – 750 g/h [141]). Most of the lubricant is removed by an exhaust system and cannot be reused. While MgSt is relatively cheap, the use of alternative lubricants can become quite cost intensive for external lubrication. De Backere et al. [148] studied the suitability of six different lubricants for this purpose. All lubricants revealed in tablets with relatively similar tensile strengths and disintegration times. Only the reference tablets with internal lubrication showed differences in the critical tablets properties and revealed higher disintegration times, especially for hydrophilic lubricants (poloxamer 188 and sucrose monopalmitate) which can be explained by the competition-for-water hypothesis [114].

A novel approach can be the distribution of the lubricant on the punches by electrostatic charging which was studied by Zimmermann et al. [149]. The authors investigated three different lubricants (MgSt, SA and PEG 6000) and could show a sufficiently high charge of the powder by corona charging, which is already used in other pharmaceutical applications like dry coating [150]. MgSt turned out to be the most promising lubricant for this process as the charge accumulation was stable for hours and resulted in tablets with a higher TS than internally lubricated ones. Applying the lubricant on the lower punches was more effective in regard to reduction of the ejection force compared to application on the upper punch. This concept can be an interesting alternative for external lubrication compared to spraying the lubricant with compressed air but is still quite new and requires more research.

Another way of external lubrication is the use of MgSt suspensions for application on the punches, which also has been used in literature [151-157]. Here, a suspension with a MgSt concentration of 3 – 5% and a volatile solvent such as acetone, isopropanol or ethanol is applied on the punches and dried prior to tableting. Xiang and Sun [157] observed increased punch sticking of APIs using a MgSt suspension at lower, but not at higher compaction pressures, which could be explained by force interactions between the punch, the API and the lubricant. However, this lubrication method is associated with the risk of residual solvent being present in the tablets.

1.1.4.2.2.3. Feed frame lubrication

A novel approach of lubrication is the feed frame lubrication described by Brands et al. [158]. It utilizes the blending capacity of the feed frame of a rotary press [159] to skip the additional lubricant blending step and can be especially of interest for continuous manufacturing processes. Using this method, tablets with higher tensile strengths and shorter disintegration times were obtained compared to the internal lubrication method.

1.1.4.3. Disintegrants

Most of the marketed ready-to-use excipients for ODTs (see Table 1) contain a disintegrant to accelerate the disintegration process of the tablet and ensure that the specifications according to Ph. Eur. / USP will be met. The used disintegrants predominantly have a huge potency for facilitating the loss of tablet integrity and are therefore often called “superdisintegrants”.

Disintegrants are insoluble in water and facilitate the intake of water into the tablet leading to its disintegration. The disintegrants can be classified according to their disintegration mechanism: for crospovidone shape recovery is proposed, for croscarmellose sodium and sodium starch glycolate it is hypothesized that they act by swelling [160]. Disintegrants that work through shape recovery, are subjected to plastic deformation during the compression process and then exhibit elastic recovery upon contact with water [161]. They also show a higher disintegrability with higher compression forces while swelling disintegrants do not show this behavior. Swelling disintegrants, especially starch- and cellulose-based excipients, demonstrate an increased water uptake and expansion in their particle sizes compared to those working by shape recovery [160, 161].

Furthermore, the filler has a huge impact on disintegration and the underlying mechanism. Fillers made of a highly water soluble material (e.g. mannitol) show a dissolution controlled behavior and disintegration times depend on the porosity of the tablet [162].

Soulairol et al. [111] examined the impact of different superdisintegrants (crospovidone, carboxymethylellulose, carboxymethyl sodium starch and calcium alginate) in varying concentrations on the development of placebo ODMTs consisting of mannitol and MCC. They reported no significant influence on the tablet properties, regardless of whether MgSt or SSF was added internally as a lubricant. According to their data, they recommend the use of crospovidone for ODMTs as this superdisintegrant led to the fastest disintegration.

1.1.5. Disintegration testing for ODMTs

The Ph. Eur. does not describe a dedicated disintegration test designed for orodispersible tablets or minitablets, and just specifies a disintegration time of 3 min to justify the attribute “orodispersible”. Hence, different non-compendial disintegration tests have been established in literature for orodispersible (mini-)tablets:

For screening of different formulations, preliminary tests like the simulated wetting test can be used [22, 163] and describe the time needed to wet the entire surface of the tablet but do not represent realistic conditions.

Hermes [164] developed a disintegration tester especially for minitablets with an automated endpoint detection by measuring the electrical resistance. Additionally, a force is applied on the minitablet which imitates the force of the human tongue. To achieve more realistic physiological conditions, a biorelevant medium mimicking the saliva properties was developed. Its application with the self-designed tester showed quite good correlation with *in-vivo* data.

Kleinebudde [165] designed a test for granules, which can be used for minitablets [35, 79, 83]. It presents only a slight modification of the Ph. Eur. disintegration test by the addition of weighted Plexiglas® cyclinders with mesh sieves of 710 µm. In general, a smaller mesh size is recommended for minitablets [166] as otherwise they could quickly pass the mesh defined in the Ph. Eur. while remaining almost intact.

The OD mate, a commercially available disintegration tester by the Japanese company Higuchi Inc., was originally developed by Kakutani et al. [167] and applies a force on the tablet through a weight imitating the force of the human tongue. The disintegration time is defined as the time the inner weight needs to move a predefined distance when the tablet is positioned on a mesh and immersed in the disintegration medium. Sieber et al. [168] compared the OD-mate and the Hermes tester to the pharmacopeial disintegration test and qualified both apparatuses as better suitable for ODMTs, while the OD-mate was also suitable for normally sized tablets.

In literature, several approaches can be found to modify the volume used for disintegration testing, as the available amount of liquid in the oral cavity is usually less than 5 ml [169, 170] and therefore far away from the volume used in the Ph. Eur. test (volume not defined, but the use of a 1000 ml beaker is specified). Hooper et al. [171] developed a modified simulated wetting test utilizing a liquid volume of 1.5 ml and a material for absorbing the liquid to imitate the conditions within the mouth cavity.

A modified method based on the test by Abdelbary et al. [172], where a force is applied on the minitablet and only 1 ml medium is used to wet the tablet, was applied by Soulairol et al. [111] for ODMT disintegration testing. The authors pleaded for the use of biorelevant disintegration media, as they found a discrepancy between the determined *in-vivo* data and the disintegration test with distilled water and reached better agreement with the use of simulated salivary fluid. The Texture Analyzer can also be used for disintegration tests, for example by El-Arini and Clas [173] and many other authors which were summarized in a recent review by Bogdan et al. [174]. Either a constant force or speed can be applied to obtain a displacement-time or force-time diagram and the disintegration time can be calculated. With the use of artificial saliva and the modified method according to Abdelbary et al., good correlation between *in-vitro* and *in-vivo* data was achieved [172].

Desai et al. [175] developed an oral cavity model which imitates movements of the tongue. This model was capable of describing the mechanism of ODT disintegration instead of just measuring a single timepoint for disintegration. Here, less variability of the disintegration data was present, but the disintegration times were much longer than the 3 min specified in the Ph. Eur.

1.2. Model APIs

1.2.1. Zolmitriptan

Zolmitriptan was chosen as a model API in this work and belongs to the group of triptans targeting the 5-HT_{1B}- and 5-HT_{1D}-receptors as a selective serotonin agonist [176]. It is indicated for the acute therapy of migraine attacks with and without aura for patients older than 18 years and is available on the market as a coated tablet, orodispersible tablet or nasal spray. As a BCS class III drug, it exhibits a high water solubility (1.3 mg/ml) besides a low permeability [177]. The dose for the initial treatment is 2.5 mg, if this does not relieve the symptoms, an increased dose of 5 mg can be given for the next treatment. The application as an orodispersible tablet may be advantageous, as many patients suffer from associated symptoms including nausea which can hamper the swallowing process of tablets. Orodispersible (mini-)tablets offer a fast disintegration process and can lead to improved bioavailability of the API [9] and improved swallowability and acceptability (see chapter 1.1.3.). Therefore, zolmitriptan should be formulated as an ODMT in this work. By reducing the diameter and using orodispersible excipients the compliance of patients might be increased, especially for patients with nausea. Moreover, the tablets available on the market belong to low-dosed dosage forms (<25 mg dose strength and <25% drug load, Ph. Eur. 2.9.40). The lower the drug content, the more challenging it is to meet the specifications of Ph. Eur. 2.9.40 and to achieve a target AV value below 15. By using the concept of minitablets this problem may be overcome as the API mass has a higher percentage in a smaller tablet.

1.2.2. Naproxen

As a second model API, naproxen was chosen due to its poor solubility in water in contrast to zolmitriptan. Naproxen is a non-steroidal, anti-inflammatory drug and inhibits the formation of prostaglandins by inhibition of cyclooxygenases [178]. Thus, naproxen is used for the treatment of acute pain and inflammatory diseases and is available on the market with doses of 250, 500 and 750 mg. At the moment, no orodispersible formulation of naproxen is available on the market, but naproxen has been formulated into orodispersible films in literature [179]. Other analgetic APIs, especially ibuprofen, are often formulated into OD(M)Ts [14, 83, 180, 181] to address swallowing issues. However, achieving the target dose may require a large number of minitablets. Compared to zolmitriptan, the solubility (15.9 µg/ml) is considerably lower and naproxen is classified as a BCS class

II drug (low solubility and high permeability) [182]. Therefore, the development of orodispersible tablets is even more challenging as hydrophobic APIs may reduce the wetting of the tablet and impact the disintegration and dissolution process.

1.2.3. Ibuprofen

Ibuprofen is the first choice API in the treatment of acute headache and pain and is a non-steroidal, anti-inflammatory drug. It is well known in literature, especially for its sticking problems and other issues in tableting [183-187] due to the low melting temperature (78°C) which can be even lowered by the interaction with the lubricant [99] and when zones of localized high temperatures are formed during tableting [188]. Therefore, it was chosen as a suitable model substance to test the effect of lubricants which should prevent sticking. As a BCS class II drug, it also has a poor water solubility of 21 µg/ml [182] and therefore makes the development of an orodispersible tablet with a fast disintegration time more challenging.

1.3. Concepts and approaches in formulation development

Different approaches can be distinguished in formulation development: The experimental, iterative strategy which results in a suitable, but not necessarily optimal formulation and the knowledge-based approach which requires a previous characterization of the excipients and APIs [189] and can implement this data in expert systems. Moreover, the Quality by Design concept (QbD) provides a systematic approach to formulation development applying methods such as experimental design.

1.3.1. Iterative approach

In an iterative approach, similar steps are repeated multiple times to approximate a solution. In formulation development it aims at the optimization of the formulation to obtain the desired product quality by changing only one factor at a time (OFAT). This approach consumes a lot of time and resources which are especially scarce at the beginning of the drug product development process [190]. Additionally, it is not capable of the identification of interactions between the investigated factors as they are studied separately [191]. Nevertheless, the approach is used for the formulation development in literature for example for ODTs [192] or also for minitablets [12]. It offers flexibility when facing unexpected problems and allows adaptations while creating new knowledge [193].

1.3.2. Design Space as part of the Quality by Design concept

The Quality by Design (QbD) concept states that quality can be designed into a product. The concept was first established by Juran [194] and later introduced into pharmaceutical manufacturing by the FDA [195]. In the annex of the ICH Q8 Guideline QbD was defined as a “systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management” [196].

First, a Quality Target Product Profile (QTPP) has to be created which prospectively summarizes the key characteristics of the ideal dosage form under consideration of the safety and efficacy of the overall product. For the QTPP, Critical Quality Attributes (CQAs) need to be defined e.g. the dosage form and dose strength, the mechanical tablet properties (mass, thickness, friability etc.) or pharmacokinetic parameters. In the next step, Critical Material Attributes (CMAs) will be determined and Critical Product Parameters (CPPs) will be identified. The relationship between the CMAs and the CPPs has to be elaborated for a better process understanding and a risk assessment will be performed. Therefore, a Design Space should be implemented as a multidimensional combination of the CMAs and CPPs which are critical for the quality of the product. The Design Space can be expressed as a range of CMAs and CPPs or by a mathematical model for either one or several unit operations by Design of Experiments (DoE). The implementation of a design space gives the marketing authorization holder the flexibility to change parameters within the design space without the need of resubmission of regulatory documents. Further elements like process analytical technologies (PAT) can be used in addition to knowledge from previous experiments [197].

Several publications address the systematic development of ODTs [198-200] and ODMTs [201-204] applying the DoE approach.

1.3.3. Expert systems

The following three approaches all represent different kind of expert systems, which try to solve complex issues by using the expertise like a specialist in this field [205]. Expert systems comprise a knowledge database as well as an interference mechanism enabling the user to add new knowledge and interact with the database, facilitating the generation of novel conclusions and recommendations by the expert system [206].

1.3.3.1. Expert system according to Herbert Stricker

Stricker described general aspects of formulation development and proposed a division in different processing steps [189]: First, a product requirement profile is created which specifies the optimal properties and their acceptable range including the characteristics of intermediate products such as granules intended for tablet compression. In the next step, development problems, steps and actions are defined with consideration of the order of the development problems to minimize the need for step backs to previous steps. Afterwards, the product properties are standardized into dimensionless numbers under consideration of the acceptable ranges. If necessary, a weighting factor can be applied to properties with a greater importance.

The proposed expert system, also named as the Galenical Development System Heidelberg (GSH) was initiated by Stricker et al. [207] and is applicable for the development of powders for capsules, granules, pellets and tablets with or without functional coatings. It was further developed by other authors for its application of other dosage forms like injectables [208] or the use of artificial neural networks [209].

For the development of tablets by direct compression, Stricker proceeded according to the aforementioned steps. In his book, he defined the requirements for the powder blends (e.g. sufficient flowability, adhesion on the punches, blend homogeneity), the API (e.g. adhesion, ejection constant, wettability, flowability, bulk density) and the resulting tablets (e.g. dose, disintegration time, dissolution, friability, hardness, ejection force) [189]. For each parameter optimal values and acceptable ranges were defined with regard to the predefined product profile, some of the parameters, such as tablet hardness, may be defined as exclusion criteria if they are not fulfilled. Possible problems during development are listed and potential solutions or alternatives are presented. For example, blend uniformity issues may arise during development, prompting the initiation of a new development run with an altered API particle size. Another problem might be variations in tablet mass, which can be solved by the addition of glidants (e.g. fumed silica) or, if that does not improve the flowability sufficiently, a previous granulation step. The adhesion of powder on the tooling system may be another challenge in the formulation development. As the adhesion of the raw materials cannot be determined sufficiently in practice, a lubricant should be added in any case, however, negative effects such as prolonged disintegration or reduced tablet hardness should be kept in mind.

Overall, the approach of Stricker described steps similar to the formulation development by the QbD concept, prior to the FDA's introduction of the term to the pharmaceutical industry. However, this expert system currently does not include specific criteria and models for both minitablets or orodispersible tablets.

1.3.3.2. Sediment Delivery Model (SeDeM)

Initially, the SeDeM system has been introduced by Suñe-Negre et al. [210] in 2005 and presented a novel approach for the formulation development by characterizing different properties of the individual components. Since then, it was implemented for several drug formulation studies in literature [211-214] and also used for the control of different API batches [215] or the evaluation of novel tablet punches [216]. Table 2 lists the 12 parameters used in the SeDeM system to describe the powder characteristics.

Incidence factor	Parameter	Symbol
Dimension	Bulk Density	Da
	Tapped Density	Dc
Compressibility	Inter-Particle Porosity	Ie
	Carr Index	IC
	Cohesion Index	Icd
Flowability	Hausner Ratio	IH
	Angle of Repose	(α)
	Powder Flow	t´´
Lubricity/ Stability	Loss on Drying	%HR
	Hygroscopicity	%H
Lubricity/ Dosage	Particles < 50 µm	%Pf
	Homogeneity Index	Iθ

Table 2: Parameters of the SeDeM system [210, 215]

Aguilar-Diaz [217] continued the development of the SeDeM system and extended the system with an orodispersibility factor for the development of ODTs. Three further parameters (disintegration time with a disk, disintegration time without a disk and effervescence) were implemented for the filler to determine the most suitable excipient for ibuprofen ODTs. This proposed ODT system was successfully used by other authors [180, 218-220] for the development of ODTs with different APIs, even for a BCS class II drug substance.

In literature, the SeDeM system was also successfully combined with statistical experimental design [214] or other QbD elements [221] and can provide a more scientific approach to formulation development.

1.3.3.3. Zoomlab®

Zoomlab® is a digital formulation assistant developed by BASF, serving as a digital expert system for identifying suitable formulations and predicting tablet properties. After publication of the first version in 2019, other modules like content uniformity check, prediction of the dissolution profile, implementation of the Developability Classification System according to Butler and Dressman [222] or a formulation finder for topicals were gradually developed. Zoomlab® is a modification of the SeDeM system, but with adapted parameters and classifies the formulation according to the Manufacturing Classification System by Leane et al. [223]. The MCS groups the formulation into four different categories: direct compression, dry granulation, wet granulation and other technologies. For each of the processes properties of an ideal material are proposed and the creation of a centralized database

is suggested. Zoomlab® aims to address this issue by providing an online-database accessible for everyone upon free registration.

The parameters used in Zoomlab® are presented in Table 3 and rated with values between 0 (insufficient) to 10 (excellent). The ranking of the parameters is performed either with a linear relationship or proprietary evaluation methods by BASF [224].

	Abbreviation	**Parameter**	**Range (0 – 10)**
Particle size	d10	d_{10} value	0 – 100 µm
	d50	d_{50} value	0 – 150 µm
	d90	d_{90} value	1700 – 300 µm
	DSP	Distribution span	4 - 1
Powder density	DBU	Bulk density	0 – 1.0 g/ml
	DTA	Tapped density	0 – 1.0 g/ml
Flowability	CAR	Carr index	40 - 10
	HAR	Hausner ratio	1.6 – 1.1
	AOR	Angle of repose	65 – 25 °
Tabletability	CPR	Compaction pressure at a porosity of 0.15	2000 – 0 MPa
	CMP	Tensile strength at a porosity of 0.15	0 – 8.0 MPa
	TST100	Tensile strength at 100 MPa compaction pressure	0 – 8.0 MPa
	TST150	Tensile strength at 150 MPa compaction pressure	0 – 12.0 MPa
	TST250	Tensile strength at 250 MPa compaction pressure	0 – 12.0 MPa

Table 3: Parameters of Zoomlab® for evaluation of the processability of the API, excipients or powder blends [224] (The range for the d90 value was adopted from 1700 – 700 to 1700 – 300 µm, as a value of 700 µm did not result in a rating of 10, but 7.14 in the Zoomlab® Processability module)

The parameters in the categories particle size, powder density and flowability are determined according to pharmacopeial methods, while the tabletability values are calculated according to the model by Reynolds et al. [225].

The API or formulation is suitable for direct compression, if the parameters flowability, tabletability and processability are rated with a value higher than 5. If only the tabletability parameter is higher than 5, dry granulation remains a viable option, whereas wet granulation is also feasible if all parameters have values below 5. Comparable to the SeDeM system, the parameters are visualized in a radar chart which is exemplarily shown in Figure 3.

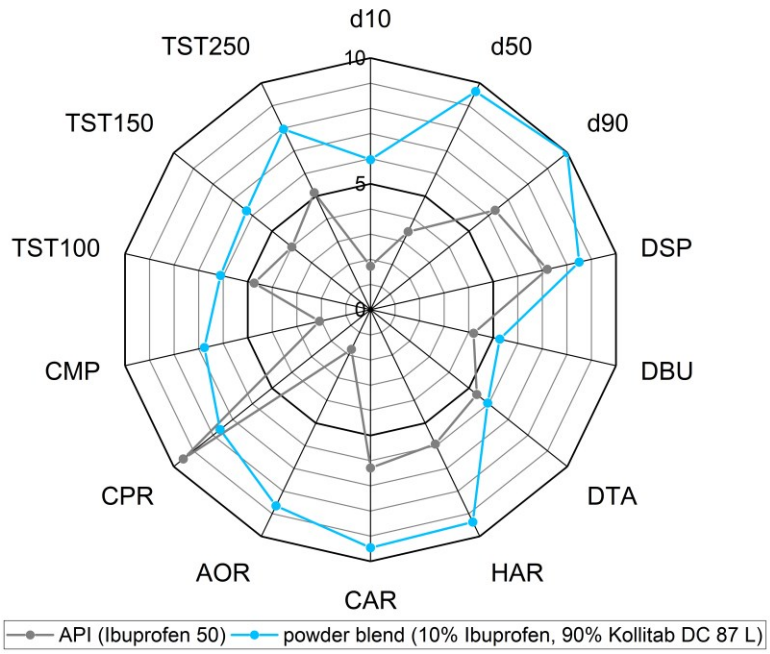


Figure 3: Exemplarily radar chart of Ibuprofen 50 as the API (10%, grey) and the powder blend consisting of 90% Kollitab™ (blue) using Zoomlab® data and software

However, the Zoomlab® software and the other expert systems do not include specific requirements for orodispersible minitablets such as disintegration time, differences in tablet size and the effect of different lubricant types and methods.

2. Aims and outline of the thesis

The objectives of this thesis are the assessment of formulation concepts for developing orodispersible minitablets and the impact of different lubrication methods on the manufacturing process and the resulting tablet properties of ODMTs. It is assumed that this dosage form is particularly affected by the lubrication system. Given the high surface-to-volume ratio of the minitablets, a greater impact of the lubricant can be expected, although this aspect has not been systematically studied yet. Subsequently, the gained knowledge of the impact of the lubrication system should be applied to the formulation development of ODMTs with their specific challenges.

In the first part, two of the most often used lubricants (MgSt and SSF) are studied comparatively regarding their lubrication efficiency and their impact on the disintegration times for five prevalent co-processed excipients for ODTs. The differences of minitablets with a diameter of 2 mm and conventionally sized tablets with a diameter of 11.28 mm should be elaborated in detail.

As external lubrication has gained increased attention in the pharmaceutical industry, this lubrication method should be systematically studied for minitablets for the first time using a compaction simulator. Suitable parameters for this lubrication system should be identified and its feasibility is evaluated for a multi-tip tooling with 19 tips per punch. Different positions of multi-tip dies are evaluated separately regarding their MgSt content, lubricant distribution on the surface and further critical quality attributes. Subsequently, the results of the compaction simulator should be compared to external lubrication on a rotary press.

Additionally, experiments with two newly introduced CPEs with integrated lubricants should be carried out to evaluate their applicability for ODMTs. They are compared with their physical mixtures containing internal lubrication, which are known to be susceptible to overlubrication. This comparison evaluates whether this issue can be mitigated by the new excipients.

As the initial experiments are performed with drug-free formulations, ODMTs containing the model drugs zolmitriptan and naproxen should be systematically developed and tested regarding their individual challenges related to the lubricant and its effect on the disintegration and dissolution behavior.

Finally, the influence of the lubricant on the prediction and modelling of tablet properties is assessed with the digital formulation assistant Zoomlab® and the suitability of this expert system for ODMT development is evaluated.

3. Results and discussion

3.1. Impact of the lubricant on the properties of ODTs of different sizes

Some parts of this chapter have already been published in the peer-reviewed journal *European Journal of Pharmaceutics and Biopharmaceutics*. The content was adapted for this chapter and additional data was added.

> Kuck, J., Breitkreutz, J. (2022), *Impact of lubrication on key properties of orodispersible minitablets in comparison to conventionally sized orodispersible tablets*, Eur J Pharm Biopharm, 180, 71-80

For normally sized tablets, the impact of lubrication was extensively studied in literature and a negative effect of MgSt on the tensile strength, disintegration and dissolution [90, 112, 226, 227] is reported. A dependency of the ejection force on the tablet diameter was suggested by Uzondo et al. [228], but was not followed up in their study, as they only used punches with 10 mm diameter.

A look into the literature for minitablets reveals that the used lubricant amount is usually higher than for conventionally sized tablets and ranges between 2 - 5% [22, 83, 164, 168, 229], but was always chosen without a systematic experimental approach as no studies have addressed the influence of lubricants for minitablets. As the surface-to-volume ratio is much higher for minitablets, it is presumed that they require different lubricant concentrations than normally sized tablets. Therefore, the first step for a rational formulation development was the characterization of the excipients and the resulting tablets with a special attention to their sensitivity to lubricants.

Hölzer and Sjögren [109] found a comparable reduction of the ejection force for 11.3 mm tablets for MgSt as well as for SSF. These findings were partly supported by Shah et al. [110] who also reported an equal decrease of the ejection force, but ranked MgSt higher in regard of lubrication efficiency. De Backere et al. [100] demonstrated a lower effective lubrication concentration for MgSt than for SSF for lactose tablets but could not find a relevant further reduction of the ejection force by the addition of more lubricant. Paul and Sun [112] noticed a superior lubrication efficiency of MgSt, as a concentration of 0.5% showed an ejection force reduction comparable to 1% SSF. These reports in literature led to the decision to use twice the amount of SSF (1, 2 and 4%) compared to MgSt (0.5, 1 and 2%) in this study. Two tablet sizes (2 and 11.28 mm) were produced with varying lubricant amounts and compared regarding their mechanical properties.

3.1.1. Powder characterization

First, the (co-processed) excipients were characterized regarding their powder properties. The excipients particle size and shape play an important role for the flowability, the compaction behavior and the resulting tablet properties [230-232]. Zhao et al. [20] suggested a maximum particle size of 1/3 of the die diameter for a successful minitablet production as otherwise the filling of the small die can be hampered and lead to mass variations. All used excipients fulfil this criterium for 2 mm minitablets as all d_{90} values are below 400 µm (Table 4). Except Ludiflash®, which is supplied as granules, all excipients show a narrow particle size distribution with a distribution span < 2. Regarding the mean particle size, Prosolv® ODT has the smallest (d_{50} = 73.8 µm) and galenIQ™ the largest particles (d_{50} = 184.4 µm). The tested lubricants have much smaller particles with a d_{50} of 7.8 µm (MgSt) and 14.9 µm (SSF), which will form a thin lubricant film on the bigger excipient particles [90, 102].

Excipient	d_{10} [µm]	d_{50} [µm]	d_{90} [µm]	distribution span
Ludiflash®	30.24	90.82	346.46	3.48
Parteck® ODT	49.18	156.15	343.15	1.88
Prosolv® ODT	28.56	73.80	148.41	1.62
galenIQ™	45.91	184.41	384.43	1.84
SuperTab® 50 ODT (abbr.: SuperTab® ODT)	60.40	125.40	217.43	1.25
MgSt	1.93	7.76	32.85	3.99
SSF	3.36	14.92	32.52	1.95

Table 4: Particle size distribution of the used CPEs and two lubricants, n = 3, mean ± SD

SEM images (Figure 4) revealed that the lubricant particles are formed as flat platelets with a relatively even surface (f and g), while most of the excipients (a – d) are irregularly shaped particles with a rough particle surface. SuperTab® ODT (e) stands out from the remaining excipients, as due to the manufacturing by spray drying [233] it consists of spherical particles. Compared to the other excipients, Prosolv® ODT (c) has a smoother particle surface which might result in a different need for lubrication.

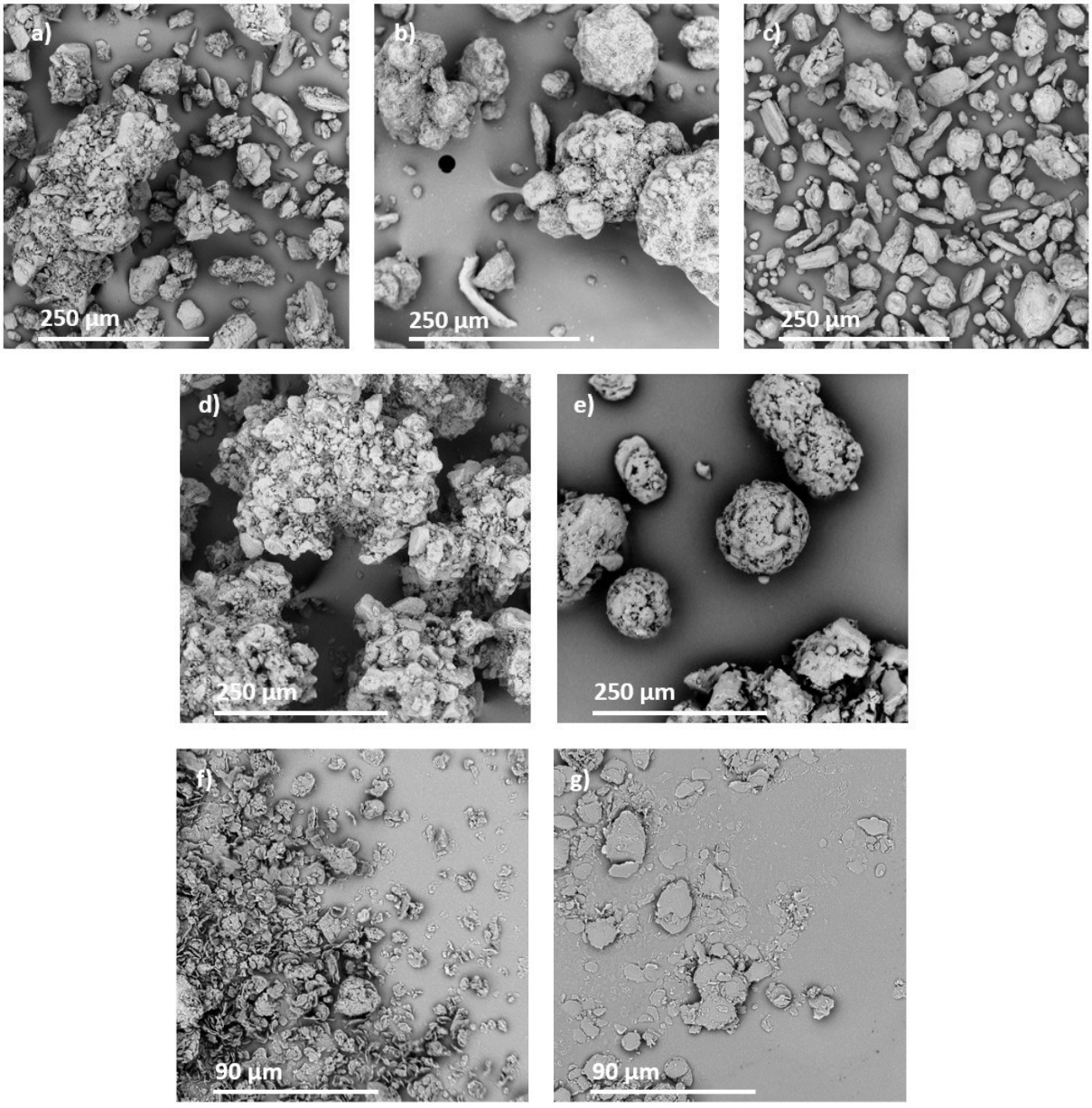


Figure 4: SEM images of the excipients (taken at 540x magnification), a) Ludiflash®, b) Parteck® ODT, c) Prosolv® ODT, d) galenIQ™, e) SuperTab® ODT and of the lubricants (taken at 1400x magnification), f) MgSt, g) SSF, scale bars are given in the illustration

Table 5 presents an overview of the specific surface area of the used excipients and lubricants, determined according to the BET theory, as the specific surface area can influence the flowability or the bonding of the particles [234]. Especially Parteck® ODT stands out as the specific surface area is much higher than for the other excipients due to the manufacturing by spray-granulation [235]. All other excipients range in a similar field around 0.5 m^2/g. The lubricants show a higher specific surface area, as they also consist of much smaller particles. With smaller particle size and higher specific surface area, a better lubrication efficiency is achieved, but also the decrease in tensile strength is

more pronounced [100, 127, 138]. In this case, MgSt is expected to demonstrate superior lubricating behavior. The measurement of the specific surface area of MgSt showed the highest deviations, as the BET methodology may not be the best method for the determination of the specific surface area of MgSt as it depends on the initial water content [236].

Excipient	Specific surface area [m^2/g]
Ludiflash®	0.43 ± 0.00
Parteck® ODT	2.78 ± 0.07
Prosolv® ODT	0.52 ± 0.01
galenIQ™	0.46 ± 0.00
SuperTab® ODT	0.22 ± 0.04
MgSt	14.77 ± 1.50
SSF	2.55 ± 0.11

Table 5: Specific surface area of the used CPEs and the two lubricants, n = 3, mean ± SD

The flowability of the excipients is crucial for the CQAs of the tablets, as problems with the uniformity of mass and content can occur if no appropriate powder flowability is given [237]. To ensure proper die filling, the particles should not be too small, as they may exhibit poor flowability, which will be especially critical for filling the narrow dies for minitablets [20]. All tested excipients should be suitable for direct compression, as they exhibited good flowability according to their Hausner ratios (HAR ≤ 1.18, according to Ph. Eur. 2.9.36), shown in Table 6. According to the angle of repose, Prosolv® ODT and SuperTab® ODT are even classified as powders with excellent flow properties. This can be attributed to the presence of fumed silica in Prosolv® ODT and the spherical shape of the particles in SuperTab® ODT.

Excipient	Angle of repose [°]	Hausner ratio
Ludiflash®	32.6 ± 1.4	1.18 ± 0.03
Parteck® ODT	30.7 ± 1.0	1.16 ± 0.02
Prosolv® ODT	29.8 ± 0.5	1.18 ± 0.02
galenIQ™	32.3 ± 1.9	1.17 ± 0.00
SuperTab® ODT	27.8 ± 0.5	1.12 ± 0.01

Table 6: Flowability properties of the used CPEs, n = 3, mean ± SD

Tranova et al. [226] studied the flowability of the lubricated powders and demonstrated a superior flowability of powders lubricated with MgSt compared with SSF. For Prosolv® ODT and Ludiflash®, a deterioration of the flow properties was found with rising lubricant concentration. This finding confirmed a previous study on the effect of MgSt on the flow properties [238].

The variations in the tablet mass also represent an indicator for the flowability. For the tablets described in chapter 3.1.2, it was max. 5% for the 2 mm minitablets, for the 11.28 mm ODT a max. mass variation of 3% occurred (n = 10), which can also be attributed to the manual die filling but is still acceptable. The Ph. Eur. 2.9.5. (Uniformity of mass of single-dose preparations) defines a max. deviation of 10% from the mean value for tablets < 80 mg and a deviation of 5% for > 250 mg (for n = 20).

3.1.2. Influence on tabletability

The elasticity and specific plastic energy for external lubrication and the highest MgSt concentration (4%) were compared to the same and double amount of SSF (2 and 4%). This comparison was made to test the hypothesis, if twice the amount of SSF is needed compared to MgSt to achieve similar tablet properties (see 3.1). The specific plastic energy (SPE) describes the work in relation to the tablet mass which is consumed for the deformation of the tableting material. In most cases, the SPE for varying tablet sizes was comparable, which was already described in literature [18]. The 11.28 mm tablets showed the highest SPE for the external lubrication (except for Prosolv® ODT), suggesting a higher tensile strength as no lubricant should be present in the inside of the tablet which can hamper the bonding of the particles (Figure 5). On the contrary, the SPE exhibits the lowest values for external lubrication of 2 mm minitablets (for Ludiflash®, Parteck® ODT and galenIQ™). This can be attributed to a presumably higher relative percentage of MgSt due to the lower total weight of the minitablets.

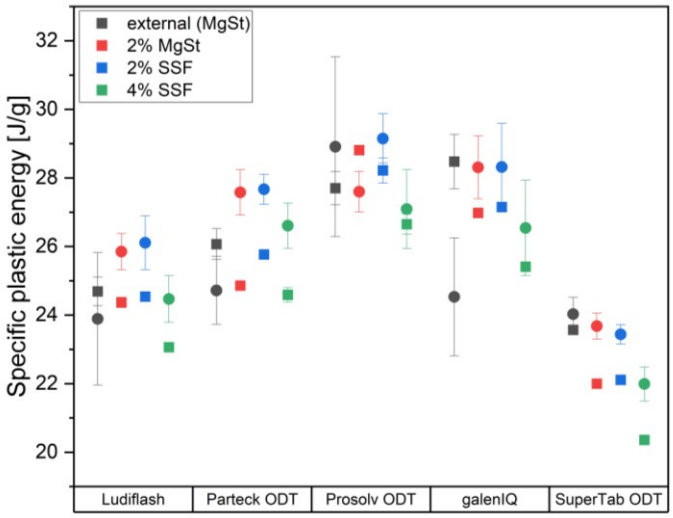


Figure 5: Specific plastic energy of all CPEs with selected lubrication methods, tableted on Styl'One compaction simulator at 200 MPa, ■ represent 11.28 mm ODTs (single tip), ● represent 2 mm ODMTs (19-tip), n = 10, mean ± SD

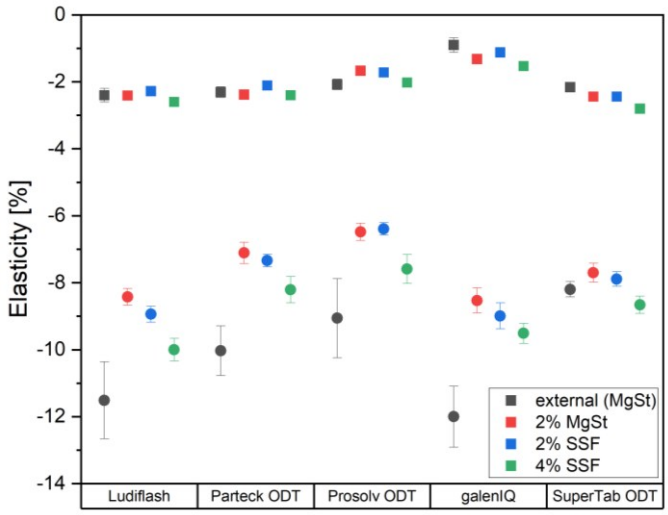


Figure 6: Elasticity of all CPEs with selected lubrication methods, tableted on Styl'One compaction simulator at 200 MPa, ■ represent 11.28 mm ODTs (single tip), ● represent 2 mm ODMTs (19-tip), n = 10, mean ± SD

This trend is also evident in Figure 6, as the elasticity showed the highest values for the external lubrication of the 2 mm minitablets indicating that external lubrication affects the deformation behavior of minitablets much more compared to its application for conventionally sized tablets. A high elastic recovery can be disadvantageous as the bonding between the particles is decreased and results in tablets with a lower tensile strength or other tablet defects [91, 239].

A comparison of MgSt and SSF did not reveal a general superiority of one lubricant regarding the deformation behavior and showed comparable values for the same concentrations. Therefore, a similar effect of both lubricants on the tensile strength can be expected.

The tabletability plots (Figure 7 - Figure 11) reveal a lubricant sensitivity, especially for the mannitol-based CPEs (Ludiflash®, Parteck® ODT and Prosolv® ODT) compared to isomalt (galenIQ™) and lactose (SuperTab® ODT). This effect was most pronounced for Prosolv® ODT, which contains the plastically deforming MCC. Numerous studies outlined the increased lubricant sensitivity on plastic substances compared to brittle materials [94, 107, 112, 136]. New, non-lubricated surfaces are formed through fragmentation during brittle deformation which can form strong inter-particle bonds, while for plastic materials all surfaces are occupied with the lubricant and lead to a weakened particle bonding. The brittle behavior of lactose can explain the different sensitivity of SuperTab® ODT to the lubricant. Furthermore, the adhesion tendency could be a reason for the higher lubricant sensitivity of mannitol-based excipients. It can be determined by the electrostatic charge which was found to be higher for mannitol than for isomalt [240] and lactose [241].

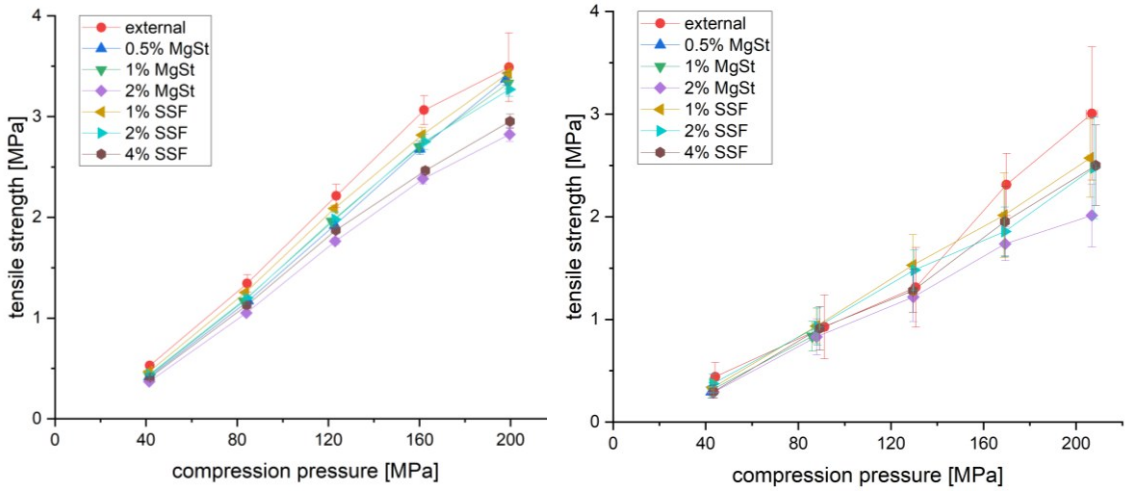


Figure 7: Tabletability of Ludiflash® 11.28 mm ODTs (left, single tip) and 2 mm ODMTs (right, 19-tip), tableted on Styl'One compaction simulator, n = 10, mean ± SD

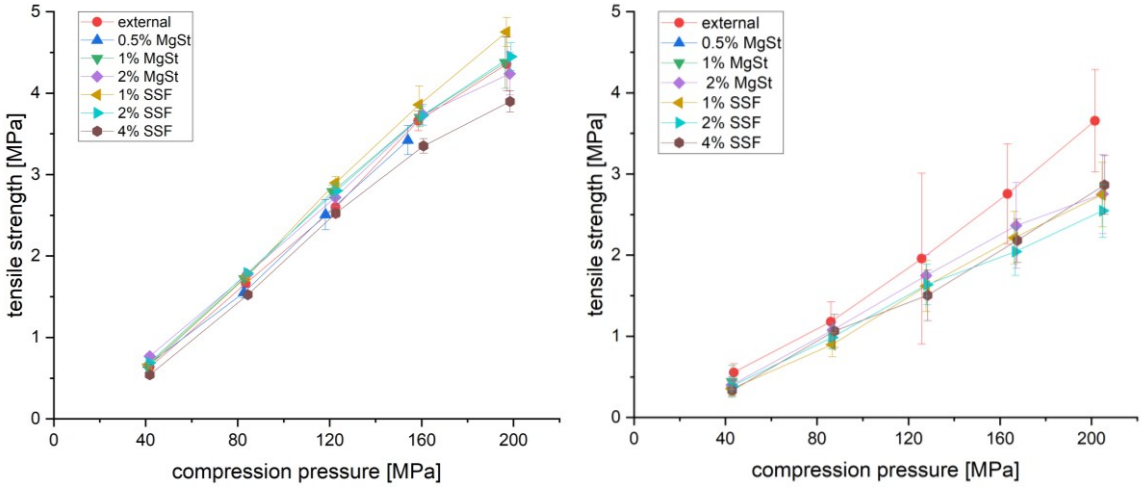


Figure 8: Tabletability of Parteck® ODT 11.28 mm ODTs (left, single tip) and 2 mm ODMTs (right, 19-tip), tableted on Styl'One compaction simulator, n = 10, mean ± SD

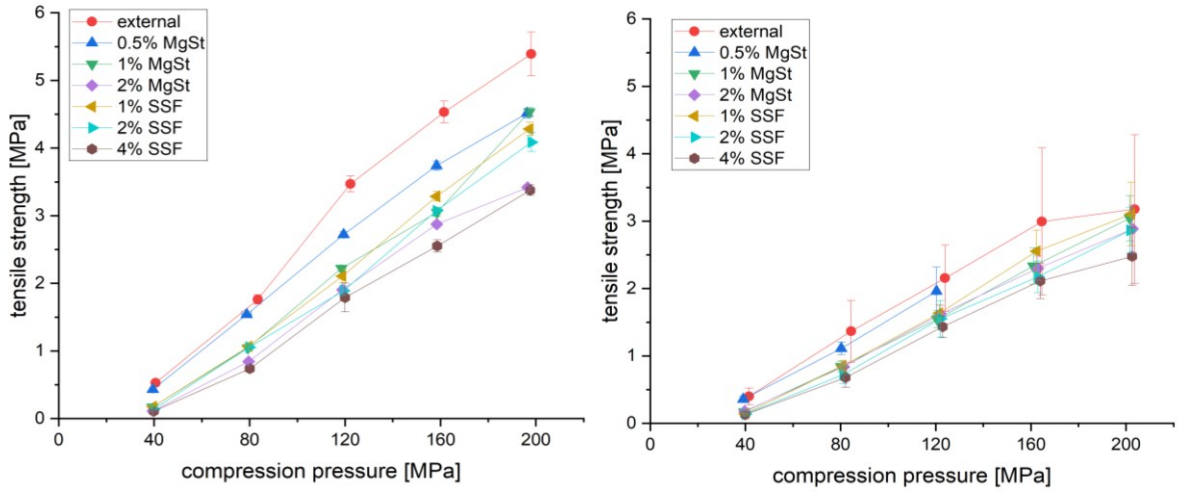


Figure 9: Tabletability of Prosolv® ODT 11.28 mm ODTs (left, single-tip) and 2 mm ODMTs (right, 19-tip), tableted on Styl'One compaction simulator, n = 10, mean ± SD

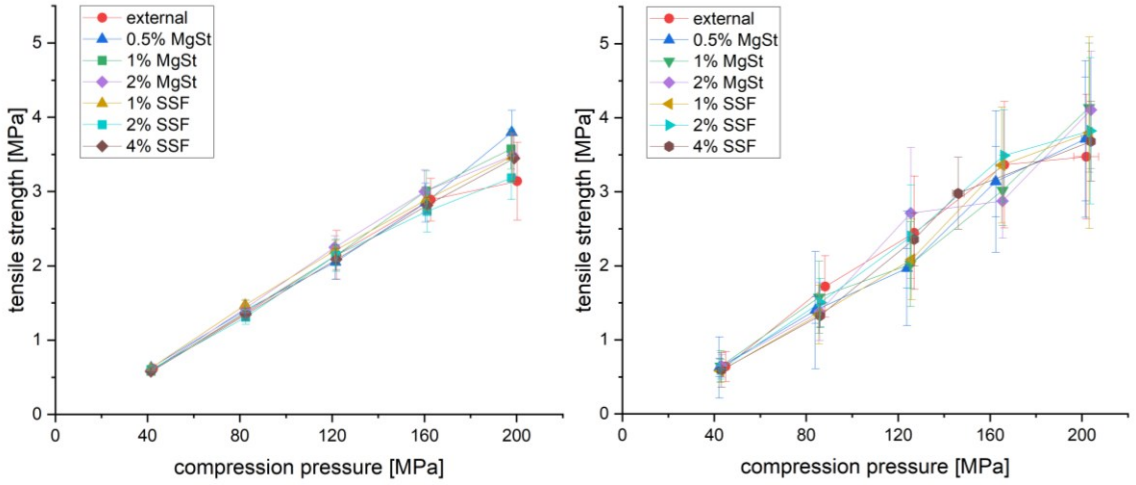


Figure 10: Tabletability of galenIQ™ 11.28 mm ODTs (left, single tip) and 2 mm ODMTs (right, 19-tip), tableted on Styl'One compaction simulator, n = 10, mean ± SD

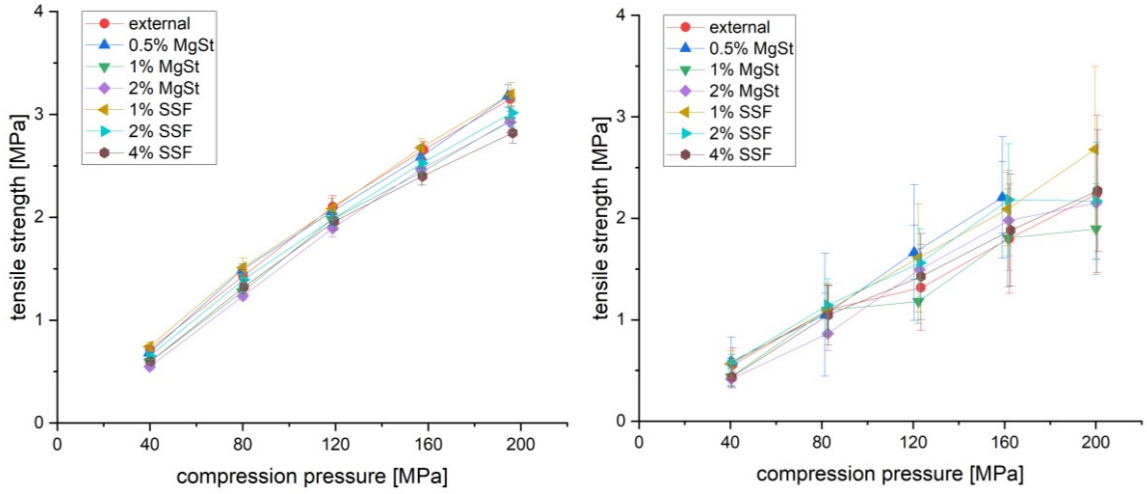


Figure 11: Tabletability of SuperTab® ODT 11.28 mm ODTs (left, single tip) and 2 mm ODMTs (right, 19-tip), tableted on Styl'One compaction simulator, n = 10, mean ± SD

As tableting of minitablets was not possible for all lubricant concentrations due to an ejection force overload (limit: 1000 N), only the data for the feasible concentrations is shown. An amount of 0.5% MgSt was not sufficient for any of the mannitol-based excipients and with 1% MgSt, only Prosolv® ODT could be compressed into minitablets. Powdered mannitol is known to exhibit high ejection forces necessitating a high amount of lubricant [242]. Especially Parteck® ODT required higher amounts of lubricant, as even tableting of 11.28 mm tablets was not possible with 0.5% MgSt, which can be attributed to the higher specific surface area of the excipient which needed to be covered by a lubricant.

In general, the tensile strength was reduced for the smaller tablet diameter which can be attributed to the more pronounced effect of the lubricant for minitablets, also apparent in the higher elasticity

values. A previous study [18] found no significantly increased tabletability for larger punch diameters. However, the authors used a different tableting speed resulting in a shorter dwell time which may explain the differences to the findings in this work. The only excipient, which showed similar tabletability for 11.28 and 2 mm tablets, was galenIQ™, but also showed high deviations making it hard to draw a reliable conclusion. This was also a general problem present for the minitablets, as they are manufactured with a multi-tip tooling, which can result in an unevenly distributed pressure on the individual single-tips and might explain deviations in the tensile strength. Additionally, the manual die filling may be a reason for the higher deviations, as a small difference in the tablet thickness can have a great impact on the tensile strength [166]. In addition, no standardized method for the measurement of the breaking force of minitablets is available. The method described in the pharmacopeia (Ph. Eur. 2.9.8.) is not suitable for minitablets and as an alternative, a method with the Texture Analyser was already described in the literature [17, 18, 22, 35], but may not present the most precise tool.

Comparing both lubricant types for conventionally sized tablets, a superior tabletability could occasionally be observed for SSF compared to the same concentration of MgSt (e.g. for Ludiflash® and Prosolv® ODT). This finding corresponds with studies in literature, which also reported less deterioration of the TS by SSF compared to MgSt [100, 109, 110, 112].

External lubrication led to an increased tabletability of the mannitol-based lubricant-sensitive excipients. Here, the reduction in TS can be avoided by applying the lubricant only on the outside of the die wall where no particle-bonding takes place. However, a negative effect on the disintegration time and higher deviations in the mass of MgSt due to an inconsistent spraying mechanism should be kept in mind. Studies in literature also concluded that external lubrication led to tablets with a higher TS compared to internal addition of the lubricant [144, 146]. On the other hand, OD(M)Ts with SuperTab® ODT and galenIQ™ (and the 11.28 mm tablets of Parteck® ODT) did not demonstrate superior TS with external lubrication. This aligns with the observations seen for internal lubrication.

3.1.3. Influence on disintegration

The disintegration test of the OD(M)Ts was performed with the tablets manufactured at 120 MPa, as this pressure resulted in mechanically stable tablets (TS > 1 MPa), but still exhibited sufficient porosity to enable the influx of water. In industry, low to moderate compression pressures are relevant for the manufacturing of orodispersible tablets [243].

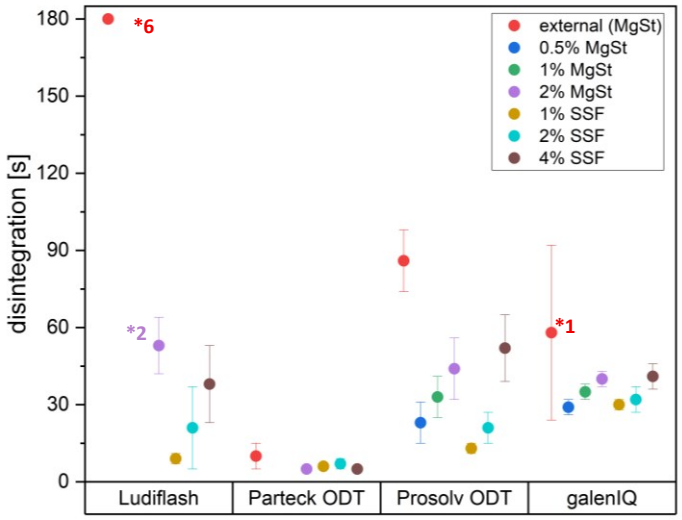


Figure 12: Disintegration time of 2 mm minitablets, tableted on Styl'One compaction simulator at 120 MPa, n = 6, mean ± SD (ODMTs consisting of SuperTab® ODT not depicted, as they disintegrated > 180 s)
**: number of tablets which did not disintegrate within 180 s*

Of all used excipients, only SuperTab® ODT did not result in orodispersible tablets according to Ph. Eur. and needs the addition of a disintegrant, as the spray-dried lactose itself did not disintegrate fast enough despite its porous nature. A clear trend of rising disintegration time with increasing lubricant content is visible for the other four excipients (Figure 12) and confirms the findings of a study on conventionally sized orodispersible tablets [226]. The disintegration delaying effect of MgSt is already known for several years [101, 132, 135, 244] and could be confirmed for minitablets in this study. Even if a smaller tablet size and mass has to disintegrate, they are still affected by the hydrophobic nature of MgSt which inhibits the influx of water into the tablet. Loo et al. [47] confirmed the findings of this study, as they observed an increased disintegration time for minitablets containing higher concentrations of MgSt particularly at higher compression pressures.

The comparison between MgSt and SSF in the same concentrations reveals a superiority of SSF in regard of the disintegration time. This is in agreement with literature [112, 126, 128] where SSF also turned out to prolong the disintegration time less than MgSt for conventionally sized tablets. This can be explained by the lower hydrophobicity of SSF enabling a faster water intrusion. The effect on Parteck® ODT minitablets was less pronounced as the ODMTs disintegrated very rapidly and the different lubrication methods and excipients could not be distinguished as good as for the other excipients. As already described in literature [79, 87], the challenging detection of the endpoint of the disintegration has to be considered, as some excipients like Ludiflash® made it hard to determine the exact endpoint as they can form a soft and sticky mass. Therefore, the results should be confirmed

using an alternative disintegration test with automated endpoint detection, such as the Hermes tester, to obtain more precise disintegration times.

The external lubrication resulted in ODMTs with the highest disintegration times, exceeding the criteria according to FDA. For Ludiflash®, not even the Ph. Eur. requirements could be met anymore. This is in contrast to the literature, where external lubrication did not show a prolongation of the disintegration time [91, 144]. However, the authors did not aim for orodispersible properties in their studies and produced bigger tablets with 9 or 10 mm diameter. The finding can be explained by the higher SVR of minitablets, resulting in a larger surface area which can be occupied by the lubricant. Alternative settings of the external lubrication system to obtain minitablets within the pharmacopeial requirements are discussed in the following chapters.

3.1.4. Lubrication efficiency

For the prevention of tablets defects the ejection force is a critical factor and should be as low as possible as it describes the necessary force to overcome the friction between die wall and tablet surface [89, 90]. An insufficient lubrication and reduction of the ejection force may lead to tablet defects such as lamination, sticking or capping or faster wear of the tablet tooling [89, 94, 245].

The hypothesis that twice of the amount of SSF compared to MgSt is required to obtain the same reduction in ejection force cannot be supported by the obtained data from this study. On the contrary, SSF showed similar or even better performance than MgSt for 11.28 mm tablets as well as for 2 mm minitablets. While some studies [100, 112] described a superior lubrication efficiency of MgSt compared to SSF, other publications [109, 246] stated a similar lubrication efficiency for both lubricants. None of these studies investigated the special effect related to the smaller size of minitablets, only Lura et al. [18, 45] reported an insufficient lubrication efficiency of externally applied MgSt, while acceptable ejection forces were achieved with SSF. Since it could not be clarified why SSF showed better lubrication performance within the present study, additional studies should be conducted to investigate possible agglomeration of the lubricant and the lubrication efficiency, as the particle size can have an impact on the lubricant performance [138-140].

For the comparison of the different lubricant types and concentrations, the ejection force was plotted against the tableting pressure, if tableting was possible for ≥ three compression pressures, and a linear regression was performed. The lower the slope of the ejection force curve, the better was the lubrication efficiency of the used method. Figure 13 shows an overview of all studied excipients and reveals the highest values for SuperTab® ODT caused by the brittle deformation behavior and resulting higher friction coefficient [18, 90, 247].

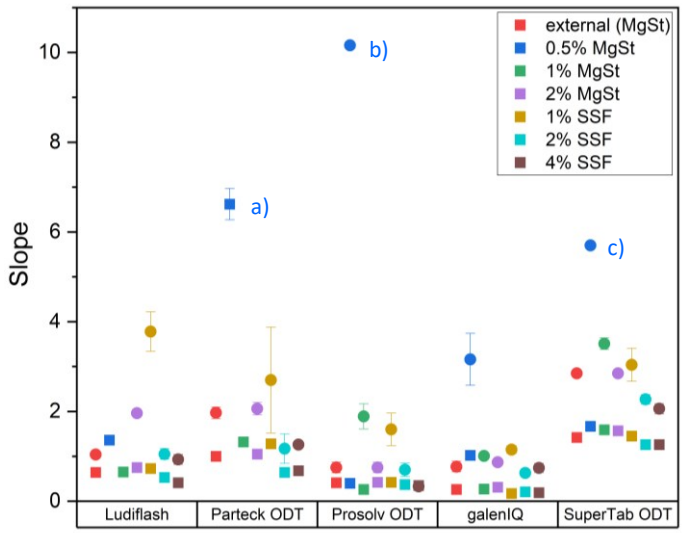


Figure 13: Slope of linear regression of the ejection force plots, ■ represent 11.28 mm ODTs (single tip), ● represent 2 mm ODMTs (19-tip), n = 5, mean ± standard error of slope

a) Tableting stopped after 8 cycles at 160 MPa due to ejection force overload
b) Tableting stopped after 2 cycles at 120 MPa due to ejection force overload
c) Tableting at 200 MPa not possible due to ejection force overload

Isomalt OD(M)Ts showed the lowest ejection forces and corresponding slopes from all tested excipients. It was the only material, where tableting of minitablets with 0.5% MgSt was feasible at all, but resulted in ejection forces above 500 N, which are not recommended for longer run times (e.g. on a rotary press) as the tooling can be damaged. The addition of 1% MgSt resulted in significantly lower ejection forces about 200 N. A further increase in the concentration did not lead to lower ejection forces and should be avoided due to negative effects on disintegration. SSF performed even better in regard of the reduction of the ejection force for 11.28 mm tablets as well as for the 2 mm minitablets. All other excipients showed a benefit by the addition of increased lubricant concentrations.

A generally higher slope of the ejection force was found for the minitablets when comparing the same lubricant concentrations. For a better comparison of the lubrication efficiency regardless of the tablet size, the ejection force was calculated normalized to the radial area (Equation(17)) and is exemplarily shown for Ludiflash® tablets in Figure 14.

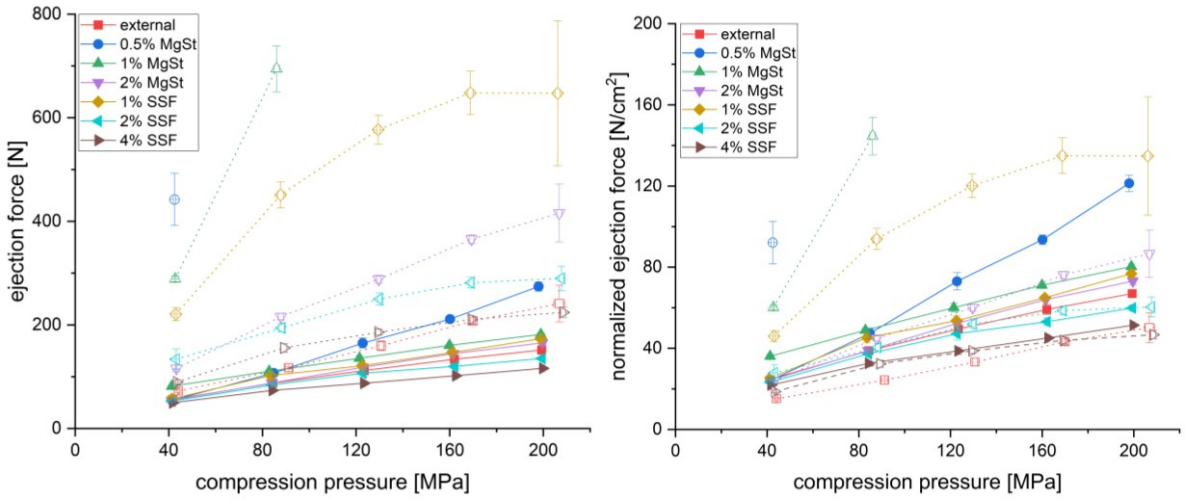


Figure 14: Ejection forces of Ludiflash® OD(M)Ts with different lubrication methods, tableted on Styl'One compaction simulator, original ejection force (left) and normalized ejection force per area (right), 11.28 mm tablets: solid line/filled symbols, 2 mm: dashed line/ hollow symbols, n = 10, mean ± SD

The normalization of the ejection force led to a better comparison of the ejection force for higher lubricant concentrations (2% MgSt, 2 and 4% SSF), but for the lowest concentrations (0.5% and 1% MgSt, 1% SSF) huge differences were still visible. In this case, the minimum effective lubricant concentration was not reached. De Backere et al. [100] defined the effective concentration of the lubricant as the concentration which resulted in ejection forces < 600 N. After exceeding the effective lubricant concentration, the normalized ejection forces are more consistent for both tablet sizes. The external lubrication showed even lower normalized ejection forces for the minitablets which can be attributed by the presumed higher relative amount of lubricant on the minitablet.

Uzondu et al. [228] proposed a dependency of the ejection force on the side band of the tablet and therefore also the die diameter. Lura and Breitkreutz [45] compared the ejection force of 2 and 3 mm minitablets manufactured with single-, 7- and 19-tips and found the highest ejection forces for 3 mm tablets manufactured with a 19-tip punch. By the calculation of the normalized ejection force, both studies can be confirmed. Minitablets produced by multi-tips will therefore exhibit higher ejection forces and a faster wear of the tablet tooling has to be considered.

3.1.5. Summary

In summary, this chapter described the impact of different lubrication methods, types and concentrations on the properties of OD(M)Ts. Different excipients were compared regarding their sensitivity to lubrication with MgSt and SSF and compared in two different tablet sizes. The mannitol-based CPEs showed a sensitivity to the addition of a lubricant while isomalt and a lactose-based excipient exhibited much lower sensitivity. The data showed a superiority of SSF over MgSt which had less negative effects on the disintegration and tensile strength while obtaining the same or even better reduction of the ejection force.

It was demonstrated that the tablet size played a crucial role in the choice of the lubricant amount as the area of friction that must be overcome by the ejection force is increased caused by the higher surface area of the minitablets. The ratio of the area of the cylindrical part of the tablet can serve as a good orientation when formulations of different sizes are compared. If a multi-tip is used, all tips have to be considered to estimate the resulting ejection force.

Based on the findings in this chapter, a minimum concentration of 2% SSF can be recommended for minitablets. However, the concentration might need to be adjusted when an API is added to the formulation as it may increase the friction between the die wall and the tablet surface.

First experiments with external lubrication were conducted, which resulted in high tensile strengths, but also prolonged the disintegration time. As this effect was not reported in that extent in the literature, experiments for the optimization of external lubrication are conducted in the next chapter to find appropriate settings for the spraying process.

3.2. External lubrication for ODMTs manufactured by a multi-tip tooling

At the beginning of this study, there have been no investigations regarding the use and suitability of external lubrication for minitablets. This presents a challenge due to the small size and area which needs to be covered with the lubricant, and due to the fact that minitablets are commonly manufactured with multi-tip dies in the pharmaceutical industry. Up to this point, all publications addressed the suitability of external lubrication only for normally sized tablets produced with a single tip punch [91, 141-146, 148].

3.2.1. Optimization of external lubrication for minitablets

As multi-tip punches and the reduced diameter of the minitablet dies may require specialized settings for the spraying process, the system was optimized in this chapter. For the previous experiments, the standard settings from a publication of de Backere et al. [91] with a spraying time of 500 ms and an atomizing pressure of 5 bar resulted in the lowest ejection forces and were used for the external lubrication experiments. As the spray rate was not given in this publication, the first trials were performed with the high spray rate to ensure sufficient lubrication.

Three alternatives were tested to minimize the negative effects of the lubricant on the MTs: The spraying time was decreased from 500 to 400 ms, the atomizing pressure was reduced from 5 to 3 bar and the lubrication was performed using the low spray rate instead of the high spray rate setting.

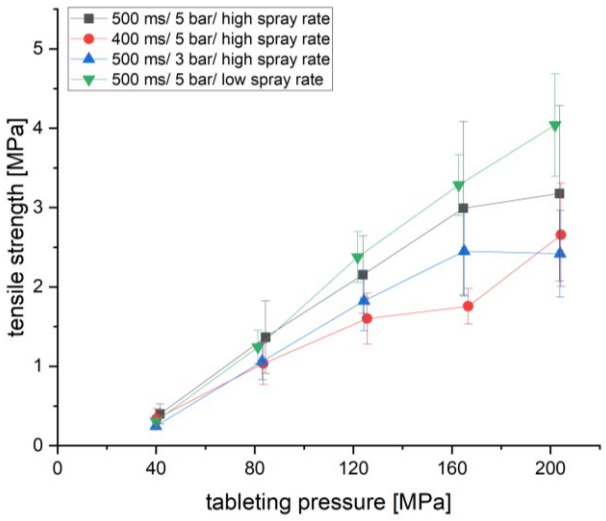


Figure 15: Tabletability of Prosolv® ODT minitablets with different spray settings for external lubrication, tableted on Styl'One compaction simulator, n = 10, mean ± SD

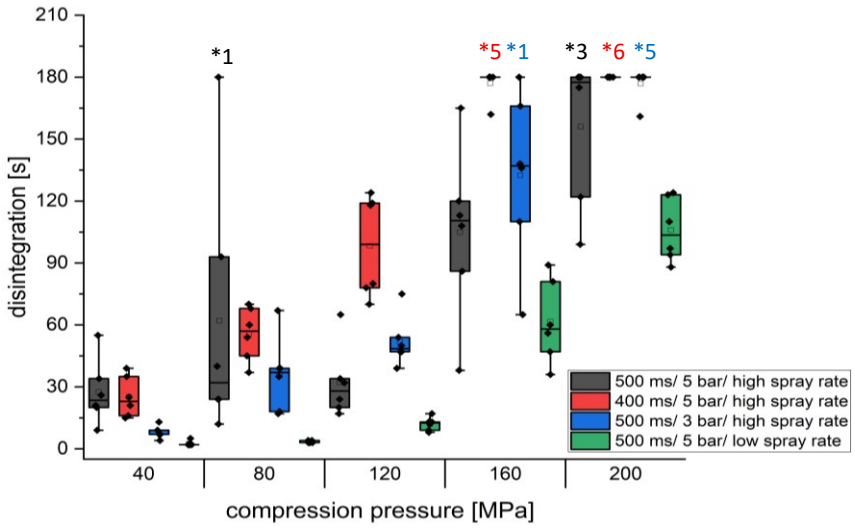


*Figure 16: Box plots of disintegration time of Prosolv® ODT minitablets with different spray settings for external lubrication, tableted on Styl'One compaction simulator, n = 6, *: number of tablets, which did not disintegrate within 180 s*

A reduction of the spraying time led to a decreased tabletability and increased disintegration times (Figure 15 and Figure 16). De Backere et al. [91] also found lower tensile strengths for lower spraying times and explained that by the higher ejection forces and tablet defects on the insufficiently lubricated tablets. The decreased atomizing pressure showed a lower tabletability and higher disintegration times compared to the standard settings. A lower pressure may result in higher agglomeration of the lubricant, as the agglomerates of MgSt are not as effectively as with the higher pressure and might result lead to higher MgSt amounts on the tablet. Only the change of the spray rate resulted in higher mean tensile strengths and a faster disintegration. The reason for this phenomenon is extensively studied and explained in chapter 3.2.3.

Unfortunately, there is no information from the manufacturer about the spray rate settings in regard of the sprayed quantity of MgSt. The sprayed amount depends on various factors including the applied pressure, the diameter of the used pipes and the type of lubricant. The determination of the sprayed amount is challenging, as not all of the sprayed MgSt remains in the die and is removed by the exhaust system to a great part (set up is depicted in Figure 84). A simple gravimetric determination was performed with a beaker, which was covered with Parafilm® and the sprayed amount was weighed. For the low spray rate, a mean value of 7.7 mg was found (SD ± 1.5 mg, n = 5), while the quantity of MgSt was five times higher for the higher spray rate (35.6 ± 14.9 mg, n = 5). As this mass is not the absolute MgSt content on the tablet, this method is not appropriate for the characterization of the spray rate as it does not consider the exhaust system. In chapter 3.2.3.2 this method was replaced by a quantitative characterization of the MgSt amount in the produced tablets.

3.2.2. External lubrication with SSF in comparison to MgSt

While SSF is commonly used for internal lubrication, the number of publications which apply SSF in external lubrication systems is quite low. As SSF is a more hydrophilic lubricant than MgSt, its negative effects on tensile strength, disintegration and dissolution profile are described as less pronounced in the literature [90, 110, 112] and could also be proven for orodispersible minitablets in chapter 3.1. De Backere et al. [148] examined six different lubricants, including MgSt and SSF, for their suitability for external lubrication and found no differences in the disintegration time of the tablets when using external lubrication.

Therefore, additional experiments were performed with SSF instead of MgSt for the external lubrication for minitablets as well as for normally sized tablets. The low spray rate was used as this resulted in faster disintegrating tablets in 3.2.1. All components of the lubrication system were cleaned thoroughly and new pipes, designated only to SSF, were used to avoid cross-contamination with MgSt.

Regarding the tensile strength, there was no difference in the use of SSF compared to MgSt for both tablet sizes (Figure 17). Taking a look at the ejection force (Figure 18), SSF revealed lower ejection forces, which was even more pronounced for the minitablets and showed a better lubrication efficiency as observed for internal lubrication (see chapter 3.1.4). Surprisingly, the assumption, that the tablets with SSF will disintegrate faster, was not confirmed as the minitablets showed higher mean disintegration times (Figure 19), which is in contradiction to the data of the internal lubrication. This effect was not visible for the 11.28 mm tablets. A possible explanation might be, that related to the tablet weight, the percentage of the lubricant is lower and therefore the lubricant layer might be thinner, resulting in less effects on the disintegration time.

While in internal lubrication, the amount of lubricant is set precisely, the sprayed mass cannot be controlled directly with the external lubrication. The sprayed amount of lubricant is also dependent on the particle size of the lubricant, which is twice as large for SSF (d_{50}(SSF) = 14.9 µm, d_{50}(MgSt) = 7.8 µm) and could result in a completely different amount of lubricant left on the tablet surface. A higher percentage of SSF on the minitablets could lead to higher disintegration times. Additionally, the competition-for-water hypothesis [100, 114] might explain the longer disintegration as SSF is more hydrophilic than MgSt and interacts with the water leaving less liquid available for the disintegration process. This effect can be more pronounced when the lubricant is only present on the outside on the tablet after external lubrication. The dispersion behavior of the lubricant should be investigated more detailed together with a quantification of SSF and MgSt to explain the differences in the tablet properties.

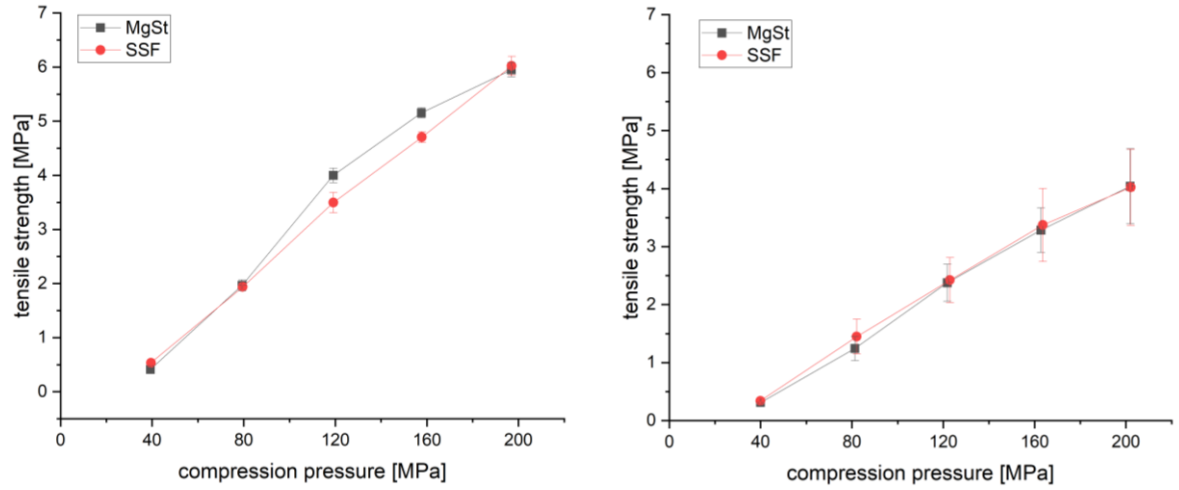


Figure 17: Tabletability of Prosolv® ODT tablets with 11.28 mm diameter (A) and 2 mm diameter (B) with external lubrication, low spray rate, tableted on Styl'One compaction simulator, n = 10, mean ± SD

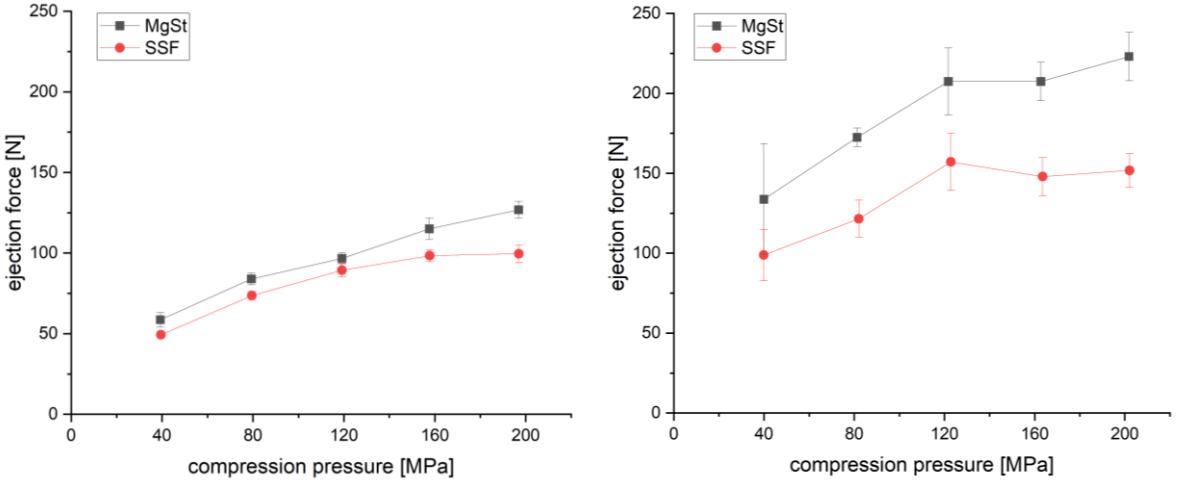


Figure 18: Ejection force of Prosolv® ODT tablets with 11.28 mm diameter (A) and 2 mm diameter (B) with external lubrication, low spray rate, tableted on Styl'One compaction simulator, n = 10, mean ± SD

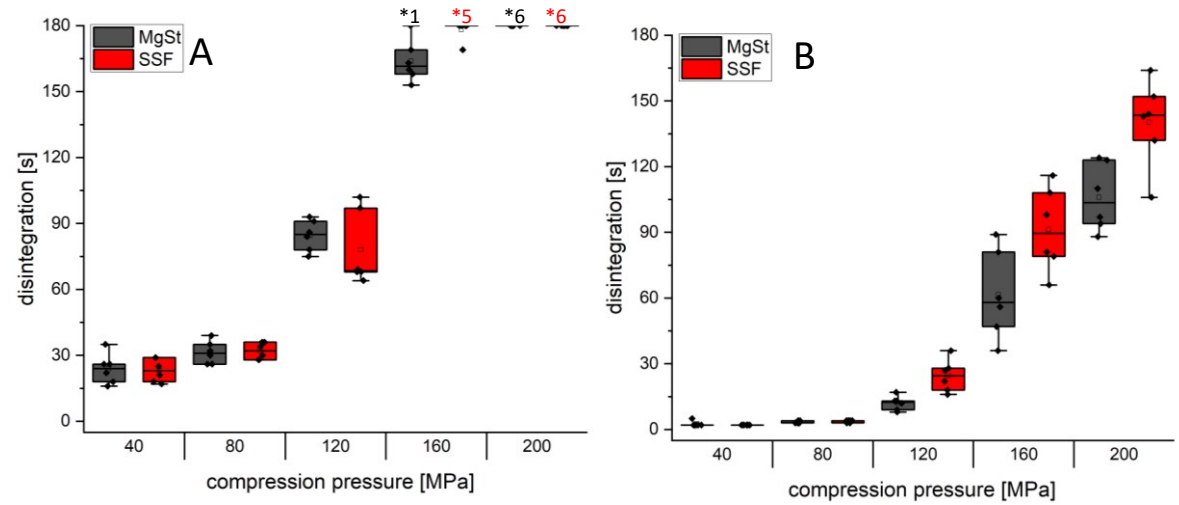


*Figure 19: Box plots of disintegration time of Prosolv® ODT tablets with 11.28 mm diameter (A) and 2 mm diameter (B) with external lubrication, low spray rate, tableted on Styl'One compaction simulator, n = 6; *:number of tablets, which did not disintegrate within 180 s*

3.2.3. External lubrication on the Styl'One compaction simulator for individual punch positions of the multi-tip

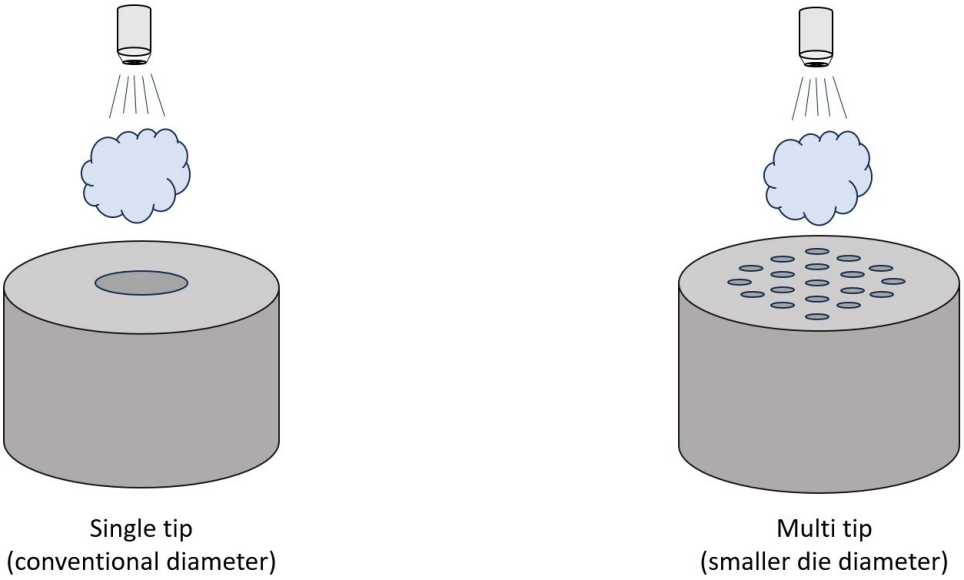


Figure 20: Schematic illustration of the spraying mechanism for the single and multi-tip (19-tip as used for 2 mm minitableting)

For conventionally sized single tips, external lubrication was extensively studied in literature [91, 141-145, 148]. As the spraying nozzle is located above the center of the die, it is unclear whether all mini-dies obtain comparable amounts of lubricant when using a multi-tip (Figure 20). A study by Lura and Breitkreutz [45] started to evaluate the different minitablet punches and their positions, but could not find a general better tabletability for multi-tips. For the different positions within one multi-tip punch, significant differences could be found between some punches and positions, but with no systematic trend. However, the settings for the external lubrication used in this study were not described completely and the impact on the disintegration was not tested.

Therefore, for this work the multi-tip was divided into three different circles (Figure 21) and the minitablets were analyzed individually per section to assess differences in the punch positions. For the experiments in this chapter, all minitablets consisted of Prosolv® ODT as the filler, as it showed a high lubrication sensitivity (see chapter 3.1) and would be expected to discriminate the best between different lubrication settings. MgSt was used for the external lubrication as it showed better disintegration properties than SSF in chapter 3.2.2. The minitablets were characterized regarding their tabletability, disintegration, mass, occupation of MgSt on the surface and overall MgSt content.

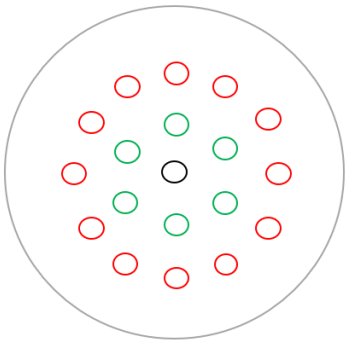


Figure 21: Schematic drawing of a 19-tip, divided into three different sections (black: inner circle, green: middle circle, red: outer circle)

3.2.3.1. Distribution of MgSt on the surface of the minitablets

In literature, there are only a few studies describing the distribution of lubricants on the tablets. Yamamura et al. [144] studied externally lubricated tablets and found a thinner MgSt layer at the center of the tablet compared to the edges. Gunawardana et al. [97] examined internally lubricated tablets and showed that MgSt was mostly located on the boundaries of the particles. Both publications used SEM imaging to study the distribution of MgSt.

For the evaluation of the lubricant distribution, Raman images were taken according to the method described in chapter 5.2.10.2. Initially, two image sizes were recorded to ensure that all particles of the lubricant are captured with the used spatial resolution. MgSt has a relatively small particle size with a d_{50} value of 7.8 µm, but also smaller particles are present (d_{10} = 1.9 µm). Pictures from a 600 x 600 µm section with a resolution of 4 µm were compared with a 150 x 150 µm section and a corresponding resolution of 1 µm. Figure 22 shows Raman images of the bottom of minitablets with internal lubrication with 2% MgSt. The distribution of MgSt on tablets from the inner, middle and outer circle is quite similar in terms of percentage (6 - 8 %). This corresponds to the expectation that for a homogeneous mixture, the MgSt content on the surface should be equal regardless of the minitablet position.

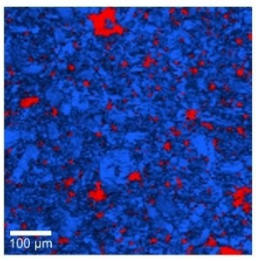
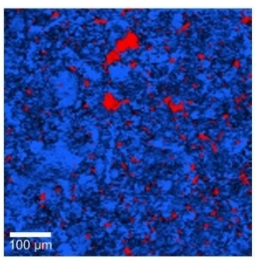
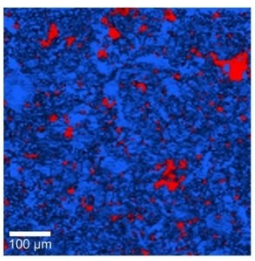
Examined punch position	**inner**	**middle**	**outer**
Raman image			
Surface coverage with MgSt	8 %	6 %	8 %

Figure 22: Raman images of internally lubricated Prosolv® ODT MTs (2% MgSt), measurement taken from the bottom of the tablet (blue = matrix, red = MgSt), 4 µm resolution

Table 7 compares the occupied surface for both spatial resolutions. For the calculation of the occupied MgSt area of the picture with 4 µm resolution, only the area depicting the section of the 150 x 150 µm picture, was used. It is notable that the amount of MgSt on the tablet surface is approx. 3 – 4 x higher than the weighted amount, which is in agreement with a report in literature [97]. As shown in Figure 22, the lubricant is not distributed completely homogeneously but forms agglomerates. In contrast to literature [90, 93, 95, 96] and the general assumption, no thin lubricant film was visible in the Raman images, which was described by Gunawardana et al. [97]. This phenomenon can be explained by the rearrangement of MgSt particles during the compression [248] or the agglomeration of individual MgSt particles due to their small particle size and the resulting strong cohesion tendency [249].

Lubrication method	**Resolution**	**Surface coverage with MgSt**		
		Inner circle	**Middle circle**	**Outer circle**
Internal (2% MgSt)	4 µm	4%	8%	6%
	1 µm	4%	8%	7%
External (MgSt, low spray rate)	4 µm	84%	63%	3%
	1 µm	84%	58%	4%

Table 7: Comparison of the MgSt-covered area for Prosolv® ODT MTs, measurements taken from the bottom of the tablet with different resolutions

For the externally lubricated tablets with the low spray rate the relative surface occupation is significantly higher, as the lubricant is only present on the outer surface of the minitablet where the pictures were taken. For the inner circle there is no difference for both resolutions, the highest gap between 1 and 4 µm resolution is found for the tablet from the middle circle with a difference of 5%. In theory, a higher proportion of MgSt should be found for the resolution of 1 µm as also the smaller particles of MgSt can be detected, which is not the case here. As the images with 1 µm resolution did not offer more detailed information regarding the lubricant occupation or finer particles, all following pictures were only taken with a resolution of 4 µm to get data for a larger area of the tablet.

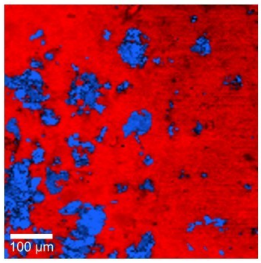
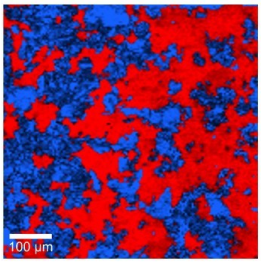
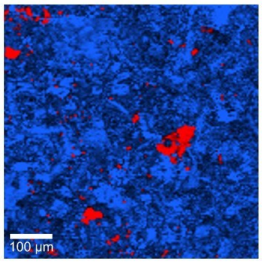
Examined punch position	**inner**	**middle**	**outer**
Raman image			
Surface coverage with MgSt	87 %	52 %	3 %

Figure 23: Raman images of externally lubricated Prosolv® ODT MTs using the low spray rate, measurement taken from the bottom of the tablet (blue = matrix, red = MgSt), 4 µm resolution

In contrast to the internally lubricated minitablets (Figure 22) the differences in the punch positions are much more pronounced for the external lubrication (Figure 23). A clear decrease from the center to the outer circle of the punch is visible (87%: inner circle to 3%: outer circle). If only the tablets from the inner circle are compared for both lubrication methods, the amount of lubricant increases by the factor of 10. As the spraying nozzle for the lubricant is located directly above the center of the multi-tip die, this results in a large amount of lubricant being deposited in the inner circle. In the outer ring, only 3% MgSt were detected, presumably because the angle for spraying of MgSt was not sufficiently wide. Therefore, only a small amount of the lubricant hit the die walls, resulting in a lower amount on the surface compared to internal lubrication.

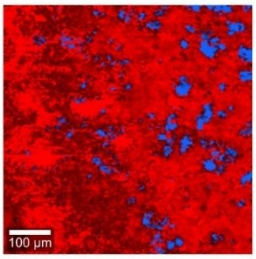
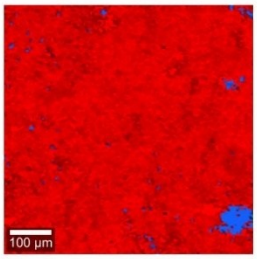
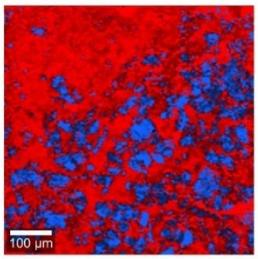
Examined punch position	**inner**	**middle**	**outer**
Raman image			
Surface coverage with MgSt	92 %	99 %	80 %

Figure 24: Raman images of externally lubricated Prosolv® ODT MTs using the high spray rate, measurement taken from the bottom of the tablet (blue = matrix, red = MgSt), 4 µm resolution

The recording of Raman images for ODMTs with the high spray rate was quite challenging, as the tablets were brittle (see chapter 3.2.3.3) making the positioning and handling of the tablets difficult. Compared to the low spray rate, the external lubrication with the high spray rate could cover all positions of the multi-tip die quite good with MgSt (Figure 24). The differences between the punch positions were not as pronounced as for the low spray rate and even the outer circle was covered with MgSt by 80%.

So far, Raman images have only been taken from the bottom of the tablet, as most of the lubricant was assumed on this part of the minitablet. However, since the lubricant may also be present in other areas of the tablet, additional images were taken of the side and the top of the tablet. The determined MgSt coverage is summarized in Table 8.

Imaged section of the tablet	Examined punch position	Surface coverage with MgSt		
		Internal (2% MgSt)	External (Low Spray Rate)	External (High Spray Rate)
Side	inner	4%	2%	25%
	middle	n.r.	6%	n.r.
	outer	n.r.	2%	n.r.
Top	inner	6%	21%	49%

Table 8: Comparison of MgSt-covered area for Prosolv® ODT MTs, measurements taken from the side and top of the tablet, 4 µm resolution (n.r.= not recorded)

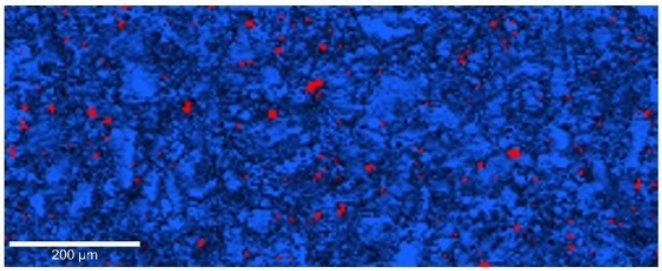
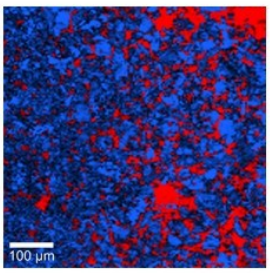
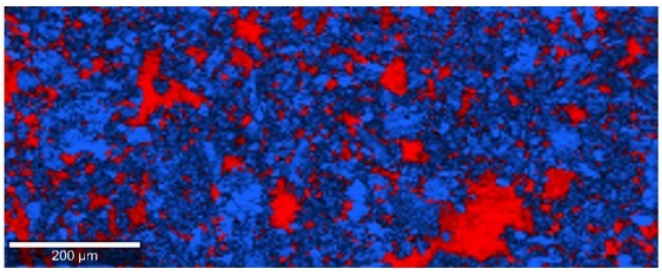
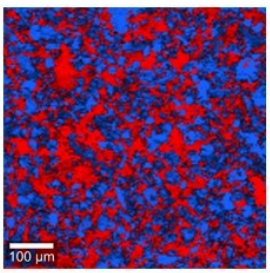
	Imaged section of the tablet	Raman image	Surface coverage with MgSt
Low spray rate	Side		2%
	Top		21%
High spray rate	Side		25%
	Top		49%

Figure 25: Raman image of externally lubricated minitablets from the inner circle of the die, measurement taken from the side and top of the tablet (blue = matrix, red = MgSt), 4 µm resolution

For the internal lubrication (side: 4%, top: 6%, Table 8) the data is in line with the determined amount on the bottom of the minitablet (6 - 8%, Figure 22). This meets the expectations as the lubricant should be distributed homogeneously on all sides of the tablet if the mixing process was sufficient. The external lubrication with the low spray rate also showed just a small extent of MgSt coverage on the lateral side (2 – 6%, Table 8), comparable to internal lubrication (4%, Table 8). However, a higher proportion of 21% MgSt was found on the top of the minitablet. Working with the high spray rate resulted in a higher surface occupation for all positions, as shown in Figure 25. Thus, the "MgSt-free" area, which was seen on the side of the MTs with the low spray rate and might allow water penetration, was not present for the high spray rate. These images will be of great interest when it comes to the disintegration of the tablets (see chapter 3.2.3.3).

In general, this data can just give a rough overview about the amount of MgSt that ends up on the minitablets, as the spraying process is highly variable and depending on the equipment. Furthermore, the pictures were taken once per position due to the high time and cost need of the Raman measurements. It would be of high interest to confirm these findings with a higher sample size and also for each of the individual 19 positions.

3.2.3.2. MgSt content of the minitablets

In the previous chapter the distribution of MgSt on the surface of the minitablets was described in detail. However, the Raman images cannot make a statement about the absolute mass of MgSt in the entire minitablet. For this purpose, atomic absorption spectroscopy was employed using a modified method by de Backere et al. [91], described in detail in chapter 5.2.7.8. Figure 26 depicts the MgSt content of three minitablets for each circle position for the low and the high spray rate. A clear increase for the higher spray rate can be seen for all circles (e.g. outer circle: low spray rate: 0.31 ± 0.08%, high spray rate: 1.09 ± 0.23%). These results confirm the findings of Kamiya et al. [142] who also identified the spray rate as an influencing factor on the MgSt content besides the compression speed and the air flow of the dust extractor. Additionally, a trend of decreasing MgSt content from the inside to the outside of the multi-tip punch is evident for both spray rates. This observation can be explained by the inhomogeneous distribution of the lubricant during the spraying process and corresponds to the data obtained by Raman spectroscopy (chapter 3.2.3.1).

The MgSt content of minitablets with internally added 2% MgSt was also determined to exclude a potential falsification of the results by MgSt in the raw excipients. A MgSt content of 2.02 ± 0.27 % (n = 3) was obtained, indicating the appropriate determination of MgSt. However, a certain range of deviations has to be considered, which could be due to inhomogeneous mixing and distribution of MgSt in the lubricated mixture or the relatively small sample amount (about 7.5 mg), where small

changes in the mass can lead to varying results. Another potential source of error is the absolute content of magnesium in the MgSt. According to the certificate of analysis, 4.0 – 5.0 % of Mg were found in the raw material, while the actual relative percentage by molar mass is 4.11 %.

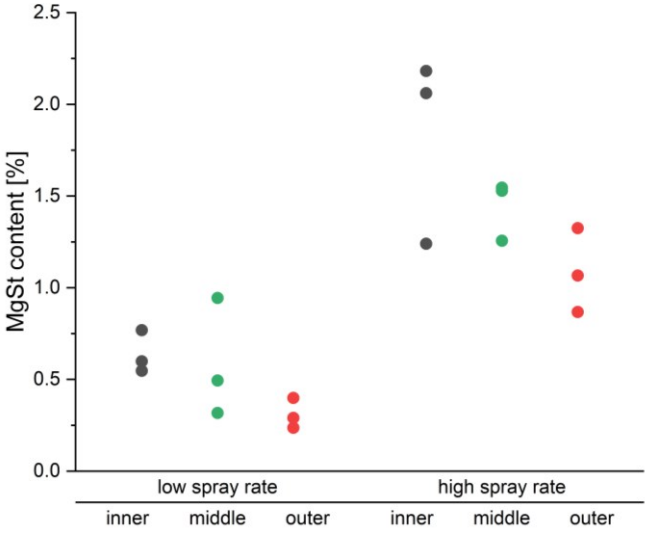


Figure 26: MgSt content for the individual punch positions of the multi-tip punch for external lubrication with low (left) and high (right) spray rate, tableted on Styl'One compaction simulator at 120 MPa, n = 3

Despite the lower MgSt content, the ejection force was hardly affected by the spray rate and showed no significant differences (Figure 27). The internal lubrication with 2% MgSt resulted in significantly higher ejection forces for pressures ≥ 80 MPa, at 40 MPa the ejection force showed higher deviations. The externally lubricated MTs contained the same or less amount of MgSt while resulting in lower ejection forces. This demonstrated that only the lubricant on the tablet surface is necessary for the reduction of the ejection force.

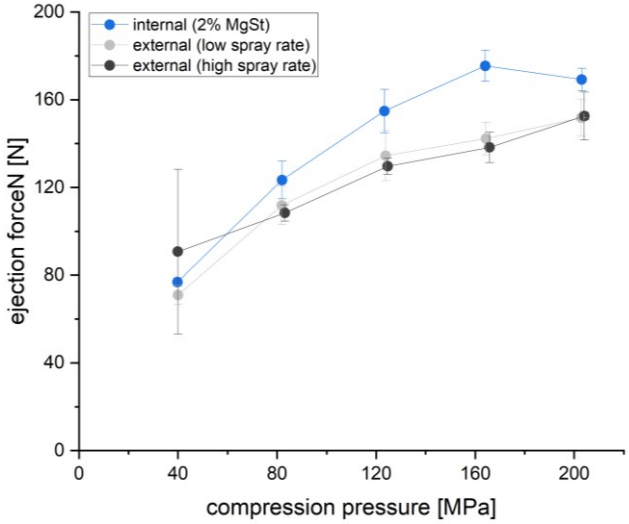


Figure 27: Ejection force for the three different lubrication methods of Prosolv® ODT minitablets, tableted on Styl'One compaction simulator, n = 10, mean ± SD

3.2.3.3. Mechanical properties and disintegration performance

After analyzing the MgSt distribution and content, the impact on the CQAs tensile strength and disintegration time was investigated. Figure 28A shows the tabletability for internally lubricated tablets for the different punch positions and only revealed significant differences in the tensile strength for MTs from the outer circle for pressures ≥ 120 MPa, which can be attributed to mass variations in the outer circle of the die [45]. Despite the inhomogeneous distribution of the lubricant in the different circles, external lubrication with the low spray rate did not result in significant differences in tabletability (Figure 28B). Significant differences could be observed for the high spray rate, where minitablets from the inner circle revealed a significantly lower tabletability than the other two circles (Figure 28C). As the nozzle is directly located above the inner circle, it sprayed a higher MgSt amount on this position which could even be observed visually (Figure 29) and therefore resulted in more brittle tablets. In industrial scale, all minitablets are united in one batch and not separated by position which emphasizes the need of a homogeneous spraying process. In this case, the CQAs for the entire batch would only be acceptable for internal lubrication or external lubrication with the low spray rate.

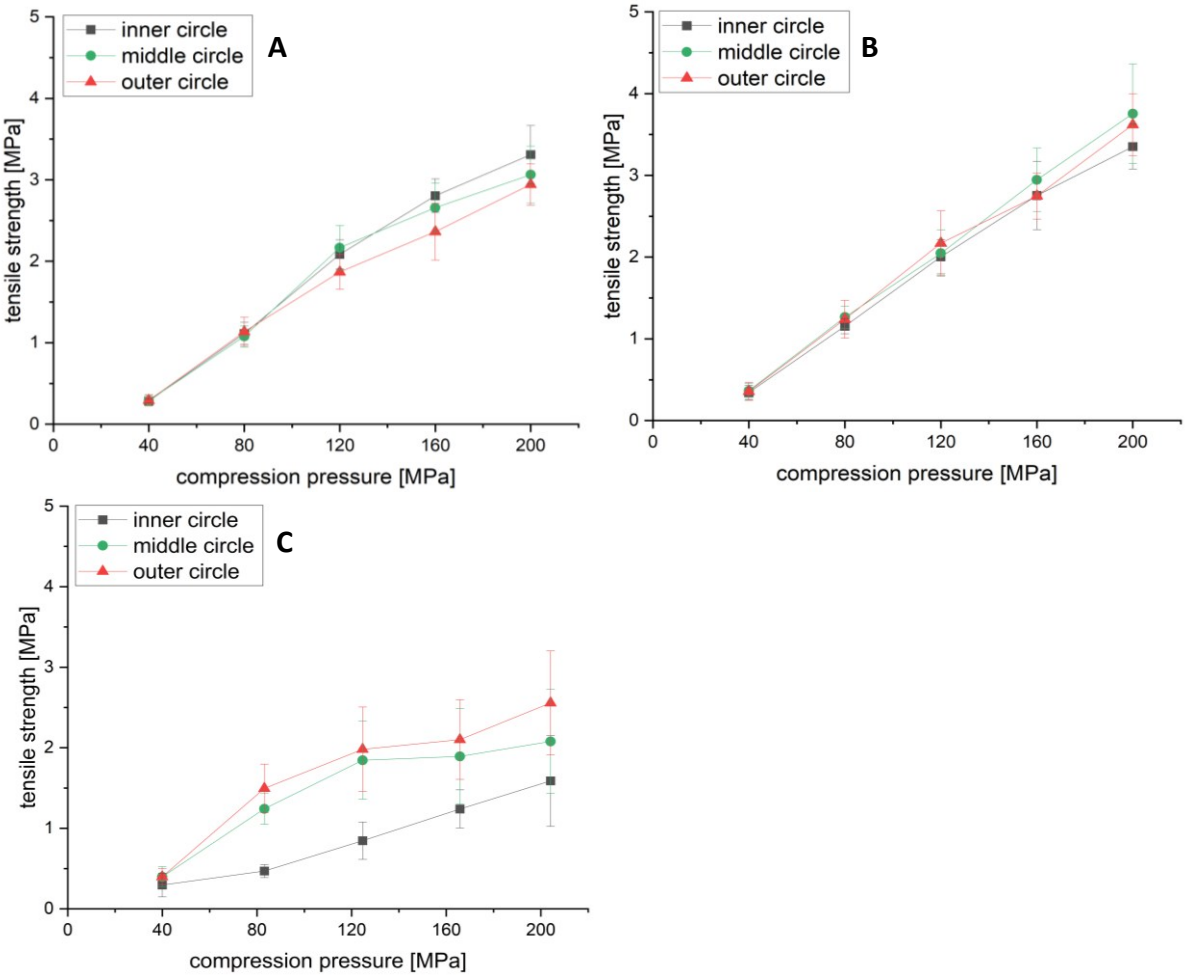


Figure 28: Tabletability of Prosolv® ODT minitablets for different lubrication methods, A: internal lubrication (2% MgSt), B: external lubrication (low spray rate), C: external lubrication (high spray rate), tableted on Styl'One compaction simulator, n = 10, mean ± SD

Figure 29: Picture of the multi-tip die after external lubrication on the Styl'One compaction simulator with a high spray rate

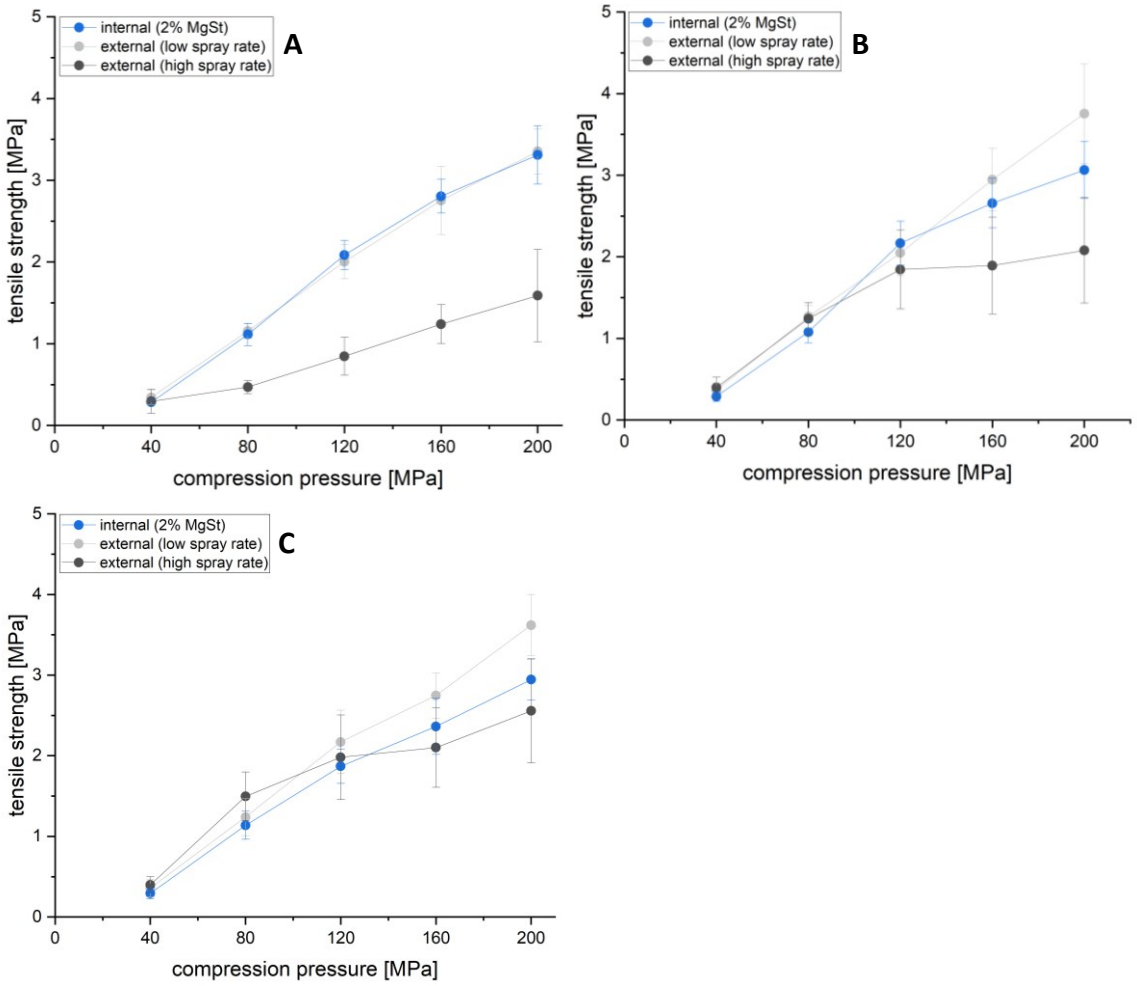


Figure 30: Tabletability of Prosolv® ODT minitablets, separated by different punch positions, A: inner circle, B: middle circle, C: outer circle, tableted on Styl'One compaction simulator, n = 10, mean ± SD

Separated by circles, the significant differences in tabletability become visible for the external lubrication with the high spray rate (Figure 30). Especially for the tablets from the inner circle, a massive drop in the tensile strength occurred compared to the other lubrication methods. The tablets from the middle circle also exhibited significant differences with the external lubrication with the high spray rate for pressures ≥ 160 MPa. While the external lubrication with the high spray rate did not

result in significantly softer tablets for the outer circle position compared to internal lubrication, the low spray rate produced tablets with a higher tensile strength than the internal lubrication.

In literature, external lubrication was described not to prolong the disintegration time [91, 144], but the spray rate was not investigated in these studies. In another study by de Backere et al. [145], the lubricant feed rate did not show an impact on the disintegration time on 8 mm tablets lubricated externally with MgSt, but for external lubrication with SSF and glyceryl dibehenate an effect on the disintegration time was visible.

Surprisingly, the minitablets with external lubrication with a low spray rate showed a significantly lower disintegration time than the internally lubricated ones. Moreover, the externally lubricated MTs from different punch positions did not show significant differences in their disintegration time and disintegrated in around 10 s, despite high variations in the MgSt occupation on the surface of the MT (see 3.2.3.1). The internally lubricated MTs showed much higher deviations in general with disintegration times from 20 - 50 s and did not fulfill the FDA criteria for orodispersible tablets anymore (Figure 31).

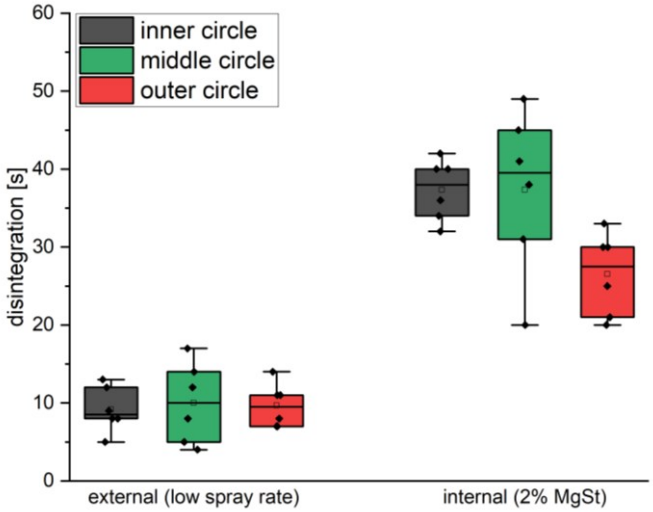


Figure 31: Box plots of disintegration time of externally and internally lubricated Prosolv® ODT MTs, tableted on Styl'One compaction simulator at 120 MPa, n = 6

The spray rate is of high importance for the disintegration time as Figure 32 illustrates the differences for both spray rate settings. While tablets from the middle and outer circle, produced using a high spray rate, needed about 90 s to disintegrate, 4 of 6 tested tablets of the inner circle did not even disintegrate after 180 s (Ph. Eur. limit) and the test was stopped. This presents another problem besides the variations in the tensile strength for the high spray rate, as minitablets from the complete multi-tip die will be collected as one batch and exhibit massive differences in their CQAs. A look at the Raman images and the results from the MgSt determination can explain the differences in the disintegration time. A smaller amount of the hydrophobic lubricant in total was sprayed onto the

minitablet with the low spray rate, located mostly on the bottom of the tablet, whereas the side and the top are almost lubricant free and allow sufficient space for wetting of the tablet. The high spray rate also covered the side and top of the minitablet, which obviously led to a prolongation of the disintegration.

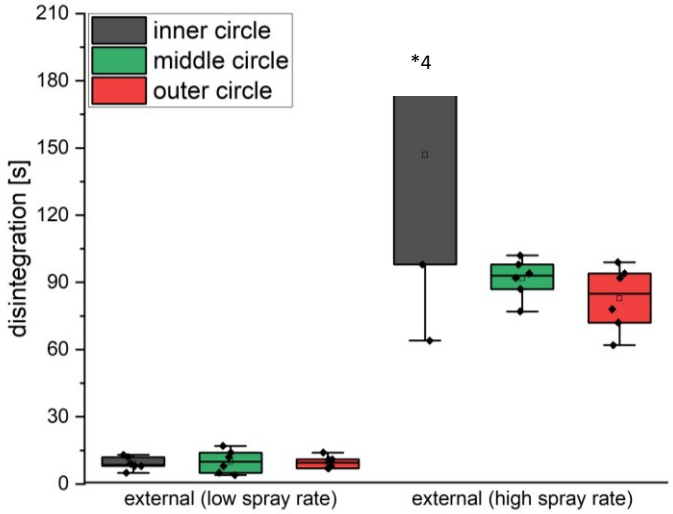


*Figure 32: Box plots of disintegration time of externally lubricated Prosolv® ODT MTs, tableted on Styl'One compaction simulator at 120 MPa, n = 6, *: number of tablets, which did not disintegrate within 180 s*

3.2.4. Transferability of the external lubrication to the rotary press Korsch XM 12

For the investigation of the relevance of the found importance of the spray rate, further experiments were performed on the Korsch XM 12 rotary press, as this represents the scale where minitablets will be produced in the pharmaceutical industry. For these experiments, the excipient Ludiflash®, another common CPE for ODTs, was used. First, the differences in the individual punch positions were investigated on the Styl'One compaction simulator for Ludiflash®.

Figure 33 shows the ejection force of Ludiflash® ODMTs with the different lubrication methods and reveals a big difference between the two spray rates. While the high spray rate effectively reduced the ejection force to acceptable values < 500 N, comparable to the internal lubrication with 2% MgSt, the low spray rate exhibited much higher ejection forces. The low spray rate was insufficient to provide adequate lubrication for the minitablets, as tableting had to be stopped after 120 MPa due to an ejection force overload. The demand of Ludiflash® for higher lubricant amounts compared to Prosolv® ODT was already visible in chapter 3.1, where Ludiflash® showed higher ejection forces than other fillers and tableting of minitablets with 1% MgSt was not possible, whereas it was feasible for Prosolv® ODT.

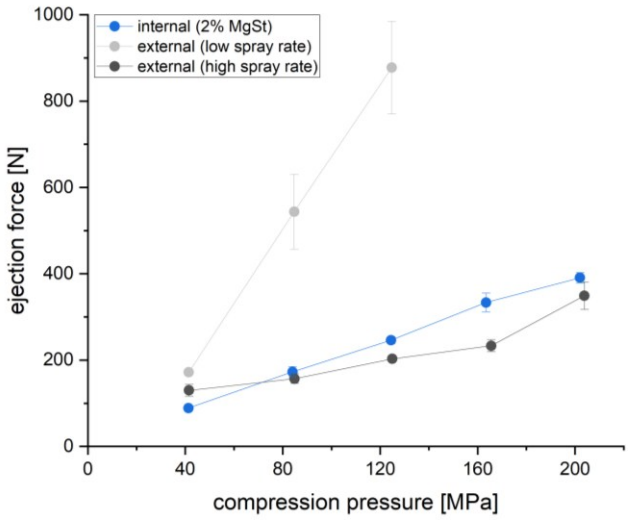


Figure 33: Ejection forces for the three different lubrication methods of Ludiflash® minitablets, tableted on Styl'One compaction simulator, n = 10, mean ± SD

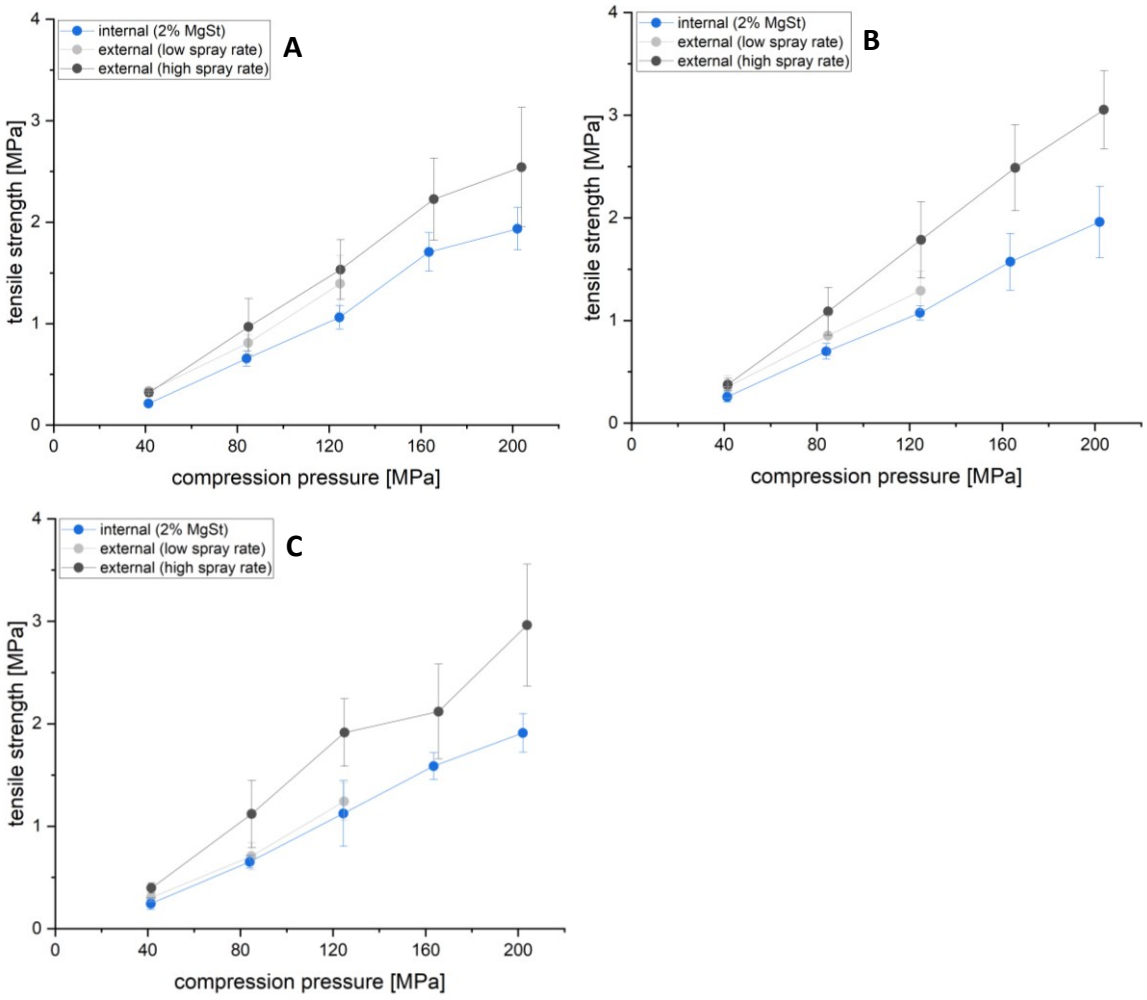


Figure 34: Tabletability of Ludiflash® minitablets, separated by different punch positions, A: inner circle, B: middle circle, C: outer circle, tableted on Styl'One compaction simulator, n = 10, mean ± SD

The tabletability (Figure 34) also indicates a different behavior compared to Prosolv® ODT. Here, no significant drop in the tensile strength for the high spray rate was visible. On the contrary, the high spray rate demonstrated superior tabletability to internal lubrication or external lubrication with the low spray rate. However, a higher variability in the tensile strength is noticeable for the external lubrication which is probably caused by a different amount of lubricant on the tablets as the spraying and subsequent removal of the excessive MgSt is not performed completely consistent.

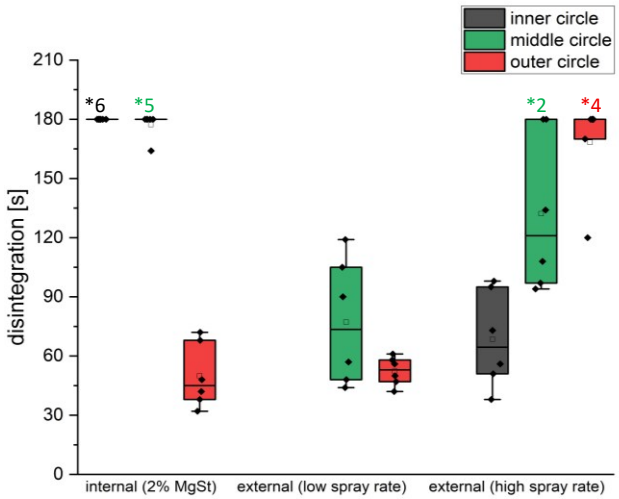


*Figure 35: Box plots of disintegration time of differently lubricated Ludiflash® ODMTs, tableted on Styl'One compaction simulator at 120 MPa, n = 6, *: number of tablets, which did not disintegrate within 180 s*

The disintegration times (Figure 35) revealed differences for the different lubrication methods, and also for the different punch positions. The internal lubrication resulted mostly in tablets which could not be classified as orodispersible anymore, only the MTs from the outer circle fulfilled the Ph. Eur. criteria. As already mentioned in chapter 3.1.3, the endpoint detection especially for Ludiflash® minitablets was quite challenging and has to be taken into account. The external lubrication with the low spray rate produced the fastest disintegrating tablets (comparable to Prosolv® ODT), but tablets from the inner circle could not be tested as not enough tableting cycles could be conducted due to an ejection force overload. A comparison for the same punch position and different spray rate pronounced the effect of the spray rate on the disintegration time, as the disintegration time was prolonged with the high spray rate and some tablets also did not disintegrate within the 180 s time limit. If the entire batch is tested, it depends on which tablet from which position is tested, if the test according to Ph. Eur. is passed or not. The probability for collecting and testing minitablets from the outer circle is the highest and consequently the tablets would not be labelled as orodispersible for external lubrication with the high spray rate.

When comparing the compaction simulator to the rotary press, several points have to be considered, as the external lubrication systems are operating in different modes. At the Styl'One compaction

simulator, the spraying process is static, as the filling shoe with the attached nozzle stops above the die to apply the lubricant on the die surface. A spraying time of 500 ms was used on the compaction simulator as this was declared as a suitable spraying time for sufficient lubrication [91]. On the Korsch XM 12, the spraying process is different, as the dies are in motion while the spraying nozzle remains stationary, resulting in spraying MgSt from different angles onto the die. The spraying time therefore depends on the turret speed of the tablet press and cannot be compared directly to the compaction simulator. Only MgSt was employed as the external lubricant for these trials as it demonstrated a better performance in chapter 3.2.2 and no superiority of other lubricants compared to MgSt was demonstrated in the literature [148].

The minimum spray rate, specified by the manufacturer of the dosing unit, was 0.2 kg/h. For this spray rate, tableting was only feasible at 40 MPa, a further pressure increase resulted in a stop of the machine, as the ejection limit (600 N) was reached, indicating that the sprayed amount was insufficient for ensuring an adequate lubrication of the minitablet punches. Therefore, tableting was conducted using four spray rates from 0.3 – 0.6 kg/h besides internal lubrication with 3% MgSt and SSF for comparison purposes (2% MgSt was not feasible for pressures > 40 MPa). A spray rate of 0.3 kg/h further reduced the ejection force, enabling tableting up to 120 MPa, but higher compression pressures resulted in a stop of the machine. Setting the spray rate to 0.4 kg/h or higher provided a sufficient reduction of the ejection force enabling tableting for all compression pressures (Figure 36). When the effective lubricant spray rate of 0.4 kg/h was reached, a further increase in the spray rate did not result in a further reduction of the ejection force. Internal lubrication with 3% SSF resulted in the same ejection forces as external lubrication with 0.4 – 0.6 kg/h, therefore no superiority of one method could be defined in regard of the ejection force. Internal lubrication with 3% SSF reduced the ejection force even more than 3% MgSt as already observed in chapter 3.1.4.

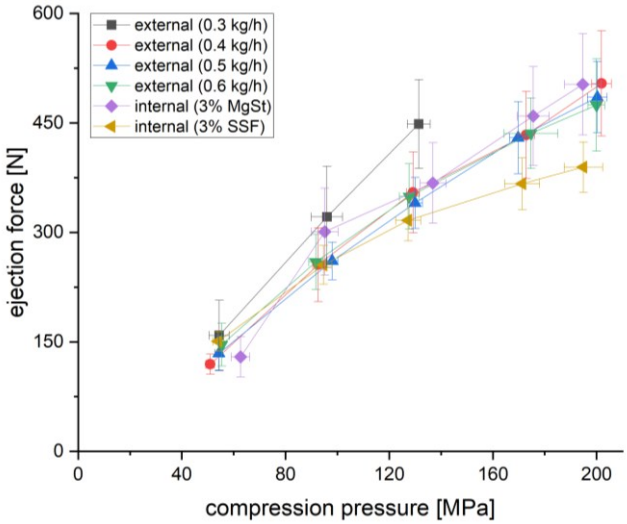


Figure 36: Ejection force of Ludiflash® ODMTs, tableted on Korsch XM 12, 10 rpm, n = 5 – 7 (depending on how many datapoints were recorded in the 30 s sampling interval), mean ± SD

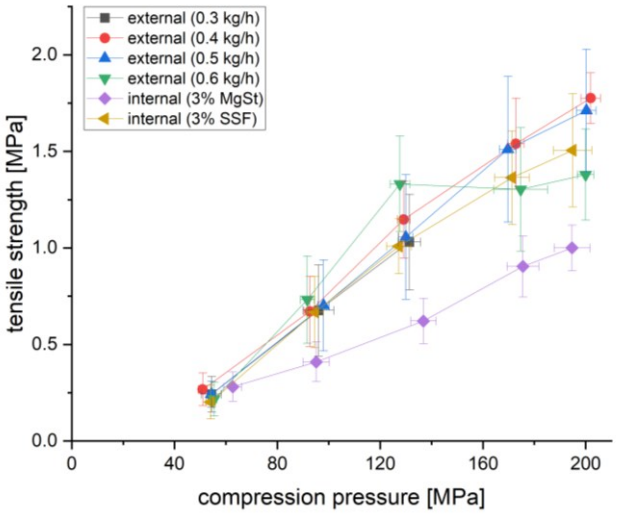


Figure 37: Tabletability of Ludiflash® ODMTs, tableted on Korsch XM 12, 10 rpm, n = 10, mean ± SD

The tabletability showed no significant changes for the different spray rates (Figure 37, except datapoint with 0.6 kg/h at 200 MPa: significant difference), but a clear drop in tensile strength was seen for the internal lubrication with 3% MgSt, which can be attributed to overlubrication caused by the shear forces of the paddles in the filling shoe. The comparability of the plots is limited due to consolidation of the blend in the feeder resulting in MTs with a higher final weight. After adjusting the tablet mass in the beginning, the filling height was kept constant during tableting. The normalized TS, adjusted by the tablet mass, was calculated to account for this effect and confirmed the same behavior for the different lubrication methods. These findings in this work are confirmed by the study of Lura et al. [250], where no significant effect of the MgSt dosing rate on the TS was observed when the run order was taken into account. The authors also found a notably higher TS for external lubrication compared to internal lubrication with 1% MgSt, which can be explained by the shear forces to which

the powder is subjected and should be considered as an additional mixing step [246, 251, 252]. The blend with 3% SSF exhibited a better tabletability, comparable to tableting with internal addition of MgSt and pronounced the lower susceptibility of overlubrication of SSF, reported in some studies [112, 246, 253].

Figure 38 summarizes the disintegration times for the different lubrication methods. A clear difference between the internal and the external lubrication can be seen and emphasizes the preferred use of the external lubrication system in regard of the disintegration times, as already found in the previous experiments on the Styl'One compaction simulator. While the batches with external lubrication fulfilled the FDA criteria for orodispersible tablets for spraying rates up to 0.5 kg/h, the internally lubricated batches did not even pass the Ph. Eur. limit as they were not disintegrated after 3 min. As already mentioned in chapter 3.1, internally lubricated MTs with SSF disintegrated faster than those lubricated with MgSt. However, it was not possible to assign the analyzed MTs from the rotary press to a special position in the multi-tip punch, as they were ejected and collected all together.

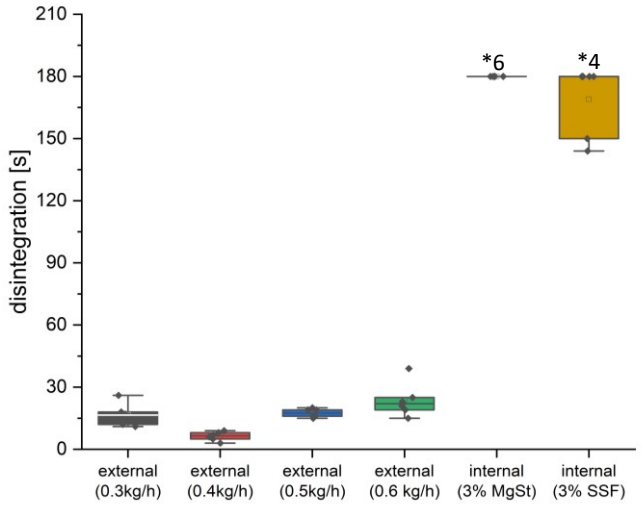


Figure 38: Box plot of the disintegration time of Ludiflash® ODMTs, tableted on Korsch XM 12 at 120 MPa, 10 rpm, n = 6
**: number of tablets which did not disintegrate within 180 s*

A dependency of the disintegration time on the spray rate was visible, but the batch with 0.3 kg/h fell out of the line. It has to be considered that this batches failed tableting for compression pressures > 120 MPa and the insufficient lubrication could lead to the creation of heat during ejection [254, 255] which could result in a higher disintegration time [256], therefore this batch should be excluded from the evaluation. The other batches showed a higher disintegration time with an increase in the spray rate, corresponding to the data of the Styl'One compaction simulator.

3.2.5. Summary

Tableting with external lubrication was feasible on the Styl'One compaction simulator as well as on the rotary press Korsch XM 12. Moreover, it significantly reduced the disintegration time of Prosolv® ODT minitablets in comparison to internal lubrication if the spray rate was chosen on a low level. In contrast to internal lubrication, SSF did not show shorter disintegration times than MgSt as an external lubricant, which can be explained by the competition-for-water hypothesis and should be confirmed with a determination of the sprayed lubricant amount on the MTs. Raman images revealed that the lubricant is distributed inhomogeneously on the different die positions for external lubrication, but the findings should be confirmed with a higher sample size per tablet position. The amount of MgSt in the single minitablets was dependent on the position and the spray rate but was mostly lower than for internal lubrication.

For Ludiflash® ODMTs, the external lubrication with MgSt also showed a better tabletability profile than internal lubrication and should be favored for the production of ODMTs. The findings of the compaction simulator could be partly confirmed using the rotary press. Here, the spray rate was a critical factor to provide sufficient lubrication for the reduction of the ejection force. When the effective spray rate was reached, no significant differences in tabletability and the ejection force were observed. The effect on the disintegration was not as pronounced as on the compaction simulator, but also showed a trend for longer disintegration times for a higher spray rate. External lubrication represents a good alternative for formulations which are close to the disintegration limit or even fail to fulfil the criteria for ODMTs with internal lubrication.

Nevertheless, the high lubricant consumption while using external lubrication has to be considered from an economic perspective, as most of the lubricant is removed by the dust extraction system and does not remain on the minitablets. Although MgSt is less expensive than SSF, rotary presses are operated for several hours in industrial minitablet production, resulting in significantly higher lubricant consumption compared to internal lubrication.

Further studies on externally lubricated minitablets should investigate the consistency of the spraying mechanism with a determination of the lubricant content and the impact of the settings of the exhaust system, which are suspected to have an impact on the spraying of the lubricant. Moreover, content uniformity could be a critical factor, especially for low-dosed MTs, if different lubricant amounts are sprayed onto the individual minitablets. Thus, a study including an API should be conducted to assess variations in the API content.

3.3. Potential of ready-to-use excipients with a co-processed lubricant for ODMTs

The lubricant plays a crucial role in the manufacturing of tablets, but is known to prolong the disintegration time as shown in the literature [90, 101, 112] and in chapter 3.1. Co-processed excipients with an integrated lubricant could be a solution to this problem, as the prolongation of disintegration and dissolution is also influenced by the blending time [93, 128-133]. This blending step is not necessary for the CPEs containing a lubricant, as the lubricant is already incorporated in the excipient.

Commercially available co-processed excipients containing a lubricant are summarized in Table 9:

CPE	Manufacturer	Composition	Reference
Kollitab™ DC 87 L (abbr.: Kollitab™)	BASF, Ludwigshafen, Germany	Lactose and 1% SSF	[257]
LubriTose™	Kerry, Tralee, Ireland	96% filler (either lactose, mannitol or MCC) and 4% glyceryl monostearate	[258]
Parteck® LM	Merck, Darmstadt, Germany	mannitol with either 3 (low) or 5% MgSt (high)	[259]
Prosolv® EASYtab SP	JRS Pharma, Rosenberg, Germany	MCC, colloidal silicon dioxide, sodium starch glycolate and 0.5% SSF	[260]

Table 9: Summary of excipients with an incorporated lubricant

Some studies on LubriTose™ and Prosolv® EASYtab SP already demonstrated their superiority to the corresponding physical mixtures as similar or better tabletability, dissolution or ejection force profiles were obtained [260-264]. The use of self-lubricating excipients offers advantages like fewer processing steps, less segregation tendency and no unfavorable lubricant effects such as prolonged disintegration or decreased TS. In the following chapter, Kollitab™ and Parteck® LM low and high were used for the evaluation of lubricated ready-to-use excipients for the use for orodispersible minitablets. As these excipients are relatively new on the market, there are no studies about their tableting behavior available yet. For comparison purposes, a physical mixture of Kollitab™ was prepared (used lactose grade: FlowLac® 100, composition see Table 10) and mixed for 2 min. The mixture and the lubricated CPEs were first tableted into 2 mm ODMTs on the Styl'One compaction simulator to test their general feasibility. Afterwards, minitablets were produced on the rotary press Korsch XM 12, as here an additional "mixing step" [251] takes place in the force feeder, which is not the case for the Styl'One compaction simulator as no filling shoe is available for minitablets. Mixtures with internally added lubricant were tableted to assess the potential superiority of the excipients with incorporated

lubricant. The data was compared to the simulation of a Korsch XM 12 rotary press on the compaction simulator.

3.3.1. Characterization of Kollitab™ as an excipient for OD(M)Ts

While most of the currently used excipients for ODTs contain mannitol as the main ingredient, the use of lactose is not so common in the literature. Kollitab™ was introduced into the market in 2022 by BASF as an all-in-one solution for tableting. The composition of Kollitab™ is listed in Table 10.

Substance	Function	Quantity (w/w %)
α-Lactose monohydrate	filler	87%
Kollidon® CL-F (crospovidone)	disintegrant	9%
Kollicoat® IR (Polyethylene glycol-polyvinyl alcohol co-polymer)	binder	3%
SSF	lubricant	1%

Table 10: Composition of Kollitab™ according to [257]

Kollitab™ is manufactured by aqueous spray drying and consists of spherical particles (Figure 39) with a mean particle size of 143.68 ± 4.91 µm ($d_{50,}$ n = 3). With an angle of repose of 21.8 ± 1.7°, it exhibited excellent flowability according to Ph. Eur. 2.9.36. Despite the incorporated lubricant, Kollitab™ demonstrated good wettability with a contact angle (CA_0s) of 13.3 ± 1.6 °.

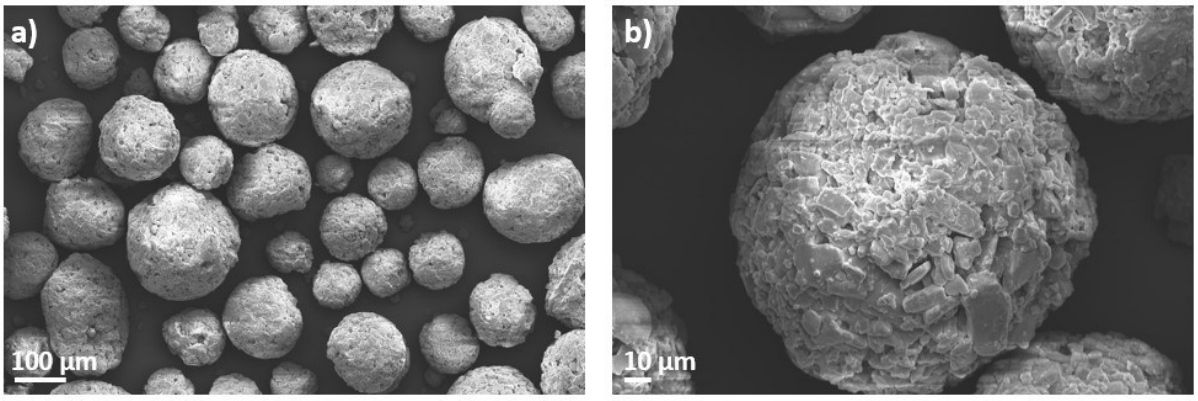


Figure 39: SEM images of Kollitab™, a) 100x magnification, b) 540x magnification

In comparison to the previously studied excipients (chapter 3.1), MTs of Kollitab™ and the corresponding physical mixture exhibited very rapid disintegration (Figure 40), which made it hard to determine the exact disintegration time as the ODMTs immediately disintegrated after being moved into the disintegration medium. Only Ludiflash® and Parteck® ODT disintegrated in the same time range but showed significantly higher ejection forces (Figure 41) which may present a problem for API containing formulations. The tabletability plot (Figure 41) revealed no inferiority compared to the other excipients with the same lubricant level. The superiority of Kollitab™ over the physical mixture

can also be seen in the tabletability and ejection force plot and pronounce the advantage of co-processing of the excipients.

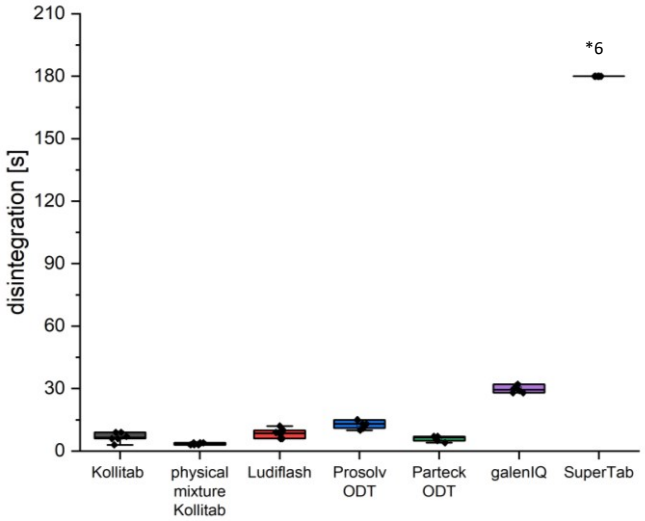


*Figure 40: Box plots of disintegration times of 2 mm ODMTs with 1% SSF, tableted on Styl'One compaction simulator at 120 MPa, n = 6, *: number of tablets which did not disintegrate within 180s*

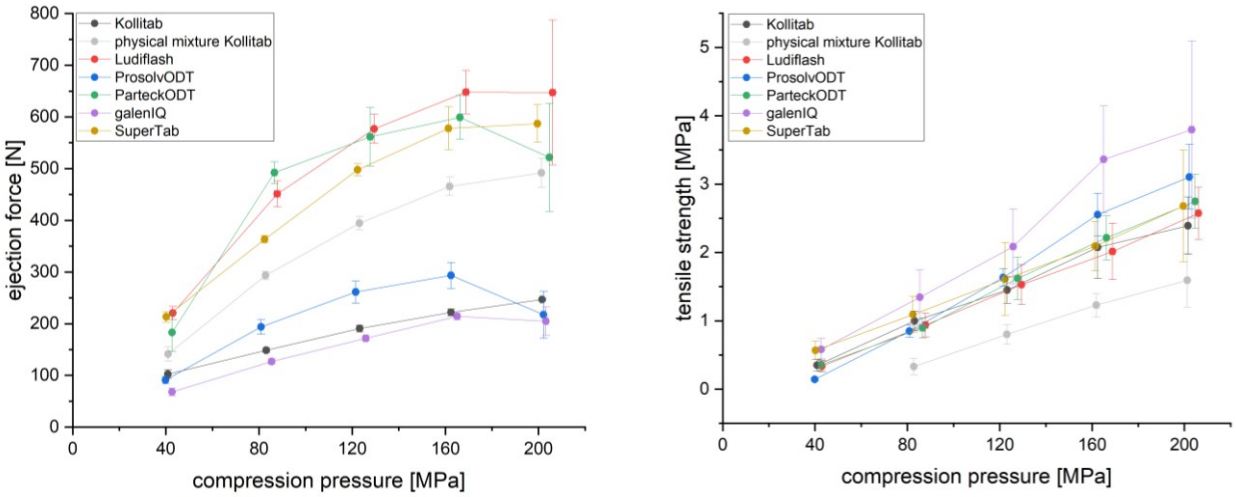


Figure 41: Ejection force (left) and tabletability (right) of 2 mm ODMTs with 1% SSF, tableted on Styl'One compaction simulator, n = 10, mean ± SD

The data from the drug-free minitablets with Kollitab™ are highly promising as a new platform for ODMTs, as it offered very fast disintegration with low ejection forces during tableting. The only disadvantage is the missing flexibility in the lubricant concentration, which is fixed to a level of 1%. It could be adapted by the addition of SSF considering the detrimental effect of mixing a lubricant into a powder.

Following this, ibuprofen (IBU) was added as a model drug in concentrations of 10 and 20% to study the influence of a poorly soluble drug with sticking issues. Even after adding up to 20% IBU, the minitablets still disintegrated within the FDA limit of 30 s (Table 11). The ejection forces were rising by

the addition of ibuprofen, as only 1% SSF were incorporated in the excipient and a higher lubricant amount can be required when API is added. The ODMTs with 20% drug load showed ejection forces > 500 N, which would not be favorable for longer tableting runs. The tensile strength was even increased by the addition of IBU, which is also discussed in chapter 3.6.2.

	Tensile strength [MPa]	Ejection force [N]	Disintegration [s]
Kollitab™	1.4 ± 0.2	191 ± 6	7 ± 2
10% IBU + Kollitab™	1.6 ± 0.2	387 ± 30	8 ± 2
20% IBU + Kollitab™	2.0 ± 0.2	565 ± 46	14 ± 4

Table 11: Properties of 2 mm (IBU-)ODMTs with Kollitab™, tableted on Styl'One compaction simulator at 120 MPa, TS and ejection force: n = 10, disintegration: n = 6, mean ± SD

Overall, Kollitab™ seems to be capable of incorporating a poorly soluble drug and still fulfilling the FDA criteria. The lubricant amount of 1% SSF was sufficient for the manufacturing of 2 mm MTs, nevertheless the ejection force has to be kept in mind when a higher API concentration is added.

3.3.2. Characterization of Parteck® LM as an excipient for OD(M)Ts

Parteck® LM is available in two types: Parteck® LM low consists of 97% D-mannitol and 3% MgSt, whereas Parteck® LM high contains 95% D-mannitol and 5% MgSt. The powder properties of both Parteck® LM grades are summarized in Table 12:

	Parteck® LM low	Parteck® LM high
d_{10} [µm]	29.61 ± 0.78	12.73 ± 0.07
d_{50} [µm]	160.76 ± 5.48	155.29 ± 0.78
d_{90} [µm]	455.56 ± 43.20	436.06 ± 12.40
DSP	2.65 ± 0.18	2.73 ± 0.07
Angle of repose [°]	31.5 ± 2.1	32.6 ± 0.8
CA_0s [°]	43.0 ± 2.6	47.0 ± 1.5
CA_30s [°]	26.4 ± 1.9	29.3 ± 2.5

Table 12: Characterized powder properties of Parteck® LM grades, n = 3, mean ± SD

The particle size distribution is similar for both grades as well as the flowability, which is classified as good according to Ph. Eur. 2.9.36. The wettability showed a non-significant trend for a smaller contact angle for Parteck® LM low. Compared to Kollitab™ (see 3.3.1), the contact angle is significantly higher,

which can be attributed to the higher lubricant amount and the presence of a more hydrophobic lubricant type (3 or 5% MgSt compared to 1% SFF).

The SEM images visualized an irregular particle form and irregular surface of Parteck® LM (Figure 42 and Figure 43). The wide span in the particle size could also be seen in the overview pictures a) where particle with varying sizes were visible. The close-up images b) showed that the big particles are covered by platelet-like structures, which might present the MgSt on the particle surface. This pronounces the difference to Kollitab™, where no platelet structures were seen and might indicate that the lubricant MgSt in Parteck® LM was only admixed to the mannitol and not fully co-processed.

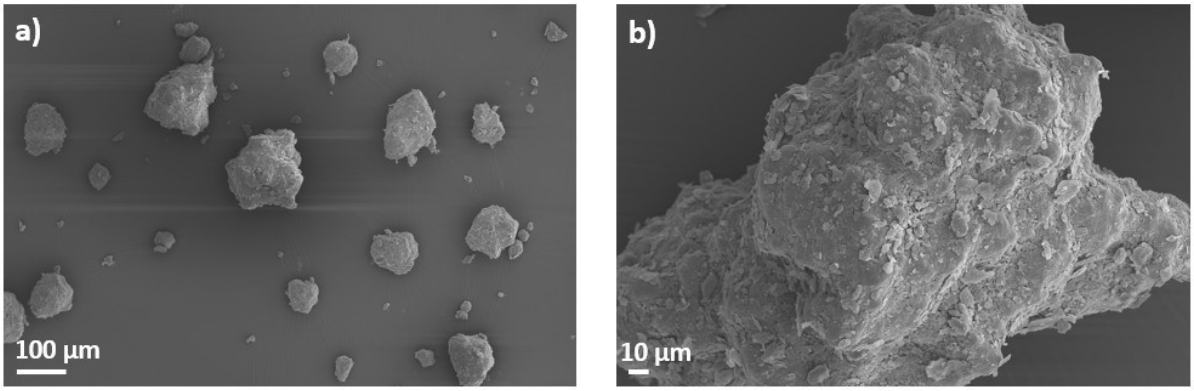


Figure 42: SEM images of Parteck® LM low (taken at 100x magnification (a) and 400x magnification (b)), scale bars are given in the illustration

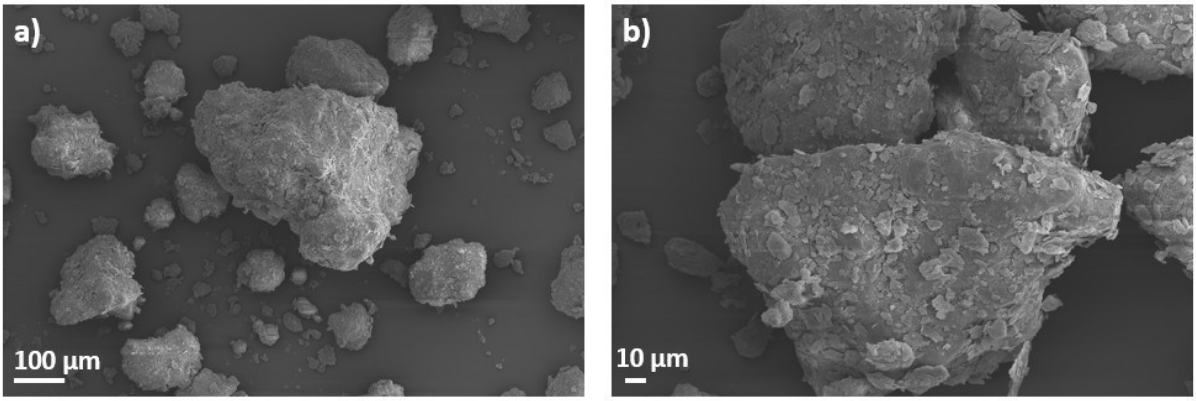


Figure 43: SEM images of Parteck® LM high, (taken at 100x magnification (a) and 400x magnification (b)), scale bars are given in the illustration

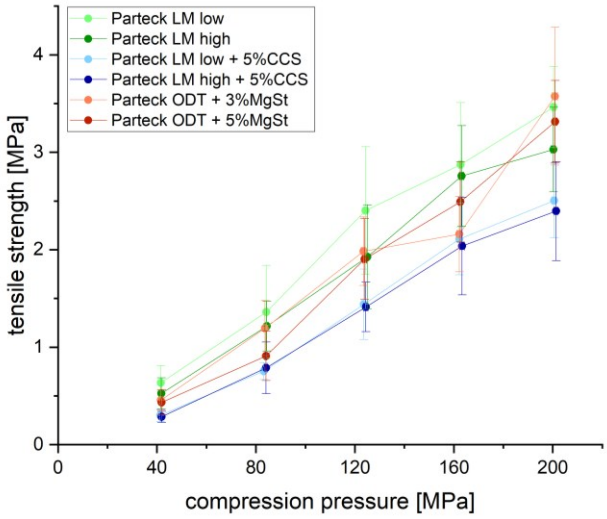


Figure 44: Tabletability of Parteck® LM (+5%CCS) and Parteck® ODT minitablets, tableted on the Styl'One compaction simulator, n = 10, mean ± SD

As Parteck® LM does not contain an incorporated disintegrant, additional blends with 5% CCS (comparable to the disintegrant amount in the CPE Parteck® ODT) were used for tableting to ensure rapid disintegration. The tabletability plot (Figure 44) showed a similar mechanical stability of the ODMTs manufactured with the new excipient compared to Parteck® ODT minitablets with the same amount of internally added MgSt. The addition of 5% CCS resulted in lower overall tabletability, which can be attributed to the additional mixing step of the disintegrant.

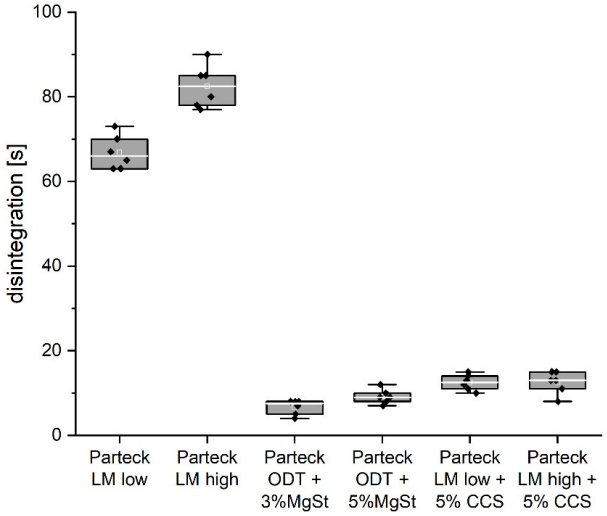


Figure 45: Box plots of disintegration time of Parteck® LM and Parteck® ODT minitablets, tableted on Styl'One compaction simulator at 120 MPa, n = 6

The disintegration test (Figure 45) revealed, that the absence of a disintegrant led to significantly prolonged disintegration times. The minitablets with 5% CCS disintegrated in about 12 s, regardless of their lubricant concentration. Without the disintegrant, Parteck® LM showed significantly longer disintegration with 5% MgSt compared to the low amount of the lubricant. Nonetheless, Parteck® ODT

minitablets with internally added lubricant showed the lowest disintegration time. Gordon et al. [265] described the favored intragranular incorporation of croscarmellose as this led to an improved dissolution performance of the tablets as they disintegrated into primary particles instead of bigger granules. Comparing both excipients, no superiority of the co-processed lubricant over Parteck® ODT could be determined.

3.3.3. Potential of CPEs with co-processed lubricants in the transfer to a rotary press

In the transfer of a formulation from lab-scale to a rotary press, differences in the tableting speed, dwell time and mixing process have to be considered and can explain varying results for differing machines [266-268]. Compaction simulators are a versatile tool for the initial characterization of powders and formulations and can be used for upscaling experiments [145, 269, 270]. Previous studies [252, 271, 272] on the transfer of formulations from the compaction simulator to a rotary press already proposed the possible phenomenon of overlubrication in the filling shoe. This might explain the discrepancy between simulation and real data in the transfer of tableting processes.

Furthermore, the feeding process has to be taken into account, as the feeders itself have a different set-up, filling volume and therefore exhibit different shear forces on the powder blend. Furukawa et al. [273] described the impact of the feed frame and the MgSt amount in the mixture and developed a model for the prediction of the tensile strength including the shear forces of the paddles. Peeters et al. [251] proposed to consider the movement through the filling shoe as an additional blending step as a change in the paddle speed affected the tensile strength significantly. A model by Puckhaber et al. [274] also included the powder characteristics of the lubricant to describe the extent of the reduction of the tensile strength by the shear forces of the paddles. Wünsch et al. [252] took a detailed view into the filling process and compared the different feeders of the Styl'One compaction simulator and the rotary press with an adapted version of the shear number by Narang et al. [275]. The authors found significantly higher shear numbers for the Styl'One feed shoe, indicating that a higher shear stress is applied on the powder, which can explain the decrease in TS. The findings of de Backere et al. [246] supported the hypothesis that the shear forces in the feeder can be considered as an additional blending step and could already assess its impact on the compaction simulator by the number of paddle passes. All these studies pronounce the importance of the consideration of the filling process in the transfer of tableting processes from a compaction simulator to a rotary press.

For the production of minitablets, this problem gains an even greater importance, as no filling shoe for minitablets is available for the Styl'One compaction simulator and therefore the complete filling process is neglected. Only a few studies for the transfer of minitablets are available in the literature [271, 272]. Lura et al. [272] investigated the transfer of placebo ODMTs from the compaction simulator

to a Korsch rotary press and found no significant differences in the tabletability and compactability. However, the disintegration increased during the production time and could be attributed either to overlubrication or the rising product temperature during the process. Another publication by Lura et al. [271] studied the transfer of losartan MTs and found a clear difference between the simulated data and the MTs from the rotary press. As the porosity of the MTs could not explain this phenomenon completely, the residual powder from the rotary press filling shoe was tableted on the Styl'One compaction simulator and corresponded with the data of the rotary press. The results of the MTs made of the residual powder indicated that the shear stress of the paddles may be an explanation for the discrepancies in TS.

In this chapter, the use of CPEs with integrated lubricants was evaluated regarding the simulation and transferability from the compaction simulator to the rotary press. As differences between the simulation and the real data on the Korsch were observed, the residual powder, which was left in the feed shoe after tableting on the rotary press, was tableted on the Styl'One compaction simulator with the simulation profile of Korsch XM 12 (see 5.2.1.2) to assess possible effects of overlubrication or densification in the feed shoe of the rotary press.

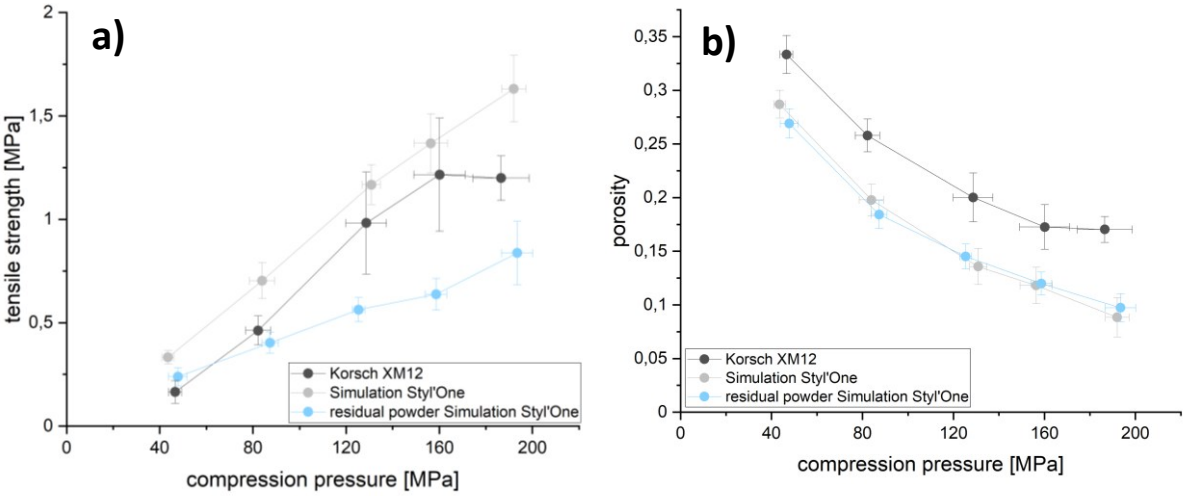


Figure 46: Tabletability (a) and compressibility (b) plot of Kollitab™ 2 mm minitablets, 10 rpm, n = 10, mean ± SD

Figure 46a depicts the tabletability of Kollitab™ on the Korsch XM 12 compared to the simulation with the initial and the residual powder. The simulation slightly overestimated the tabletability on the rotary press. A clear change in the powder properties can be seen in the comparison of the tabletability of the original and the residual powder of the filling shoe. This indicates an impact of the shear forces of the paddle feeders for Kollitab™, even if the lubricant was incorporated in the excipient. The overestimation of the Styl'One compaction simulator can be explained with the differences in the porosity of the tablet (Figure 46b), which is higher for the Korsch XM 12 than for the Styl'One

compaction simulator. While the die was filled manually on the Styl'One compaction simulator, the Korsch XM 12 consists of two paddle feeders, which could lead to the incorporation of air and therefore a higher porosity, as the air inside the filling shoe can influence the weight and flowability of the powder [276, 277].

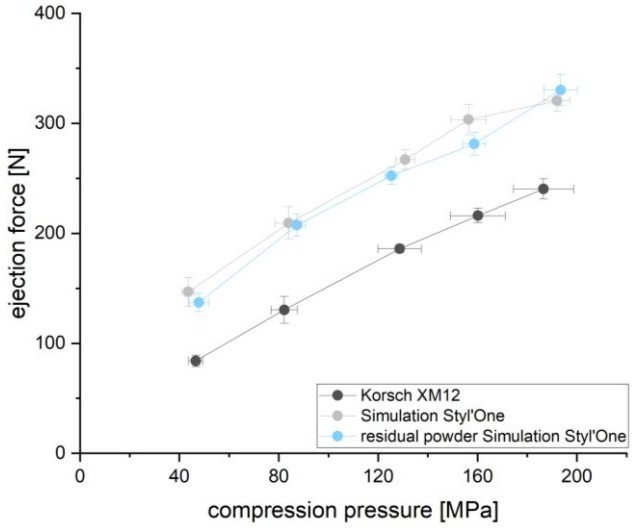


Figure 47: Ejection force of Kollitab™ 2 mm minitablets ,10 rpm, n = 10 (for Styl'One compaction simulator) bzw n = 6 (for Korsch XM 12), mean ± SD

The ejection forces on the Korsch XM 12 rotary press were higher than the ones of the simulated compression profiles (Figure 47). The measurement of the ejection stress during scale-up can be helpful for the prediction of tablet failure in the industrial scale [278]. In this case, the Styl'One compaction simulator even obtained higher ejection forces and no tablet defects were visible for the Kollitab™ minitablets produced on the rotary press. The disintegration times (data not shown) were below 10 s for all Kollitab™ ODMTs, regardless of the machine used.

In the next step, the experiments on the rotary press were repeated with both Parteck® LM grades, as they contain a higher lubricant concentration and are available with two different amounts of MgSt. Figure 48 shows the tabletability profiles of Parteck® LM low and high and the profile of the corresponding simulation. For both Parteck® LM grades, the simulation predicted the tabletability profile of the rotary press adequately, but exhibited high variations in the TS data which make it difficult to draw a clear conclusion. Tableting of the residual powder of Parteck® LM low on the compaction simulator only showed a minor decrease in TS indicating less alteration of the powder properties by the shearing and possible overlubrication process in the filling shoe. The same behavior applied for the Parteck® LM grade with the higher amount of MgSt, here the decrease of the residual powder was pronounced a little more.

In contrast to Kollitab™, no differences in the porosity were notable (Figure 49) and can explain the better fit of the simulation with the MTs produced on the rotary press, confirming transfer experiments of API-free minitablets in the literature [272].

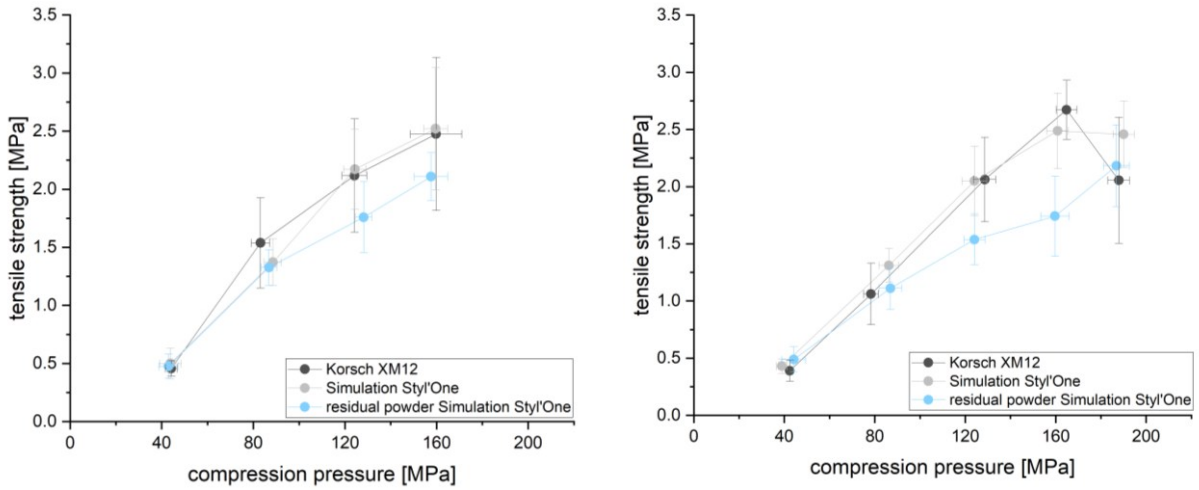


Figure 48: Tabletability of both Parteck® LM grades, left: Parteck® LM low, right: Parteck® LM high, 10 rpm, n = 10, mean ± SD

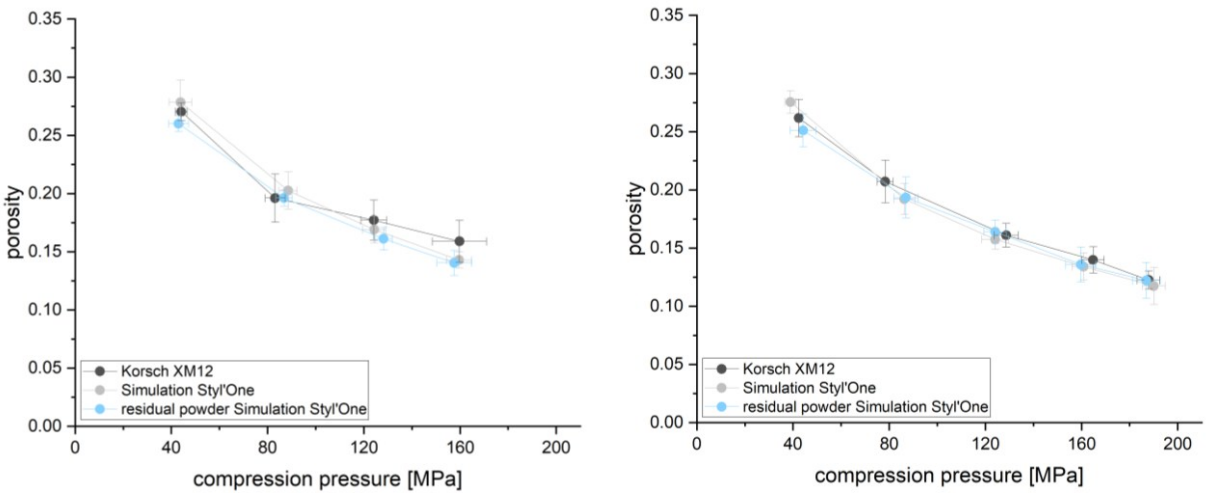


Figure 49: Compressibility plot of both Parteck® LM grades, left: Parteck® LM low, right: Parteck® LM high, 10 rpm, n = 10, mean ± SD

In Figure 50, the tabletability of the mixtures of Parteck® ODT with an internally added lubricant is depicted. As for the preliminary experiments on the compaction simulator (see 3.3.2), the mixtures of Parteck® ODT showed similar behavior as Parteck® LM. The Parteck® LM minitablets with 5% CCS showed a decreased TS. As a look onto the compressibility (Figure 50) revealed no differences in the porosity of the MTs, the decreased TS of the blend with 5% CCS can be attributed to the additional mixing step of the disintegrant.

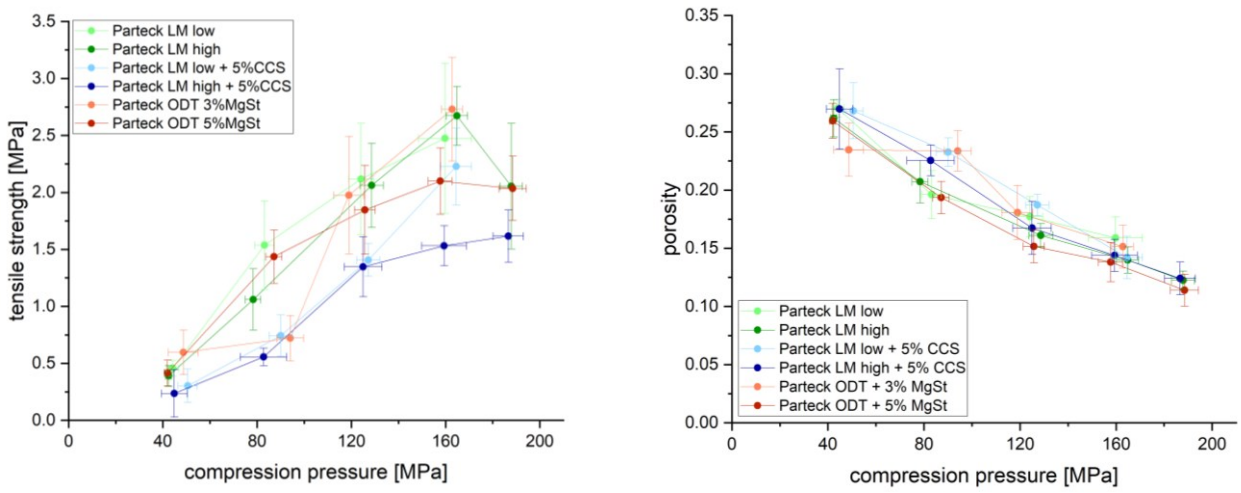


Figure 50: left: Tabletability of 2 mm minitablets of Parteck® LM (+addition of 5% CCS) and the corresponding mixture of Parteck® ODT + MgSt, right: compressibility plot, tableted on Korsch XM 12, 10 rpm, n = 10, mean ± SD

The ejection forces of both Parteck® LM grades (Figure 51) differed signficantly and tableting of Parteck® LM low was not possible with the highest compression pressure of ~ 200 MPa, as the ejection force limit of 600 N was exceeded, which was also the case for the Parteck® ODT with 3% MgSt. Therefore, the grade with the higher lubricant concentration can be used for tableting at higher compression pressures or with higher drug loads, which might increase the ejection force.

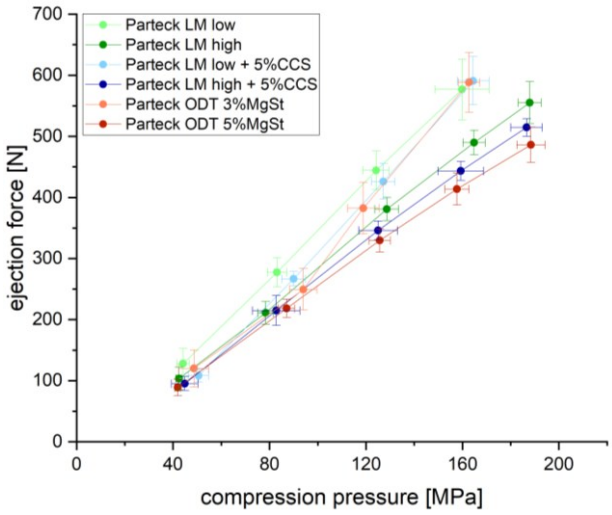


Figure 51: Ejection force of 2 mm minitablets of Parteck® LM (+ addition of 5% CCS) and the corresponding mixture of Parteck® ODT + MgSt, tableted on Korsch XM 12, 10 rpm, n = 6, mean ± SD

As in the preliminary trials on the Styl'One compaction simulator, the disintegration of Parteck® LM low, shown in Figure 52, was shorter than of Parteck® LM high, where 3 MTs did not fulfil the criteria of the Ph. Eur. for ODMTs. The addition of 5% CCS decreased the disintegration time, as well as the comparison with Parteck® ODT and the corresponding MgSt amount, so the criteria of the FDA for ODMTs were met.

Overall, Parteck® LM showed a good transferability from the compaction simulator to a rotary press with similar tabletability and compactability. However, Parteck® LM needs the addition of a disintegrant to achieve disintegration times within the FDA criteria, which can lead to a decreased tensile strength due to the additional mixing step. Therefore, Parteck® ODT should be preferred for ODMTs, even if the lubricant has to be added internally.

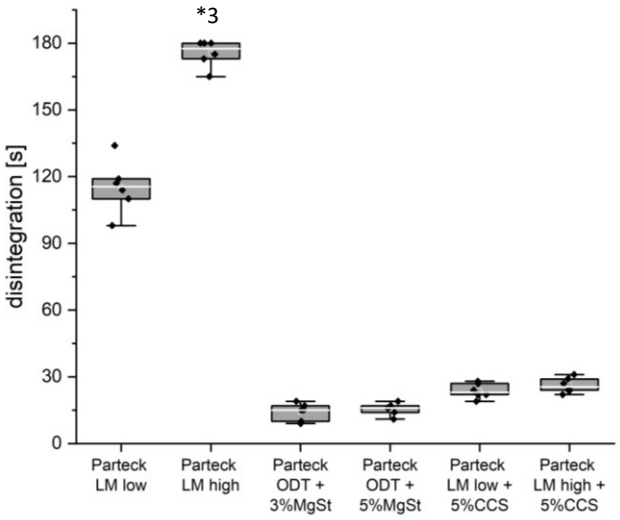


*Figure 52: Box plots of disintegration time of Parteck® LM and Parteck® ODT minitablets, tableted on Korsch XM 12 at 120 MPa, 10 rpm, n = 6, *: number of tablets which did not disintegrate within 180 s*

3.3.4. Summary

In summary, excipients with a co-processed lubricant offer a high potential for a fast and simple formulation development and can avoid the negative influence of lubricants such as prolonged disintegration and dissolution behavior. Also, they save time as the second mixing step can be skipped, therefore they are of high interest especially when it comes to continuous manufacturing.

The studied excipients showed sufficient tensile strengths, acceptable ejection forces and fast disintegration and fulfilled the Ph. Eur. requirements for ODMTs. To fulfill the FDA criteria, further development is needed for Parteck® LM. The missing disintegrant led to disintegration times above the 30 s limit, and a comparison to Parteck® ODT demonstrated no superior performance of the co-lubricated excipient. The two grades of Parteck® LM showed similar properties for the mechanical stability and the disintegration of the MTs, regardless of their MgSt amount.

The transfer experiments from the compaction simulator to the Korsch XM 12 rotary press could exclude overlubrication as the reason for inaccurate predictions of the compaction simulator. Therefore, the use of CPEs with an incorporated lubricant did not offer a benefit for the transfer of processes to a bigger scale. The shear stress exhibited by the paddles in the feeder and possible

incorporation of air by the paddle movement might explain the different tabletability and compressibility. While the simulated tableting process of Kollitab™ showed slightly different TS and porosities compared to the rotary press, the compaction simulator could describe the tablet properties for Parteck® LM quite good.

3.4. Influence of the lubricant on the properties of an ODMT formulation containing the water soluble model API zolmitriptan

Following the evaluation of the effect of lubricants on drug-free ODMTs, the experiments were repeated on the Styl'One compaction simulator with an API-containing formulation to enable the analysis of the lubricant effect on the dissolution profile. Zolmitriptan (ZMT) served as the model drug for a water soluble API and is supposed to impact the tableting behavior. Due to the good solubility of the API (1.3 mg/ml [177]), only a minor influence on the disintegration time can be expected, so the disintegration should be primarily governed by the choice of the filler and lubricant.

ZMT was provided in micronized form (d_{50} = 6.52 ± 0.24 µm), resulting in a bad flowability (angle of repose 47.2 ± 0.5°). SEM images (Figure 53) confirmed the high distribution span of the particle size (DSP = 4.78 ± 0.26) as agglomerates of very fine particles on bigger particles were visible.

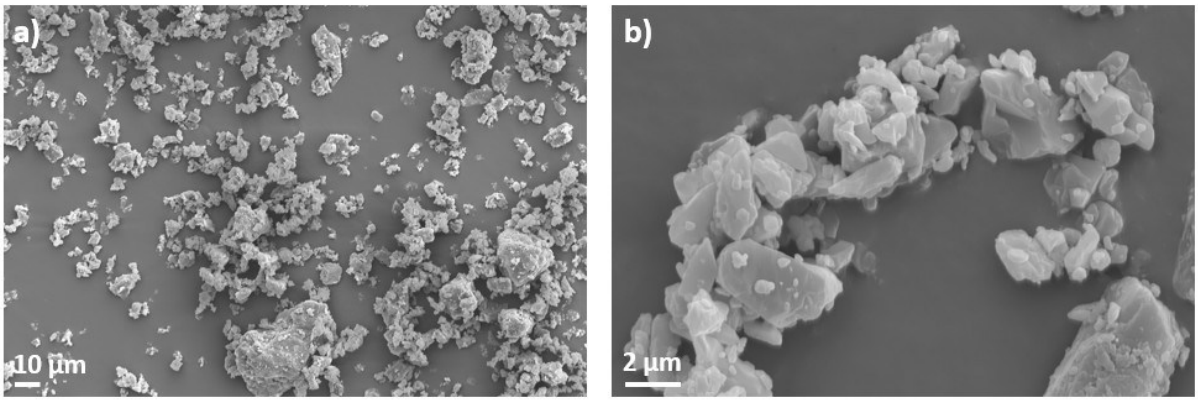


Figure 53: SEM images of zolmitriptan, (taken at 500x magnification (a) and 5430x magnification (b)), scale bars are given in the illustration

3.4.1. Choice of the filler

As a first screening for a suitable formulation, all excipients used in chapter 3.1, lubricated internally with a concentration of 3% SSF, were tested besides Kollitab™ (characterized in 3.3.1). As galenIQ™ and SuperTab® ODT are not co-processed with a disintegrant and a glidant as the mannitol-based excipients, 0.5% fumed silica and Kollidon® CL-SF were added. In case of SuperTab® ODT, 5% crospovidone was included, corresponding to the concentration included in Ludiflash® or Prosolv® ODT. For galenIQ™, 4% were considered sufficient as demonstrated by Lura et al. [79].

In preliminary trials, a drug load of 20% was tested, but resulted in massive capping and ejection force overloads (>1000 N). In addition, the filling of the minitablet dies proved to be challenging, as the API and therefore also the blend exhibited bad flowability. The powder had to be swiped manually several times over the die to enable complete die filling. Therefore, the drug load was decreased to 10%, and with a target tablet mass of 6.25 mg, the administration of four minitablets would be necessary to

reach the therapeutic dose of 2.5 mg [279]. Even with the reduced drug load, tableting was not possible at all using Ludiflash® and Parteck® ODT. The production of minitablets was feasible with Kollitab™ for low compression pressures, but the ejection force and capping tendency strongly increased in the tableting process at the desired pressure of 120 MPa and had to be aborted after the 7th tableting cycle. In contrast to the other excipients, Kollitab™ already contains 1% SSF, which was sufficient for drug-free ODMTs and could also be compressed with higher drug loads for other drugs (see chapter 3.5 and 3.3.1). Zolmitriptan ODMTs showed huge problems with lubrication in general, as many tablets could not be produced due to exceedance of the ejection force limit.

Tableting with Prosolv® ODT, SuperTab® ODT and galenIQ™ was feasible at 120 MPa and showed no capping or lamination. Minitablets with Kollitab™ were also obtained but showed massive capping and were excluded from further evaluation. The critical quality attributes of the ODMTs and some process parameters are displayed in Table 13.

Used excipient	**RSD mass [%] (n = 10)**	**Tensile strength [MPa] (n = 10)**	**Ejection force [N] (n = 10)**	**Disintegration [s] (n = 6)**
Prosolv® ODT	3.44	1.3 ± 0.3	487 ± 27	24 ± 22
SuperTab® ODT	3.75	1.2 ± 0.4	263 ± 17	2 ± 0.4
galenIQ™	1.87	1.6 ± 0.3	255 ± 11	25 ± 4

Table 13: Properties and process parameters for ODMTs with 10% ZMT and 3% SSF, tableted on Styl'One compaction simulator at 120 MPa, mean ± SD

Of the three feasible excipients, galenIQ™ showed the lowest mass variations, indicating a good flowability, the highest tensile strength and the lowest ejection force. Only for the disintegration test, tablets with SuperTab® ODT disintegrated very rapidly, but made the visual determination of the endpoint quite hard. To evaluate the differences in disintegration for further modifications in the formulation, galenIQ™ was chosen, as it presented the best properties for the rest of the CQAs and showed a disintegration time within the FDA limits.

3.4.2. Impact of the lubricant

For the following experiments, the formulation developed in 3.4.1 was used (Table 14):

Trade name	Material	Quantity (w/w %)
-	Zolmitriptan	10
galenIQ™ 721	Isomalt	85.5
Kollidon® CL-SF	Crospovidone	4
Aerosil® 200	Fumed silica	0.5
Parteck® LUB	MgSt	Varying (internal or external)
Pruv®	SSF	Varying (internal)

Table 14: Formulation of orodispersible zolmitriptan minitablets

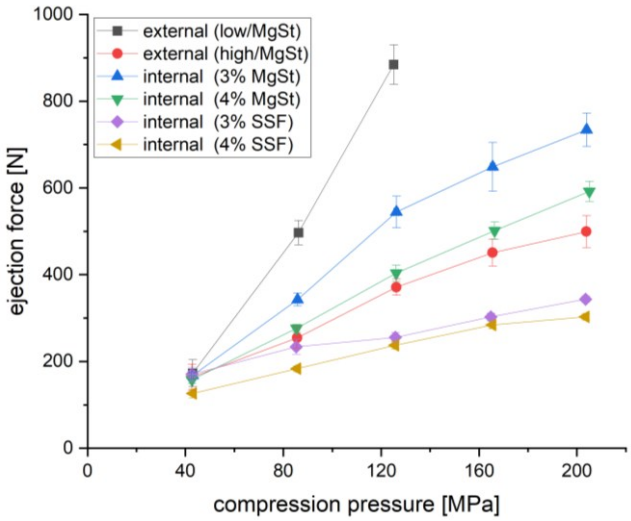


Figure 54: Ejection force of zolmitriptan ODMTs with galenIQ™ with different lubrication methods, tableted on Styl'One compaction simulator, n = 10, mean ± SD

Preliminary trials with 2% MgSt resulted in an ejection force overload and tableting was not feasible. Here the influence of the API is clearly evident, as 2% or even lower concentrations of MgSt were sufficient for the manufacturing of drug-free tablets with galenIQ™. Additionally, external lubrication with MgSt was also taken into account in comparison to internal lubrication. In case of ZMT-ODMTs, the low spray rate did not provide a sufficient lubricant amount and reached high ejection forces about 900 N at a compression pressure of 120 MPa (Figure 54). External lubrication with the high spray rate demonstrated a better ejection force profile but showed the highest disintegration times (Figure 55). Sodium stearyl fumarate showed a much higher lubrication efficiency than MgSt in the same concentrations, confirming the findings of chapter 3.1. The ODMTs lubricated with MgSt exhibited significantly higher ejection forces and longer disintegration times (Figure 55), which did not fulfil the criteria of the FDA guideline anymore. The trend towards slower disintegration with rising lubricant

concentrations or an increased spray rate, already seen for the drug-free tablets (see 3.1) could be confirmed with the zolmitriptan ODMTs.

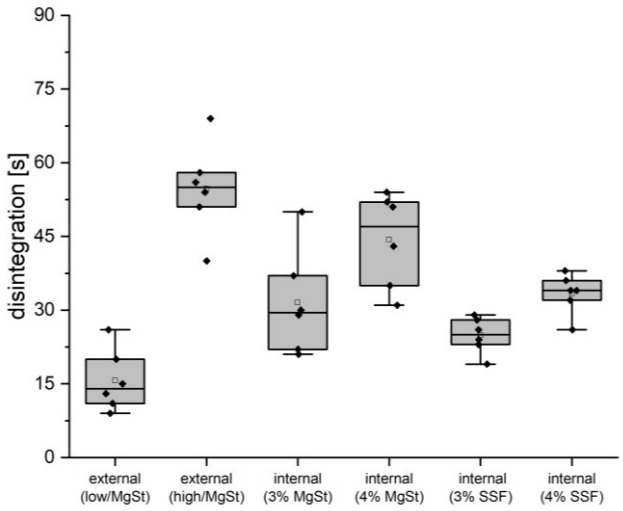


Figure 55: Box plots of the disintegration time of zolmitriptan ODMTs with galenIQ™, tableted on Styl'One compaction simulator at 120 MPa, n = 6

The tensile strengths of the minitablets was satisfactory (> 1 MPa [18, 34]) for all lubrication methods and did not show a superiority for one lubrication method (Table 15). Only the formulation with 4% MgSt showed a significant difference to the formulations with 3% MgSt, 4% SSF and external lubrication with the high spray rate.

	External (low/MgSt)	**External (high/MgSt)**	**Internal (3% MgSt)**	**Internal (4% MgSt)**	**Internal (3% SSF)**	**Internal (4% SSF)**
Tensile strength [MPa]	1.7 ± 0.5	1.7 ± 0.4	1.7 ± 0.3	1.4 ± 0.3	1.6 ± 0.3	1.8 ± 0.4

Table 15: Tensile strength of ZMT-ODMTs, tableted on Styl'One compaction simulator at 120 MPa, n = 10, mean ± SD

Hydrophobic lubricants are known for their ability to prolong the dissolution time [90, 280, 281] if used in higher concentrations. As minitablets have a high SVR, the effect of the lubricant could even be more pronounced but was not studied yet in the literature. The dissolution tests were first performed in 0.1N HCl, as this dissolution medium is required by the USP in the monograph for zolmitriptan orally disintegrating tablets [282]. As a reference, a commercially available ODT ZMT product was also subjected to the release study. The fastest dissolution, comparable to the marketed product, was achieved by the formulation with the external lubrication with a low spray rate (Figure 56). Even with the higher spray rate, ZMT dissolved very quickly and reached the plateau within 5 min. Therefore, the MgSt layer formed on the minitablet by external lubrication did not impede the dissolution of the API, and can be an alternative, if the other tablet properties meet the criteria for the CQAs.

A comparison of the dissolution profiles of ODMTs with the same lubricant type, but different concentrations showed a trend of a prolonged dissolution with an increase of +1% lubricant. However, this trend was not significant and has to be interpreted carefully as the scattering of the data was quite high. The high variations could be due to the rapid dissolution process in general, as the sampling was performed by hand and may vary a few seconds from the exact time point. Besides, the minitablets could stick together and form an agglomerate with less surface available for wetting and dissolution of the API. The same problem was present for the comparison of the different lubricant types, where also a trend for the superiority of SSF over MgSt was notable but was not significant. Of all formulations with internal lubrication, the ODMTs with 3% SFF showed the best performance. Although the externally lubricated minitablets showed the fastest dissolution performance, they should not be preferred over the formulation with 3% SSF, as problems with increased disintegration time (high spray rate) or exceeding ejection forces were encountered (low spray rate).

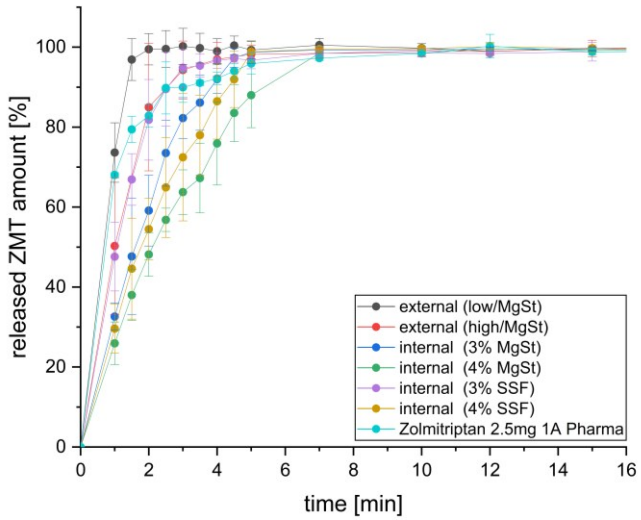


Figure 56: Dissolution profile of zolmitriptan ODMTs, tableted on Styl'One compaction simulator at 120 MPa, in comparison to the marketed product, USP apparatus I, 0.1N HCl, 37 °C, 50 rpm, n = 3, mean ± SD

As the developed formulation is an orodispersible minitablet, the disintegration takes place in the oral cavity, where also the drug dissolution will start. Several studies tried to develop a dissolution medium for orodispersible tablets and to consider factors such as adapted volume and alternative media [283-286]. For this work, a 25 mM phosphate buffer with a pH of 7.35 was chosen, as these conditions were described by Hermes [164] to adapt the pH and osmolality of human saliva samples. The best formulations of internal and external lubrication were subjected to the dissolution test in the alternative medium (Figure 57) in comparison to the marketed product. All formulations met the criteria for orodispersible tablets and reached a plateau within 15 min. In phosphate buffer, a slight difference between internal and external lubrication became notable, whereas the two tested formulations showed a similar dissolution profile in 0.1N HCl. According to the equation of Noyes-

Whitney [287] the dissolution rate is also determined by the saturation solubility, which is higher in HCl (27.82 ± 0.29 mg/ml) than in phosphate buffer (3.05 ± 0.21 mg/ml). The hydrophobic layer on the tablet formed by the lubricant appears to slow down the dissolution process, when the API is less soluble in the medium. To investigate these findings, dissolution experiments on the effect of external lubrication were repeated with a poorly soluble API in the following chapter.

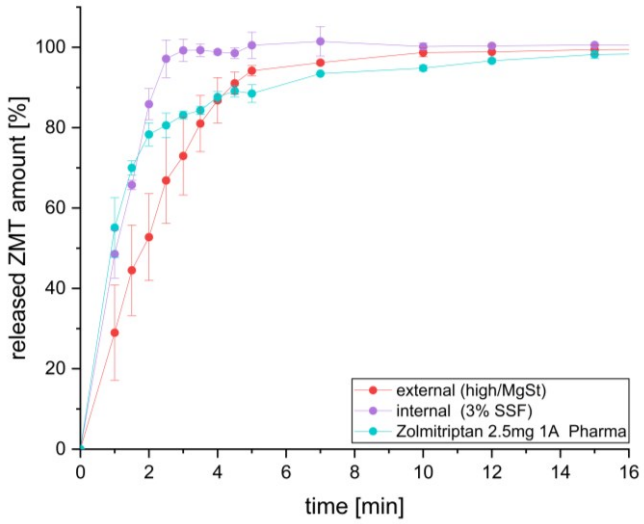


Figure 57: Dissolution profile of selected zolmitriptan ODMT formulations, tableted on Styl'One compaction simulator at 120 MPa, in comparison to the marketed product, USP apparatus I, phosphate buffer pH = 7.35, 37 °C, 50 rpm, n = 3, mean ± SD

3.4.3. Summary

Several challenges emerged during the formulation development of ODMTs with zolmitriptan. Some tablets showed capping and exceeded the ejection force limit and the removal of the minitablets was quite difficult as they stuck on the punches. Moreover, the filling of the minitablet dies was challenging due to poor flowability, so only batches with 10% drug load were produced. Overall, galenIQ™ was chosen for the further characterization of the lubricant influence for API-containing minitablets. All formulations with galenIQ™ can be labeled as orodispersible according to Ph. Eur., but only the formulation with 3% SSF or external lubrication with a low spray rate fulfilled the FDA criteria. Overall, external lubrication did not offer a general advantage for this formulation. With a low spray rate, the ejection force limit was exceeded while with a high spray rate the disintegration time increased. Additionally, the dissolution process in phosphate buffer, which should imitate the conditions in the oral cavity, was slower than for internal lubrication. Therefore, the formulation with 3% internally added SSF was the most favorable one for zolmitriptan ODMTs.

3.5. Influence of the lubricant on the properties of an ODMT formulation containing the poorly soluble model API naproxen

In the following chapter, the impact of the lubrication is tested with a poorly soluble API, as minitablets including ZMT as a drug with good water solubility did not show a significant effect of the lubricant on the dissolution profile (see chapter 3.4.2.). Development of an OD(M)T formulation with a poorly soluble drug presents a challenge as the low solubility might have an impact on the disintegration and dissolution behavior [288]. It can be hypothesized that the lubricant has a more pronounced effect on the disintegration and dissolution process of a poorly soluble drug. In this case, less pores might be formed within the tablet enabling the disintegration process.

Naproxen (NPX) was chosen as a model drug with poor water solubility (15.9 µg/ml [182]). SEM images (Figure 58) showed that NPX had a relatively even particle surface and uniform particle size. This assumption was confirmed by laser diffractometry, as the distribution span was 1.53 (± 0.06, n = 3) indicating a narrow particle size distribution, with a d_{50} of 32.89 µm. The flowability of NPX was classified as poor according to Ph. Eur. 2.9.36. with an angle of repose of 53.5° (± 1.0, n = 3).

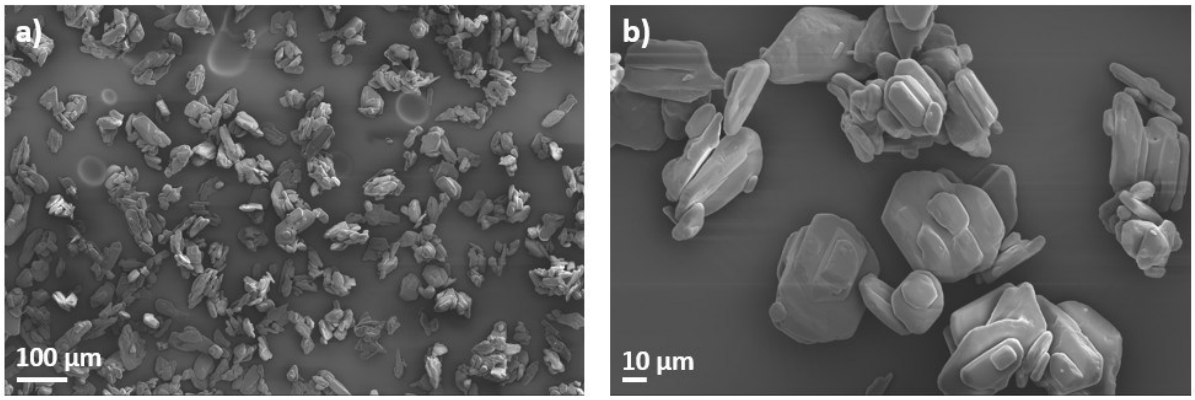


Figure 58: SEM images of naproxen, a) 100x magnification, b) 480x magnification

3.5.1. Choice of the filler for naproxen ODMTs

In the first step, powder blends with the excipients, characterized in chapter 3.1, and Kollitab™ were produced. They contained 10% NPX and 3% SSF, as this lubricant concentration was feasible in the previous development of ZMT minitablets. As Kollitab™ already contained 1% of co-processed SSF, but not sufficient for the manufacturing of ZMT ODMTs, an additional blend with a final concentration of 3% SSF was prepared. All blends were tableted into 2 mm MTs (see 5.2.1.2) and characterized.

Table 16 summarizes the properties of the produced minitablets. Compared to the development of ZMT minitablets, manufacturing of ODMTs with 10% naproxen was possible for all excipients. The significantly bigger particle size, the smaller distribution span and the particle morphology of NPX might be reasons contributing to the differences. No tablet defects like capping or lamination occurred,

as the resulting ejection forces were below 500 N for the relevant compression pressure of 120 MPa. ODMTs with Prosolv® ODT, Kollitab™ with 3% SSF and Ludiflash® exhibited the lowest ejection forces (ascending order). The highest friction was generated during tableting with galenIQ™, SuperTab® ODT and Kollitab™ without additional lubricant. The mechanical stability of the produced ODMTs was in the acceptable range for all formulations (TS > 1 MPa [18, 34]). Because of the high scattering of the data, no superior excipient regarding the TS could be identified. Only SuperTab® ODT had a significantly lower tensile strength than Prosolv® ODT and galenIQ™. Except Prosolv® ODT, all tablet formulations fulfilled the FDA limit for orodispersible tablets, as two ODMTs exceeded the pharmacopeial disintegration limit.

Used excipient	RSD mass [%] (n = 10)	Tensile strength [MPa] (n = 10)	Ejection force [N] (n = 10)	Disintegration [s] (n = 6)
Ludiflash®	4.68	1.5 ± 0.5	223 ± 6	8 ± 3
Parteck® ODT	2.73	1.6 ± 0.3	274 ± 7	4 ± 1
Prosolv® ODT	2.73	1.9 ± 0.4	153 ± 6	30 ± 32 *1
galenIQ™	2.62	1.9 ± 0.5	352 ± 15	18 ± 5
SuperTab® ODT	4.43	1.2 ± 0.4	390 ± 9	2 ± 0 *2
Kollitab™	2.33	1.4 ± 0.2	348 ± 14	2 ± 0 *2
Kollitab™ + 3% SSF	1.64	1.4 ± 0.2	184 ± 5	4 ± 1

Table 16: Mechanical properties and process parameters for ODMTs with 10% NPX and 3% SSF, tableted on Styl'One compaction simulator at 120 MPa
**1: 2 ODMTs exceeded the FDA limit of 30 s*
**2: ODMTs disintegrated very rapidly*

Taking all parameters into consideration, Ludiflash®, Parteck® ODT and Kollitab™ with 3% SSF demonstrated the best performance. As Ludiflash® showed less problems with lower lubricant concentrations than for the drug-free formulation (see 3.1), it was preferred over Parteck® ODT for further studies where the lubricant and API concentration should be modified. The mass variations were the highest for Ludiflash® but this might be attributed to the manual die filling. Thus, Ludiflash® and Kollitab™ were chosen for the further experiments in the following chapters.

3.5.2. Impact of the lubricant

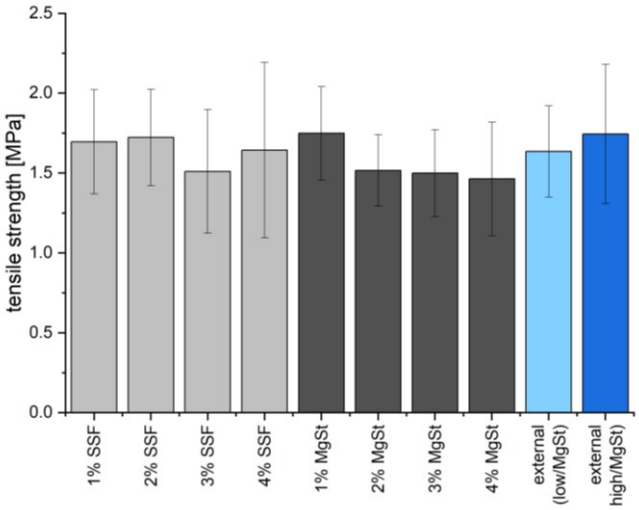
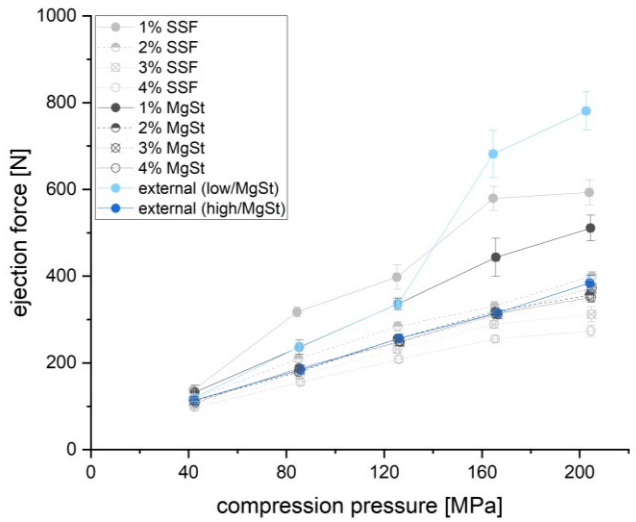


Figure 59: Tensile strength of Ludiflash® ODMTs with 10% NPX and different lubrication methods, tableted on Styl'One compaction simulator at 120 MPa, n = 10, mean ± SD

In the previous experiments, a fixed lubricant concentration of 3% SSF was utilized for a comparison of the different excipients. In the next step, the lubricant concentration should be varied to assess the impact of the lubricant and to determine the minimal feasible concentration for the DoE (see 3.5.4.).

Figure 59 shows that all lubrication methods resulted in tablets with a sufficient tensile strength (>1 MPa [18, 34]). An ANOVA analysis revealed no significant difference in the mean values of the tensile strength for any formulation. The varying lubricant concentrations and types demonstrated an impact on the ejection force (Figure 60), as the ejection force decreased with rising concentrations of SSF. For MgSt, a plateau was reached with 2% MgSt and the ejection force did not decrease further with higher MgSt amounts. External lubrication was feasible with both spray rate settings but showed different ejection force profiles. The high spray rate resulted in ejection forces similar to 2% MgSt, while values for the low spray rate matched with those ones for 1% MgSt for pressures ≤ 120 MPa. For higher pressures the ejection force even reached the maximum values of all investigated lubrication methods.



Lubrication method	Ejection force [N]
Internal 1% SSF	398 ± 28
Internal 2% SSF	284 ± 11
Internal 3% SSF	232 ± 10
Internal 4% SSF	208 ± 9
Internal 1% MgSt	336 ± 13
Internal 2% MgSt	256 ± 6
Internal 3% MgSt	247 ± 7
Internal 4% MgSt	249 ± 8
External (low/MgSt)	336 ± 15
External (high/MgSt)	257 ± 10

Figure 60: Ejection forces of Ludiflash® ODMTs with 10% NPX and varying lubrication methods, tableted on Styl'One compaction simulator, left: plotted against the compression pressure, right: ejection forces for the compression at 120 MPa, n = 10, mean ± SD

Figure 61 depicts the disintegration time of the studied formulations and emphasized the preferred use of SSF over MgSt (see 3.1). While an increase in the SSF concentration did not lead to significantly different disintegration times, the addition of higher MgSt amounts resulted in rising disintegration times. The formulation with 4% MgSt did not fulfil the FDA limit due to one outlier above the specification. This is in line with the literature [289], as SSF showed a less pronounced effect on the disintegration time on the disintegration of MTs than MgSt. Significant differences were also present for the two spray rates of the external lubrication, as the high spray rate exhibited longer disintegration times with higher scattering of the data. As shown in chapter 3.2, the high spray rate resulted in a higher lubricant amount on the surface and in the tablet which can explain the slower disintegration.

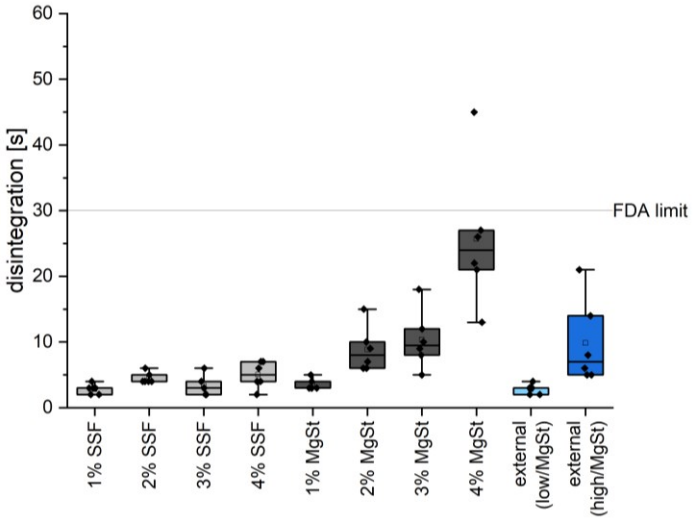


Figure 61: Box plots of the disintegration time of Ludiflash® ODMTs with 10% NPX and different lubrication methods, tableted on Styl'One compaction simulator at 120 MPa, n = 6

Compared to the drug-free Ludiflash® minitablets (see 3.1.3), the disintegration times were even lower for all lubrication types. An explanation might be differences in the porosity, but was not confirmed by the data, as drug-free and drug-loaded ODMTs had similar porosities around 11%. It would be expected that the incorporation of a poorly soluble API would lead to a prolonged disintegration time [288] which was not the case here. Paus et al. [290] studied the interaction between naproxen and mannitol and PVP (included in Ludiflash®) among other excipients. They found an increased drug solubility and intrinsic dissolution rate of NPX if it was combined with mannitol or PVP, which can be explained by the formation of water-soluble complexes with PVP [291]. A publication of Waldner et al. [289] described the significant role of the solubility of the API on the disintegration of minitablets, as a API with a poor water solubility exhibited reduced disintegration times compared to caffeine, an API with a moderate water solubility. They explained this observation with the competition-for-water hypothesis [114], where soluble fillers lead to longer disintegration times as they bind the water which therefore cannot enable the disintegration. This finding for the combination of naproxen and Ludiflash® should be further investigated to confirm the shorter disintegration by the interaction between API and filler.

3.5.3. Impact of the drug load

After the first trials with 10% NPX, the drug load should be increased. The commercially available naproxen products contain 250 – 750 mg NPX, requiring numerous minitablets for the target dose. However, NPX only served as a model drug here due to its poor water solubility. Kollitab™ and Ludiflash® were used as fillers with 3% SSF, for Kollitab™ SSF was added to obtain a total concentration of 3%.

The production of minitablets with up to 40% drug load was feasible and all minitablets achieved acceptable mechanical stability > 1 MPa (Table 17) with no significant impact of the drug load. While the drug load showed no impact on the disintegration time of ODMTs manufactured with Kollitab™, a higher NPX amount resulted in an increase for Ludiflash® minitablets and crossed the FDA limit for orodispersible tablets for drug loads ≥ 30% (Figure 62). The ejection force was rising for higher drug loads, but for the relevant tableting pressure of 120 MPa, the values were below 500 N for both fillers. A look on the mass variation exhibited no correlation with the drug load indicating that the flowability was not influenced by the addition of higher API amounts. However, the mass variation might be impacted by the manual die filling and the flowability should additionally be evaluated by an assessment of the properties of the powder blend.

Drug load/ filler	RSD mass [%] (n = 10)	Tensile strength [MPa] (n = 10)	Ejection force [N] (n = 5)
20% NPX/ Ludiflash®	4.89	1.6 ± 0.5	285 ± 9
30% NPX/ Ludiflash®	4.27	1.7 ± 0.4	378 ± 12
40% NPX/ Ludiflash®	4.04	1.8 ± 0.4	423 ± 18
20% NPX/ Kollitab™	2.03	1.7 ± 0.3	356 ± 4
30% NPX/ Kollitab™	1.90	1.4 ± 0.4	307 ± 8
40% NPX/ Kollitab™	4.06	1.5 ± 0.4	462 ± 14

Table 17: Properties of the ODMTs with varying drug load, tableted on Styl'One compaction simulator at 120 MPa, Kollitab™ + 3% SSF, mean ± SD

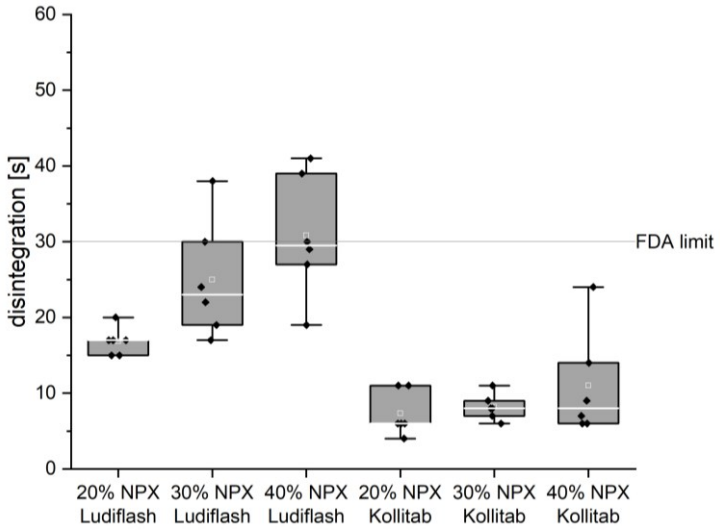


Figure 62: Box plots of disintegration time of ODMTs with different drug loads, tableted on Styl'One compaction simulator at 120 MPa, Kollitab™ + 3% SSF, n = 6

Overall, the drug load only showed an impact on the ejection force and disintegration time of ODMTs with Ludiflash®, while for Kollitab™ the drug load exhibited no systematic trend on the minitablet properties.

3.5.4. Formulation development by Design of Experiments (DoE)

The previous chapters studied the effect of the lubricant and the drug load on naproxen ODMTs with Ludiflash® or Kollitab™, but do not present a formulation development according to the QbD approach. Therefore, an experimental design by DoE was conducted (see chapter 5.2.2) to identify the significant factors in the formulation development and for the creation of a design space. Preliminary experiments (see chapter 3.5.3) revealed that a drug load up to 40% was feasible. Tableting of a powder blend with 40% drug load and pure Kollitab™ without extra addition of a lubricant resulted in ejection forces just below the machine limit of 1000 N and were not considered for further experiments as tableting over a longer period of time with this high friction would lead to defects on

the tooling. SSF was chosen as the lubricant, as it performed better than MgSt, and was applied only internally in concentrations between 2 and 5%.

A 2^3 full-factorial plan was conducted using the Styl'One compaction simulator and the filler type, the lubricant concentration (lub conc) and the drug load (DL) were chosen as factors (see 5.2.2). Following variables were chosen as responses: tensile strength, disintegration time, ejection force, mass variation and drug release after 15 min of the dissolution test.

The experimental runs were evaluated with Modde® 13.0.2 and suitable models were created. Table 18 summarizes the quality of the tuned models after excluding insignificant factors:

Response	R^2	Q^2	$R^2 - Q^2$	Model validity	Reproducibility
Tensile strength	0.6710	0.0910	0.5800	0.5084	0.8802
Ejection force	0.9739	0.7927	0.1812	-0.0585	0.9987
Disintegration time	0.9648	0.3524	0.6124	0.4528	0.9802
Mass variation	0.9704	0.6300	0.3404	0.5563	0.9748
Drug release after 15 min	0.8995	0.7832	0.1163	0.6674	0.9418

Table 18: Quality of the models

R^2 describes the model fit, Q^2 describes the precision of predicted values and should be > 0.5 for a good model and > 0.1 for a significant model. The difference between these values should be small (preferably < 0.3) for a good model [292]. The model validity tests various model problems as outliers or missing interactions and should have a value > 0.25. The reproducibility is calculated by the variation of the center points in comparison to the overall variability.

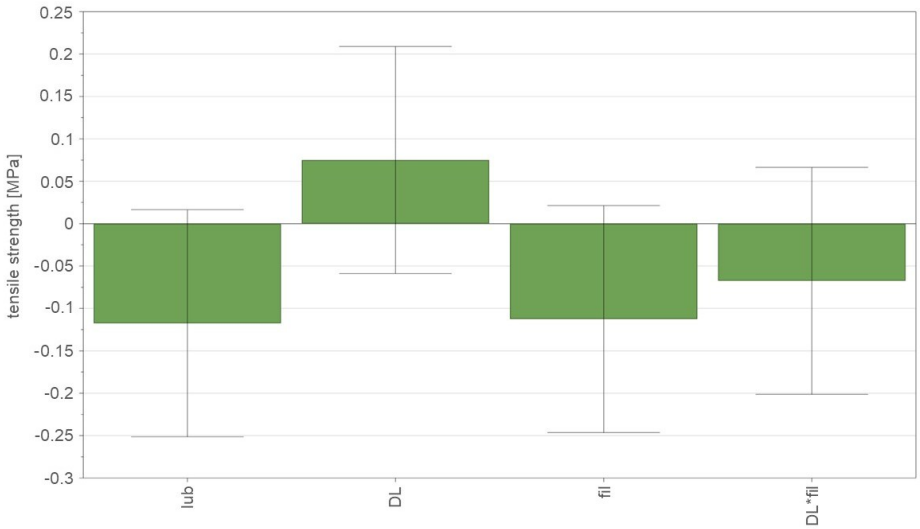


Figure 63: Coefficient plot of the tensile strength, N = 11, R2 = 0.671, RSD = 0.1548, DF = 6, Q2 = 0.091, Confidence = 0.95

The coefficient plot of the tensile strength showed no significant effects for any of the factors (Figure 63). The raw data for the tensile strength exhibited quite high deviations for all runs, which explains why no significant effects could be seen. This issue is also reflected in the bad reproducibility and the insufficient R^2 and Q^2 values. The high deviations in the TS of minitablets was a general problem, also present in the previous chapters (e.g. in 3.1.2) and can be attributed to different reasons. One may be the use of the multi-tip tooling, where the pressure distribution may not be homogeneous over the entire tip. Another reason might be the manual die filling, which could lead to mass variations within the different tips. To solve this problem, standardized filling procedures should be implemented for the multi-tip dies if a feed shoe for minitablets becomes available. Otherwise, single-tips could be used for the formulation development, but for the industrial production multi-tips are commonly used, which exhibit different tableting behavior [45, 47].

The coefficient plot of the ejection force (Figure 64) highlighted the lubricant amount and the drug load as critical factors for the ejection force and also described a significant interaction between both factors. A change in the filler did not lead to significant changes. Formulations with Kollitab™ resulted in the lowest (169 ± 5 N, 10% NPX/ 5% SSF) and highest ejection forces (512 ± 36 N, 40% NPX/ 2% SSF).

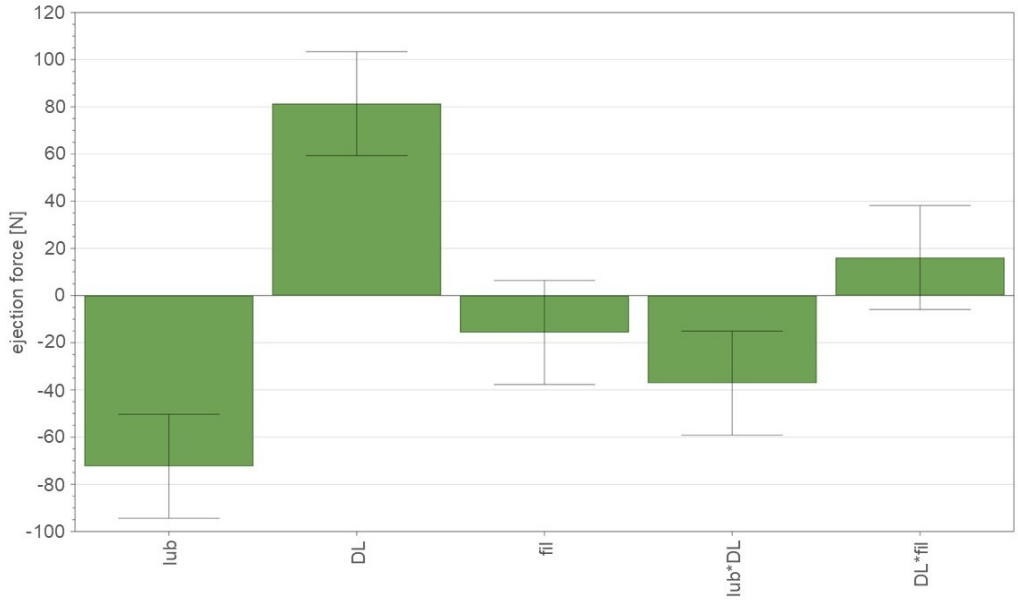


Figure 64: Coefficient plot of the ejection force, N = 11, R2 = 0.974, RSD=24.26, DF = 5, Q2 = 0.793, Confidence = 0.95

The model validity is unsatisfactory for the ejection force (-0.058), which may be attributed to the high reproducibility of center points for the ejection force (0.999), as the other values fulfilled the criteria. The difference R^2 - Q^2 is more meaningful for the evaluation and fulfilled the criteria for a good model.

The coefficient plot of the disintegration time showed a significant influence for all three factors (Figure 65). With an increasing amount of lubricant, the disintegration time increased, as well as with a higher drug load. This confirmed the findings of the previous experiments, where the lubricant showed an impact on the disintegration time (see 3.1.3). The drug load also played an important role as NPX has a poor water solubility and can be expected to prolong the disintegration time. Only the interaction between the drug load and filler demonstrated a significant effect towards a lower disintegration, while the other interactions were not significant.

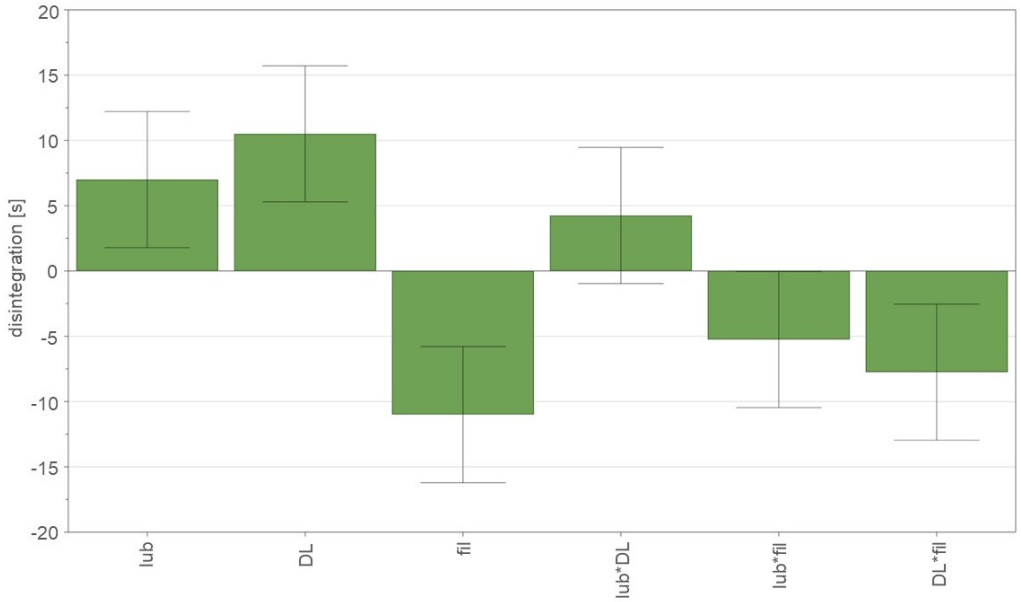


Figure 65: Coefficient plot of the disintegration time, N = 11, R2 = 0.965, RSD = 5.308, DF = 4, Q2 = 0.352, Confidence = 0.95

The model for the disintegration time did not meet the desired value of < 0.3 for the difference between R^2 and Q^2. This might be assigned to the manual endpoint determination of the disintegration test, which was especially challenging for Ludiflash®, as also reported in literature [79, 87].

As the disintegration time is the most critical parameter for OD(M)Ts, contour plots were created to find the optimal formulation (Figure 66). ODMTs with Kollitab™ resulted in satisfactory disintegration times for all possible combinations of the lubricant and the drug load. Ludiflash® ODMTs showed an impact of the NPX concentration, as above a drug load of 20%, the choice of the lubricant concentration determined if the FDA limit was still met.

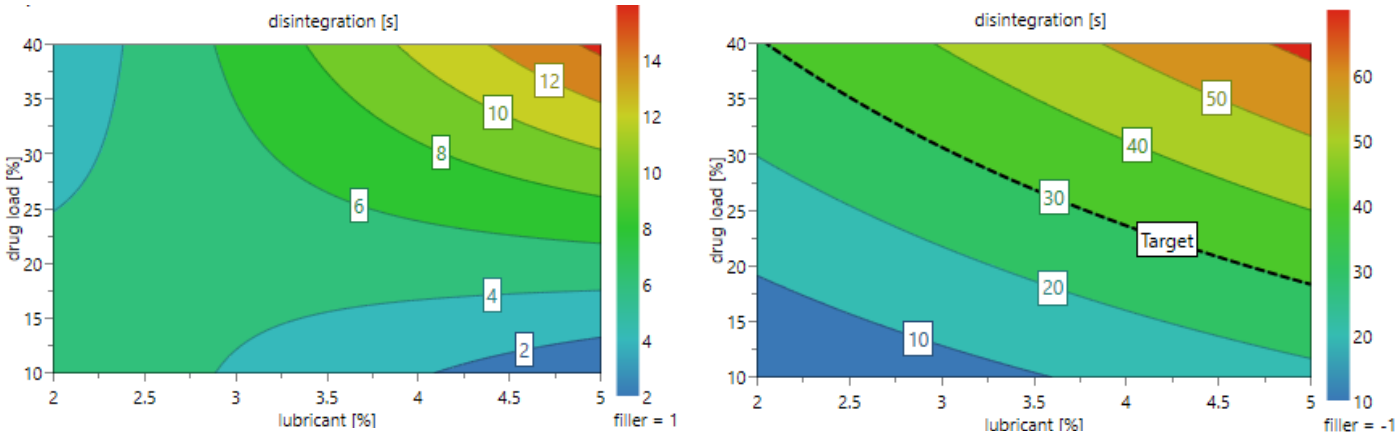


Figure 66: Contour plot of the disintegration time for naproxen ODMTs, left: with Kollitab™ as filler (+1), right: with Ludiflash® as filler (-1)

The mass variation of the minitablets was considered as a parameter for the flowability of the powder blend. However, this parameter has to be considered critically, as the dies were filled by hand due to a missing feed shoe for minitablets and could impact the results as no completely homogeneous filling process could be ensured. The coefficient plot (Figure 67) pointed out the drug load as the most influential factor, while the lubricant concentration and the filler did not affect the flowability significantly. Besides, the interaction between the lubricant and the filler and also the drug load and the filler showed a significant impact on the deviations in the mass and the filling process. The quality of the model for the mass variation showed satisfactory values for R^2, Q^2, the model validity and the reproducibility, but with 0.3404 the difference R^2 - Q^2 exceeded the recommended value of 0.3. Special attention should be given to the mass variations in further experiments, as minitablets require a good flowability in order to fill the small dies adequately.

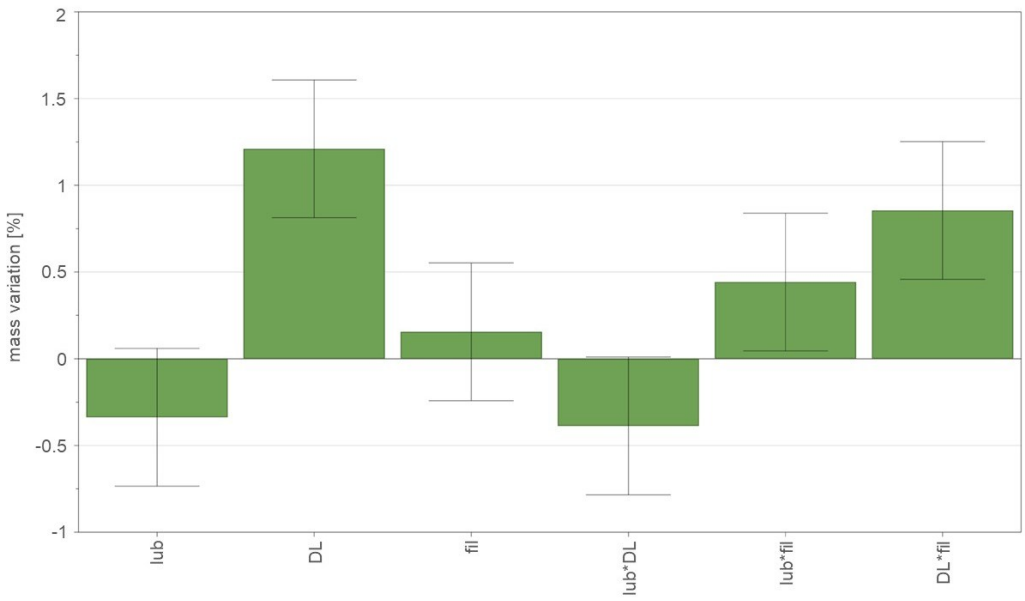


Figure 67: Coefficient plot of the mass variations, N = 11, R2 = 0.970, RSD = 0.4045, DF = 4, Q2 = 0.630, Confidence = 0.95

The USP only contains a general monograph for naproxen tablets, where 80% of the drug should be released within 45 min. For orodispersible tablets, no monograph with special requirements exists. Comparable to the monograph of zolmitriptan ODTs [282], the drug release after 15 min was evaluated. The drug load, the filler and the interaction between the two factors were identified as significant factors for the drug release, while the concentration of SSF did not have a significant impact (Figure 68).

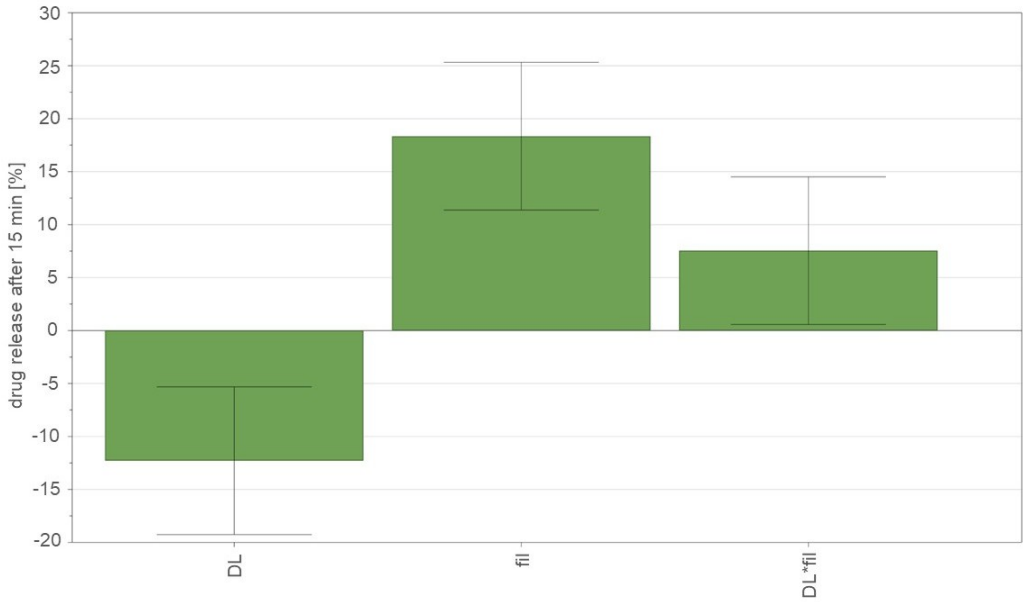


Figure 68: Coefficient plot of the drug release after 15 min, N = 11, R2 = 0.8995, RSD = 8.337, DF = 7, Q2 = 0.783, Confidence = 0.95

For the three center point runs, there was one outlier for the later sampling points (after 10 min) which released about 10% less than the other two points and can explain the reproducibility value of 0.9418 for the drug release after 15 min. The coefficient of determination (R^2) was not ideal for the dissolution experiments, but some deviations in the single sampling points occurred. They can be attributed to the sampling by hand at closely timed sampling points or the dissolution testing of 10 minitablets in one basket. The minitablets can either dissolve individually or form an agglomerate, which might show different dissolution behavior.

Figure 69 and Figure 70 confirm the significant influence of the filler on the drug release, especially for the formulation with the higher drug load. While ODMTs with 40% NPX with Kollitab™ can still be classified as immediate release tablets (>80% released within 45 min), this is not the case for the Ludiflash® tablets. After 60 min, NPX was still not released completely from the Ludiflash® formulation, and the dissolution profile appeared to follow a √t-kinetic at the first sight.

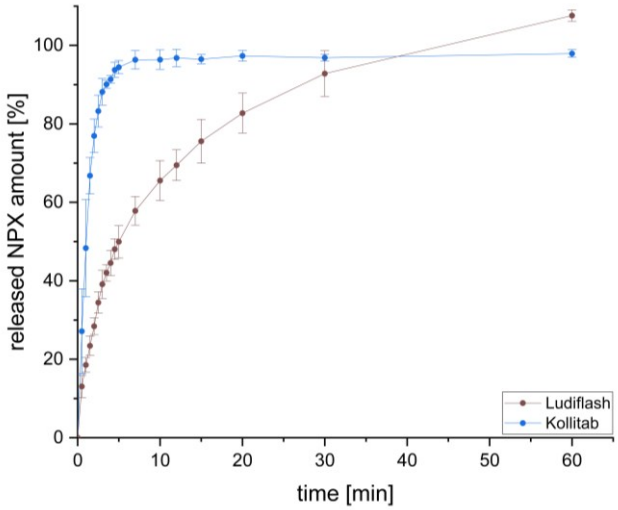


Figure 69: Dissolution profile of NPX-ODMTs with 10% drug load, 5% SSF and different fillers, tableted on Styl'One compaction simulator at 120 MPa, USP apparatus I, phosphate buffer pH = 7.35, 37 °C, 50 rpm, n = 3, mean ± SD

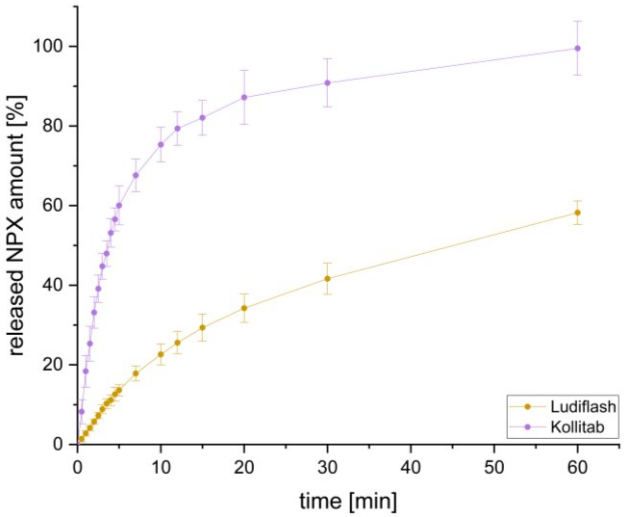


Figure 70: Dissolution profile of NPX-ODMTs with 40% drug load, 5% SSF and different fillers, tableted on Styl'One compaction simulator at 120 MPa, USP apparatus I, phosphate buffer pH = 7.35, 37 °C, 50 rpm, n = 3, mean ± SD

The Higuchi plot was applied for a verification of this assumption and the coefficient of determination (R^2) was calculated (see 5.2.9.2.3). If the R^2 value is close to 1, this indicates a √t-kinetic, which describes no immediate release, but a prolonged release dissolution behavior.

Drug load/ lubricant concentration	Kollitab™	Ludiflash®
5% SSF/ 40% NPX	0.8003	0.9952
5% SSF/ 10% NPX	0.3512	0.9289
2% SSF/ 40% NPX	0.6443	0.9901
2% SSF/ 10% NPX	0.3322	0.9240

Table 19: R^2 of the Higuchi plot of different formulations

The Higuchi plot supported the hypothesis, that Ludiflash® revealed a dissolution behavior according to √t-kinetic, as R^2 is above 0.9 for all formulations (Table 19). Especially the formulation with a drug load of 40% showed a linear behavior of the Higuchi plot ($R^2 > 0.99$). In contrast to that, minitablets with Kollitab™ did not follow this dissolution kinetics, as the R^2 ranged between 0.33 and 0.80.

The significantly prolonged drug release of Ludiflash® tablets compared to other co-processed excipients was already noted by other authors [86, 293, 294]. They attributed this dissolution behavior to the polyvinyl acetate contained in Ludiflash® as this excipient is normally used as a film forming agent for prolonged release. According to the manufacturer [295], the drug release is completed after max. 30 min, even for drugs with a poor water solubility like loperamide, which is contradictory to the literature and the obtained results of this work. Additionally, it was visually observed that the minitablets were not dissolved completely and residues remained in the basket of the dissolution apparatus after 60 min, as illustrated in Figure 71. Due to this phenomenon, an adaption of the released NPX amount to the maximum achieved concentration could not be made, resulting in limited comparability of the dissolution profiles.

Figure 71: Picture of the residues in the dissolution basket after 60 min dissolution test (Ludiflash® ODMTs with 40% NPX and 5% SSF)

Additionally, the Sigma-Minus-plot was performed to verify a first order kinetic for the Kollitab™ minitablets. Table 20 summarizes the coefficients of determination. All formulations showed a good linearity and therefore indicated a dissolution behavior after 1. order kinetic.

Drug load/ lubricant concentration	Kollitab™
5% SSF/ 40% NPX	0.9966
5% SSF/ 10% NPX	0.9758
2% SSF/ 40% NPX	0.9984
2% SSF/ 10% NPX	0.9750

Table 20: R^2 of the Sigma-Minus plot of different Kollitab™ formulations

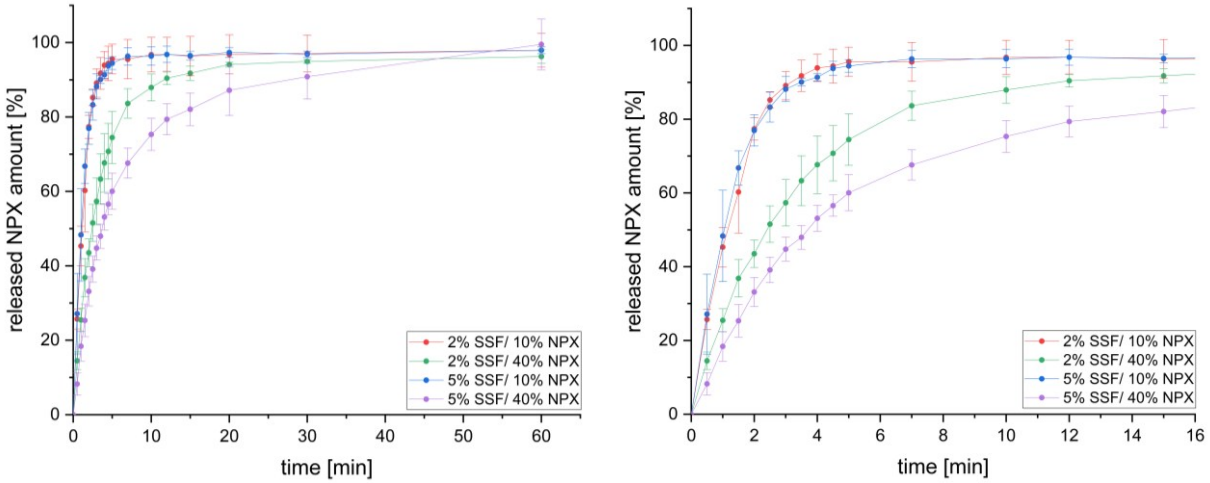


Figure 72: Dissolution profile of NPX-ODMTs with Kollitab™ over 60 min (left) and 15 min (right), tableted on Styl'One compaction simulator at 120 MPa, USP apparatus I, phosphate buffer pH = 7.35, 37 °C, 50 rpm, n = 3, mean ± SD

The dissolution profiles of all Kollitab™ formulations passed the 80% drug release limit after 20 min (Figure 72). The lubricant did not have a significant effect for a drug load of 10%, for the higher drug load of 40% a trend toward slower drug release can be observed with the lower SSF concentration.

This observation was also confirmed with the Ludiflash® minitablets (Figure 73). Here, the lubricant revealed a significantly different dissolution profile for ODMTs with the 40% drug load.

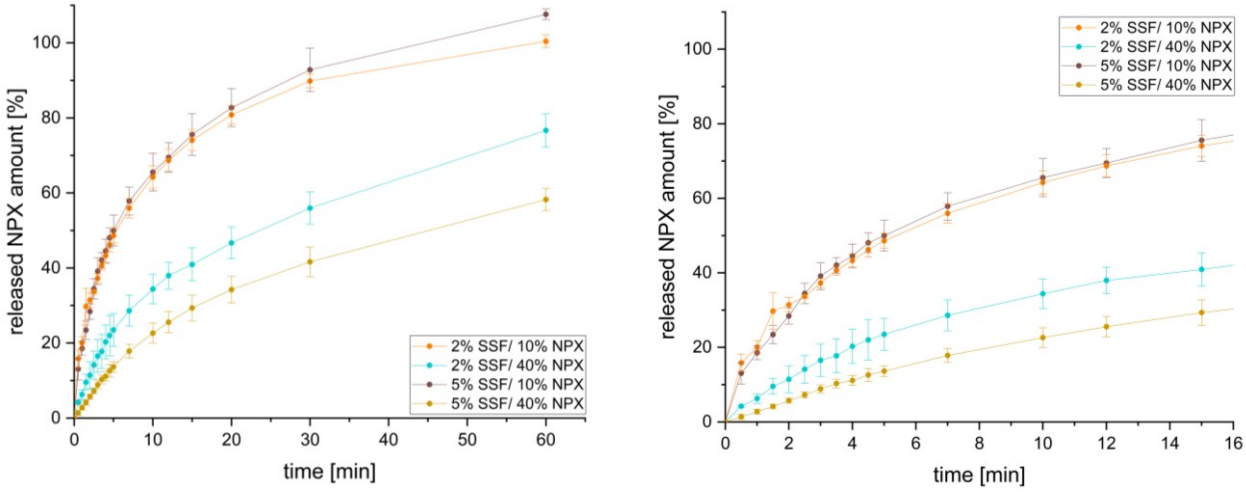


Figure 73: Dissolution profile of NPX-ODMTs with Ludiflash® over 60 min (left) and 15 min (right), tableted on Styl'One compaction simulator at 120 MPa, USP apparatus I, phosphate buffer pH = 7.35, 37 °C, 50 rpm, n = 3, mean ± SD

Overall, the lubricant showed the highest impact on the disintegration time and the ejection force, for the dissolution behavior only a minor effect was visible for ODMTs with 40% NPX. The drug load played an important role for all studied response factors and should be chosen carefully in order to fulfil all requirements. Based on this experiment, Kollitab™ would be the preferred filler, as it showed much faster disintegration and dissolution times and could incorporate a higher amount of NPX while still fulfilling the FDA criteria. It was also not impacted by the lubricant, making adaptations easier. This chapter confirmed the study design by DoE as an important tool for the rational formulation development.

3.5.5. Additional dissolution experiments for naproxen ODMTs

As some of the results in the previous chapter, especially for Ludiflash® ODMTs, were quite interesting, additional dissolution experiments with the soluble sodium salt of NPX, other fillers and external lubrication were performed.

The prolonged dissolution behavior of Ludiflash® ODMTs presented a disadvantage of Ludiflash® for the manufacturing of orodispersible minitablets. The minitablets with 10% drug load disintegrated in < 30 s, but released about 80% NPX after 20 min, indicating that the minitablet is disintegrated, but the API is still attached to the water insoluble polyvinyl acetate [294], which is one component of Ludiflash®. As Ludiflash® is commonly used for the manufacturing of ODTs [22, 79, 84, 86, 87, 293], this effect was further investigated by comparison with the highly soluble naproxen sodium. The solubility of naproxen sodium in water is very good (184.1 mg/ml, 25°C: calculated from the data of [296]), while in comparison the solubility of naproxen is decreased by the factor 10^4 (15.9 µg/ml [182]). Therefore, ODMTs with 10 and 40% naproxen sodium and 2 and 5% SSF were produced and their release behavior was examined. As shown in Figure 74 , the drug release of naproxen sodium ODMTs was very rapid and reached the plateau after about 3 min while ODMTs with the poorly soluble naproxen showed a significantly longer drug release. A similar picture emerged for the comparison of both API forms with a lubricant concentration of 5% SSF (data not shown), which showed the same effect as for 2% SSF. It is notable that MTs with NPX-sodium showed a released NPX amount > 100%. This might be explained by an insufficient blend homogeneity for the affected batch, as the released NPX amount was expressed as percentage of the target dose.

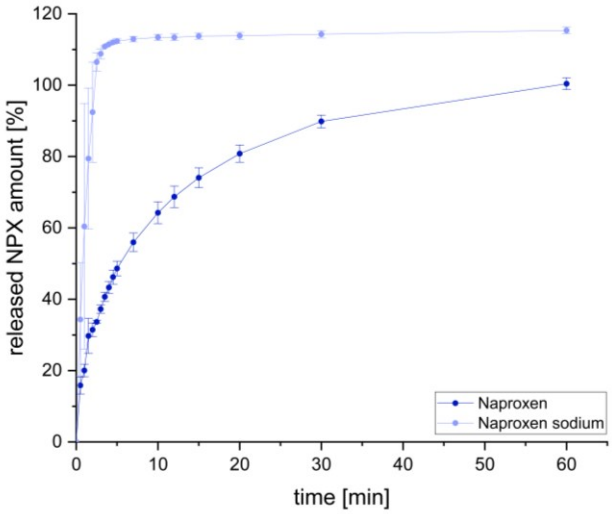


Figure 74: Dissolution profile of Ludiflash® ODMTs with 10% drug load and 2% SSF, tableted on Styl'One compaction simulator at 120 MPa, USP apparatus I, phosphate buffer pH = 7.35, 37 °C, 50 rpm, n = 3, mean ± SD

Figure 75 depicts the dissolution profile of Ludiflash® minitablets with a drug load of 40% and 5% SSF. The release of NPX was even more prolonged with the higher drug load and only reached 58% drug release after 60 min, whereas the highly soluble salt form of NPX was completely dissolved in about 5 min, comparable to the formulation with 10% drug load (Figure 74). It has to be noted, that ODMTs with NPX showed remaining residues after 60 min, highlighting the incomplete drug release and limited comparability of the dissolution profiles. This property of Ludiflash® should be carefully considered in the choice of excipients for ODMTs when poorly soluble drugs are used.

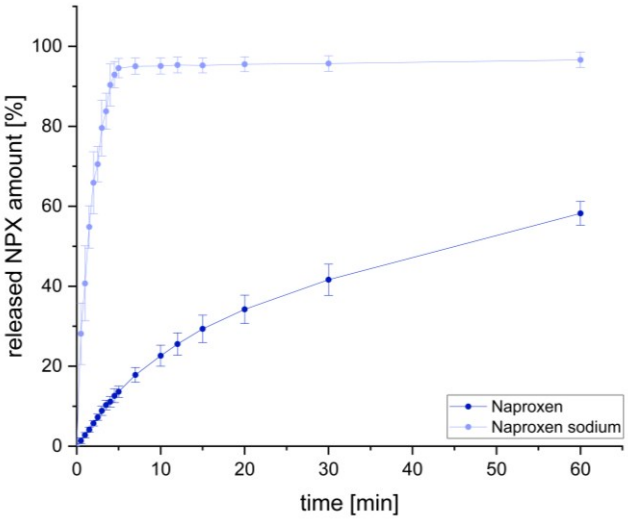


Figure 75: Dissolution profile of Ludiflash® ODMTs with 40% drug load and 5% SSF, tableted on Styl'One compaction simulator at 120 MPa, USP apparatus I, phosphate buffer pH = 7.35, 37 °C, 50 rpm, n = 3, mean ± SD

Based on the findings with the different NPX forms and the importance of the filler for the dissolution behavior, further experiments with the excipients, which were not chosen for the further development in 3.5.1., were carried out. For this purpose, ODMTs with 40% drug load and 5% SSF were produced as "worst-case" scenario for dissolution, differing in the choice of the filler. As galenIQ™ and SuperTab® ODT do not contain a disintegrant and partly did not show sufficient disintegration times in chapter 3.1.3, 4% crospovidone was added for these excipients. The dissolution profile is depicted in Figure 76, showing a rapid API release for SuperTab® ODT, Kollitab™, Parteck® ODT and galenIQ™ (> 80% after 15 min). On the other hand, Prosolv® ODT exhibited a slower dissolution, reaching only approx. 80% of the theoretical amount after 60 min and showing residues in the basket. This behavior can be attributed to the higher disintegration times (Table 16) and the incorporation of MCC in the co-processed excipient. Nevertheless, the delay in dissolution was not as pronounced as for the Ludiflash® ODMTs, which only reached 58% of the theoretical amount after 60 min.

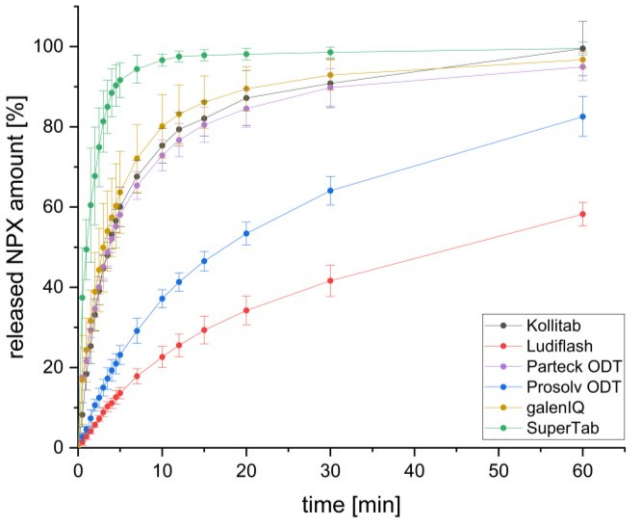


Figure 76: Dissolution profile of ODMTs with 40% NPX, 5% SSF and different excipients, tableted on Styl'One compaction simulator at 120 MPa, USP apparatus I, phosphate buffer pH = 7.35, 37 °C, 50 rpm, n = 3, mean ± SD

To get a comparison to ZMT minitablets, the internal lubrication was additionally compared with external lubrication using both spray rates: Ludiflash® ODMTs with 10% drug load were examined, as they showed complete drug release within the tested time of 60 min. Figure 77 shows that internal lubrication exhibited slightly superior dissolution performance compared to external lubrication, regardless of the spray rate. Until the time point of 15 min, there is a significant higher drug release for internal lubrication.

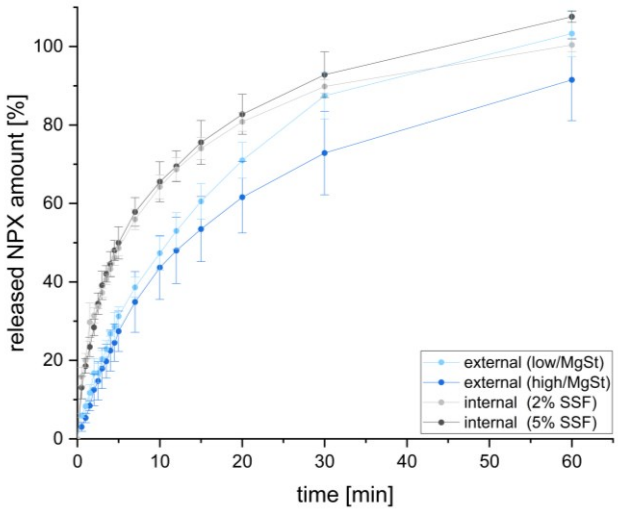


Figure 77: Dissolution profile of Ludiflash® ODMTs with 10% NPX and different lubrication methods, tableted on Styl'One compaction simulator at 120 MPa, USP apparatus I, phosphate buffer pH = 7.35, 37 °C, 50 rpm, n = 3, mean ± SD

Taking together the dissolution data and the tablet properties (see 3.5.2), the external lubrication was feasible for formulations with 10% drug load and also achieved acceptable disintegration times, but resulted in a slightly prolonged dissolution process compared to internal lubrication.

This effect was also seen for the highly soluble API zolmitriptan (see 3.4.2) for dissolution in phosphate buffer (pH = 7.35). The MgSt, present on the surface of the minitablet, formed a hydrophobic layer on the minitablet slowing down the diffusion of the poorly soluble API into the medium. In literature, there are almost no investigations on the effect of external lubrication on the dissolution behavior as most studies used placebo formulations. Otsuka et al. [146] examined the dissolution of externally lubricated trypsin tablets and found faster dissolution behavior for external lubrication. They attributed this to the higher water absorption of these tablets. As they used external lubrication with a different mode of operation and produced 8 mm tablets, further studies on the dissolution behavior of externally lubricated minitablets should be conducted. As minitablets have a higher SVR, they offer a larger surface area relative to their volume for the lubricant, which might result in a higher relative amount of the lubricant per tablet compared to normally sized tablets. Moreover, MgSt was used for the external lubrication while the internal lubrication was conducted with SSF, as it showed superior behavior compared to MgSt in chapter 3.5.3. For a direct comparison, the same lubricant should be used for internal as well as for external lubrication and the lubricant content should be determined to find correlations with the dissolution performance.

3.5.6. Summary

The development of ODMTs with naproxen was feasible with a drug load up to 40%. In line with the previous chapters, SSF should be preferred over MgSt as it also showed less effect on the disintegration times of NPX-ODMTs. An increased drug load resulted in ODMTs with slower disintegration for Ludiflash®, ODMTs with Kollitab™ demonstrated similar mean disintegration times for all drug loads.

The DoE revealed that internal lubrication predominantly influenced the ejection force and the disintegration time, while it had no significant effect on the tensile strength and the drug release of the tablets. The hypothesis, that the lubricant concentration shows more impact for a poorly soluble drug could only be supported for the ODMTs with the highest drug load (40%), while it exhibited no effect on the tablet with 10% NPX. The choice of a filler can impact the tablet properties, as Ludiflash® turned out to show prolonged dissolution times and therefore is less suitable for poorly soluble drugs. Kollitab™ turned out to be a suitable excipient for the development of naproxen ODMTs as it showed rapid disintegration, sufficient hardness and could incorporate a high drug load. If necessary, additional SSF can be added to the lubricated excipient to further reduce the ejection force.

The external lubrication resulted in acceptable ejection forces, disintegration times and tablet hardness, but did not show superior dissolution properties compared to internal lubrication. This effect should be further investigated in future studies with a focus on different tablet sizes and the resulting amount of lubricant on the individual tablets.

3.6. Formulation development of ODMTs using the digital assistant Zoomlab®

While most formulations are developed by iterative steps or statistical experimental design, Zoomlab®, described in chapter 1.3.3.3 and 5.2.5, presents a digital expert system which should provide guidance in the formulation development. Zoomlab® includes a database of characterized fillers and just requires the input of the API data. After this characterization of the individual components, the excipients and the API are rated and the ratings for mixtures are calculated. According to these ratings, the best formulation should be chosen. The characteristics of the mixtures are based on predictions, which rely on the model according to Reynolds [225]. In this chapter, the materials for ODMTs were characterized and the different properties of two tablet sizes with varying lubricant concentrations were elaborated. In the second step, the ability of Zoomlab® to accurately predict the tabletability of minitablet formulations is evaluated and compared using the root mean square error of prediction (RMSEP). The focus in this work was on the formulation development by direct compression, but Zoomlab® also offers other modules such as prediction of dissolution data, finding coating formulations or solubility enhancement.

3.6.1. Characterization of the raw materials

The characterization of the excipients is the first crucial step and presents the basis for the further choice of the formulation. As shown in chapter 3.1, the tablet properties can vary depending on the used lubrication method, type and concentration. For a first impression, the parameters for the excipients were calculated with external lubrication for conventionally sized tablets (Table 21) to exclude lubricant effects.

All excipients showed sufficient tabletability, particle size and flowability ratings above 5, which are needed for direct compression [224]. Only the powder density of galenIQ™ did not reach a rating above 5 and would therefore not fulfill the requirements of Zoomlab®. The choice of an excipient should be made depending on the property which should be improved.

As Prosolv® ODT showed the best tabletability data, but also a sensitivity to the lubricant (shown in chapter 3.1), the tabletability values were compared for different lubrication methods and two tablet sizes (Table 22 and Table 23). This comparison should assess the dependency of the parameter calculation on the used lubrication method.

Parameter	Ludiflash®	Parteck® ODT	Prosolv® ODT	galenIQ™	SuperTab® ODT
D10	3.02	4.92	2.86	4.59	6.04
D50	6.05	10.00	4.92	10.00	8.36
D90	9.67	9.69	7.42	9.40	10.00
DSP	2.59	7.79	8.44	7.91	9.37
DBU	5.60	5.70	6.4	4.00	6.80
DTA	6.60	6.60	7.6	4.70	7.60
CAR	8.28	8.79	8.07	8.37	9.82
HAR	8.43	8.84	8.25	8.5	9.65
AOR	8.10	8.58	8.8	8.18	9.30
CPR	7.60	6.40	7.72	7.63	7.15
CMP	7.02	9.03	7.68	6.91	7.41
TST100	6.23	6.96	7.20	6.26	6.46
TST150	6.57	7.19	7.70	6.37	6.37
TST250	8.36	9.04	9.46	7.92	7.72
Particle size	5.33	8.10	5.91	7.98	8.44
Flowability	8.27	8.74	8.37	8.35	9.59
Powder density	6.10	6.15	7.00	4.35	7.20
Tabletability	7.16	7.72	7.95	7.02	7.02

Table 21: Calculated Zoomlab® ratings of the excipients, determined with 11.28 mm tablets and external lubrication (MgSt, high spray rate), values < 5 were marked in orange color

	CPR	CMP	TST100	TST150	TST250
Extern (low/MgSt)	7.43	8.67	7.40	8.19	9.91
Extern (high/MgSt)	7.72	7.68	7.20	7.70	9.46
0.5% MgSt	7.78	7.22	6.81	7.32	9.24
1% MgSt	7.53	7.04	5.67	7.01	9.40
2% MgSt	7.55	6.28	5.10	6.39	9.29
1% SSF	7.31	7.38	5.65	6.96	9.37
2% SSF	7.45	6.98	5.39	6.74	9.37
4% SSF	7.55	6.01	4.83	6.11	9.18

Table 22: Calculated Zoomlab® tabletability ratings of Prosolv® ODT 11.28 mm tablets with different lubrication methods, values < 5 were marked in orange color

	CPR	CMP	TST100	TST150	TST250
Extern (low/MgSt)	7.62	7.01	6.01	6.88	9.10
Extern (high/MgSt)	7.75	6.43	5.92	6.40	8.43
0.5% MgSt (*)	7.94	6.15	6.01	6.72	9.01
1% MgSt	7.82	5.36	5.03	5.77	8.42
2% MgSt	7.94	5.11	5.01	5.69	8.24
1% SSF	7.68	5.63	4.97	5.88	8.82
2% SSF	7.80	5.15	4.50	5.57	8.35
4% SSF	8.04	3.98	4.13	5.35	7.63

Table 23 Calculated Zoomlab® tabletability ratings of Prosolv® ODT 2 mm minitablets with different lubrication methods, values < 5 were marked in orange color

**: Linear regression was only performed for 3 instead of 5 points as tableting was not possible for all pressures*

As generally known in literature and shown in chapter 3.1, the lubricant has a clear influence on the tablet properties which was also reflected in the tabletability parameters. With increasing lubricant content, the CMP and TST values were decreasing, as the lubricant led to weaker bonds between the powder particles [104, 107]. For the external lubrication, the observed trend of the spray rate (chapter 3.2.1/3.2.3) was also apparent in the ratings and favored the low spray rate. The differences in the rating for the two tablet sizes also emphasize the importance of the individual characterization of the excipients depending on the desired tablet size. As Prosolv® ODT showed clear differences between 11.28 mm and 2 mm tablets, characterization of the excipients irrespective of the tablet size could lead to a suboptimal choice of excipients for ODMTs. Sufficient tensile strength of the Prosolv® ODT minitablets with SSF (> 1 MPa [18, 34]) could be obtained at 120 MPa for the previously studied minitablets, which questions the threefold weighting of the TS factor in the Zoomlab® ratings.

The characterization of APIs specifically for minitablets was hardly feasible. Either the APIs were not compactable without the addition of excipients or only conventionally sized tablets could be produced, as the minitablet dies were too small for the poorly flowing APIs. The calculation of the API data, extrapolated from data of blends with the API, was already shown to be inaccurate [297] as different parameters were calculated for API mixtures with different excipients.

Overall, the characterization of the used substances sets the foundation for further decision and processing but has to be considered critically. Even if the software offers a more systematic approach for the choice of a specific formulation, several points have to be criticized for using Zoomlab®. A previous master thesis [297] investigated the potential of Zoomlab® for the first time and already identified the characterization of the APIs and excipients as a critical point, as variations in these data occurred depending on the used batch. In addition, the calculated parameters also depend on the used

methodology, which is not clearly defined in Zoomlab®. For example, the particle size can be measured with different methods like laser diffraction or dynamic image analysis or different settings such as air pressure, which may lead to different results. Also, the tabletability data is highly dependent on the used tableting machine, the used speed and compaction profile etc. Without a standardization or detailed description of the used settings, the combination of self-determined data by the user and the data for the excipients from the BASF database is not useful and will probably lead to inaccurate predictions.

Moreover, the lubricant is completely neglected in Zoomlab® but plays a crucial role in the development of tablets and more specifically of minitablets, as shown in the previous chapters. In the updated database of Zoomlab®, properties for some lubricated excipients are available (e.g. FlowLac® 100 + 1.4% sodium stearyl fumarate), but do not offer flexibility in the amount of lubricant as the concentration of SSF is fixed and cannot be adjusted. Recently, a new module on the lubricant effect on tabletability [298] was released, which is based on the publications of Puckhaber et al. [299, 300]. However, the influence of the lubricant can only be predicted for one individual filler and not the entire formulation. Additionally, the varying amount of lubricant required for different tablet sizes is not taken into account.

Additionally, some parameters are weighted more than once and can lead to a distortion of the excipient properties (e.g. two ratings for the flowability or three different parameters for the tensile strength). The calculation of the ratings, which has not been disclosed by BASF, should be considered carefully. Depending on the desired dosage form and further processing (e.g. film coating), the optimal and tolerated values should be adapted, which is not possible for the user at the moment. For example, the d_{50} value particle size reaches its optimal value at 150 µm, but it is of importance that the particle sizes between API and excipient are similar to avoid segregation of the blend.

In Zoomlab®, the disintegration time is completely neglected and still has to be implemented, especially if a formulation for orodispersible tablets is designed. The approach of the SeDeM-ODT system [217] can provide a first step in the characterization of the excipients, but neglects the influence of the API on the disintegration time as only the parameters according to the SeDeM expert system were characterized. Krupa et al. [288] elucidated the impact of the dose and solubility of the API on the ODT properties including the disintegration time. Szlęk et al. [301] studied different disintegrants and pointed out that crospovidone was the most effective one regardless of the lipophilicity of the API, whereas the disintegrating ability of sodium starch glycolate and croscarmellose sodium depended on the lipophilicity of the API or other excipients.

3.6.2. Assessment of the prediction ability of Zoomlab® for ODTs and ODMTs

After the characterization of the individual components, the prediction ability should be tested for ODMTs. Ibuprofen (IBU) was used for the modelling of the tablet properties, as it could be tableted into MTs in different API concentrations and the data for the API was listed in the database of BASF. Prosolv® ODT was chosen as the excipient for modelling, as it showed good parameter values for those to be optimized for IBU (DBU, AOR, CMP, TST100, TST150, Table 21). The D10 and D50 value for IBU reached a rating < 5 and Prosolv® ODT did not obtain the highest values for these parameters but was selected as it had a similar particle size, which is expected to have less segregation effects [302, 303].

As Prosolv® ODT was not listed in the database, not all parameters could not be determined for the powder blend, as the mixing rules are not disclosed. For the calculation of the tabletability, the equations described in chapter 5.2.5 and the IBU data from the Zoomlab® database were used. The tableting of IBU-ODMTs was successfully conducted on the Styl'One compaction simulator for drug loads from 5 - 25%. This was in line with the calculated ratings for tabletability, which reached acceptable values between 6.6 (25% IBU) and 7.2 (5% IBU) and therefore classified the formulations as suitable in regards of tabletability. As the effect of the lubricant is not assessed in the prediction of powder mixtures, tableting was performed with external lubrication and compared to the predicted values.

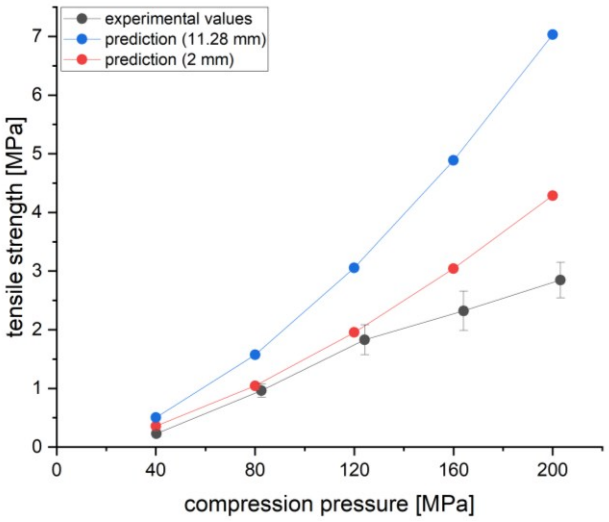


Figure 78: Tabletability of 2 mm ODMTs with 5% ibuprofen and Prosolv® ODT and the corresponding predictions based on two different tablet sizes, external lubrication (MgSt) with the low spray rate, tableted on Styl'One compaction simulator, n = 10, mean ± SD

The prediction of ODMTs with 5% ibuprofen showed accurate predictions for 2 mm minitablets for pressures up to 120 MPa, but for higher pressures, the prediction overestimated the tabletability (Figure 78). The results highlight the importance of the excipient characterization with the targeted

tablet size, as the prediction based on 11.28 mm tablets, overestimated the tablet properties, showing a higher RMSEP value than the prediction based on 2 mm minitablets. (RMSEP (11.28 mm) = 2.29 MPa, RMSEP (2 mm) = 0.76 MPa).

Incorporation of a higher drug load of 25% IBU also led to an overestimation of the minitablets for higher compression pressures with the prediction based on 11.28 mm (Figure 79). However, it was less pronounced than with a lower drug load (RMSEP (11.28 mm/ 25%) = 0.91 MPa, RMSEP (11.28 mm/ 5%) = 2.29 MPa). Increasing the IBU concentration and thus also the volume fraction, leads to a smaller contribution of the excipient data to the prediction and can explain the better fit of the prediction based on 11.28 mm tablets for compression pressures ≤ 120 MPa. However, it is not disclosed which tablet size was used for the generation of API data embedded in Zoomlab®.

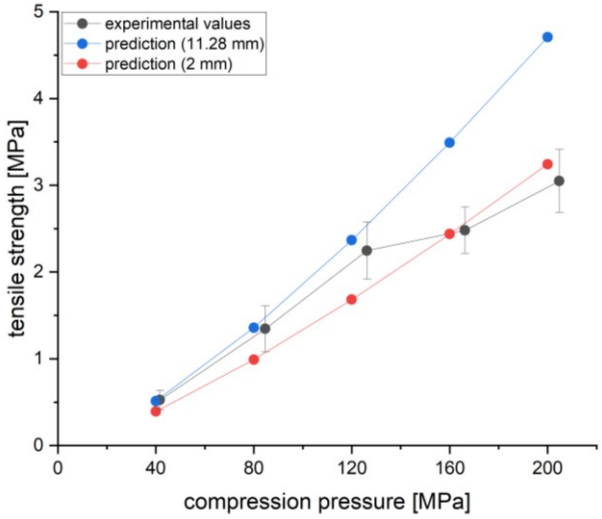


Figure 79: Tabletability of ODMTs with 25% ibuprofen and Prosolv® ODT and the corresponding predictions based on two different tablet sizes, external lubrication (MgSt) with the low spray rate, tableted on Styl'One compaction simulator, n = 10, mean ± SD

Overall, the modelling for 2 mm minitablets with 25% drug load provided the most accurate prediction data with a RMSEP of 0.41 MPa. For both IBU concentrations, the data based on 11.28 mm tablets provided inferior predictions, emphasizing the importance of characterizing the excipients with the intended tablet size.

In Figure 80, the predictions were evaluated at a compression pressure of 120 MPa for all drug loads, as this pressure resulted in tablets with sufficient hardness, but still acceptable disintegration times. A general decrease in tensile strength with increasing drug loads, as predicted, can be seen for 11.28 mm tablets, while for minitablets the trend seems to be vice versa. A previous work [304] also described a similar observation, where the tensile strength for higher ibuprofen drug loads for 1.5 and 2 mm minitablets did not show significant differences but could not find an explanation. As the minitablets

showed high relative deviations in the hardness, the trend of increasing TS (Figure 80) was not significant and should not be overinterpreted.

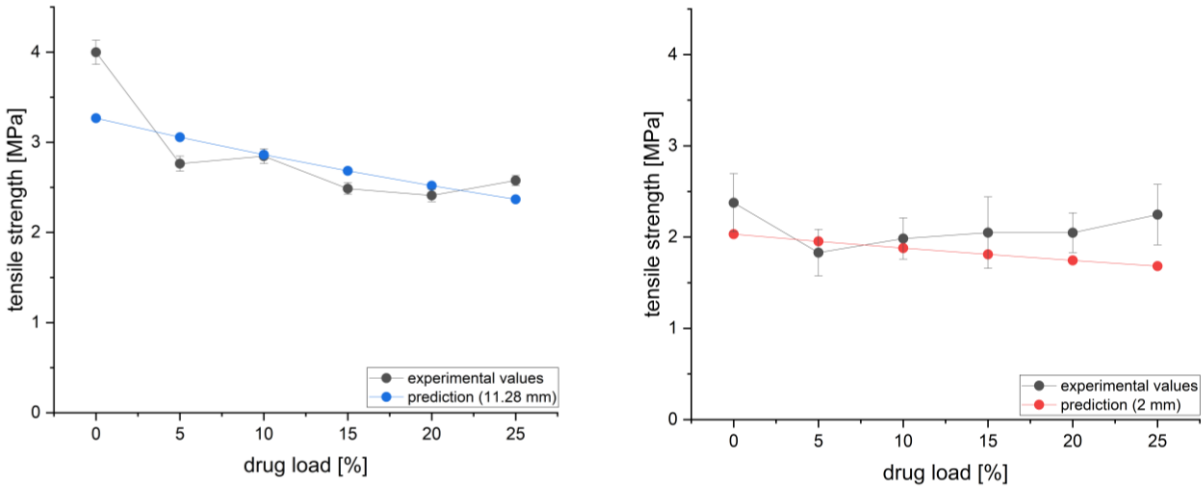


Figure 80: Predicted and experimental tensile strength of ODMTs with Prosolv® ODT in relation to the ibuprofen content, left: 11.28 mm tablets, right: 2 mm tablet, external lubrication (MgSt) with the low spray rate, tableted on Styl'One compaction simulator at 120 MPa, n = 10, mean ± SD

As the predictions did not correspond accurately to the experimental data, the expert system was tested with pre-lubricated excipients to avoid lubricant effects. Their impact can be critical for minitablets with a high surface-to-volume-ratio, especially if external lubrication is used and a high amount of lubricant is deposited on the surface (see 3.2.3.3.). The comparison of the tabletability (Figure 81) depicts that the prediction most closely matched the experimental values for the ODMTs with 15% drug load (RMSEP = 0.34 MPa). For the 20% drug load, the prediction agreed the least with the experimental data (RMSEP = 0.64 MPa). This could be explained by a non-linear mixing behavior of IBU [305] or a possible percolation phenomenon [306]. Additionally, it has to be considered, that the die was filled by hand, which can also influence distribution of IBU in the blend. However, the high standard deviation of the MT hardness limits the interpretation of the prediction accuracy. Overall, even the use of excipients with an incorporated lubricant did not result in more accurate predictions.

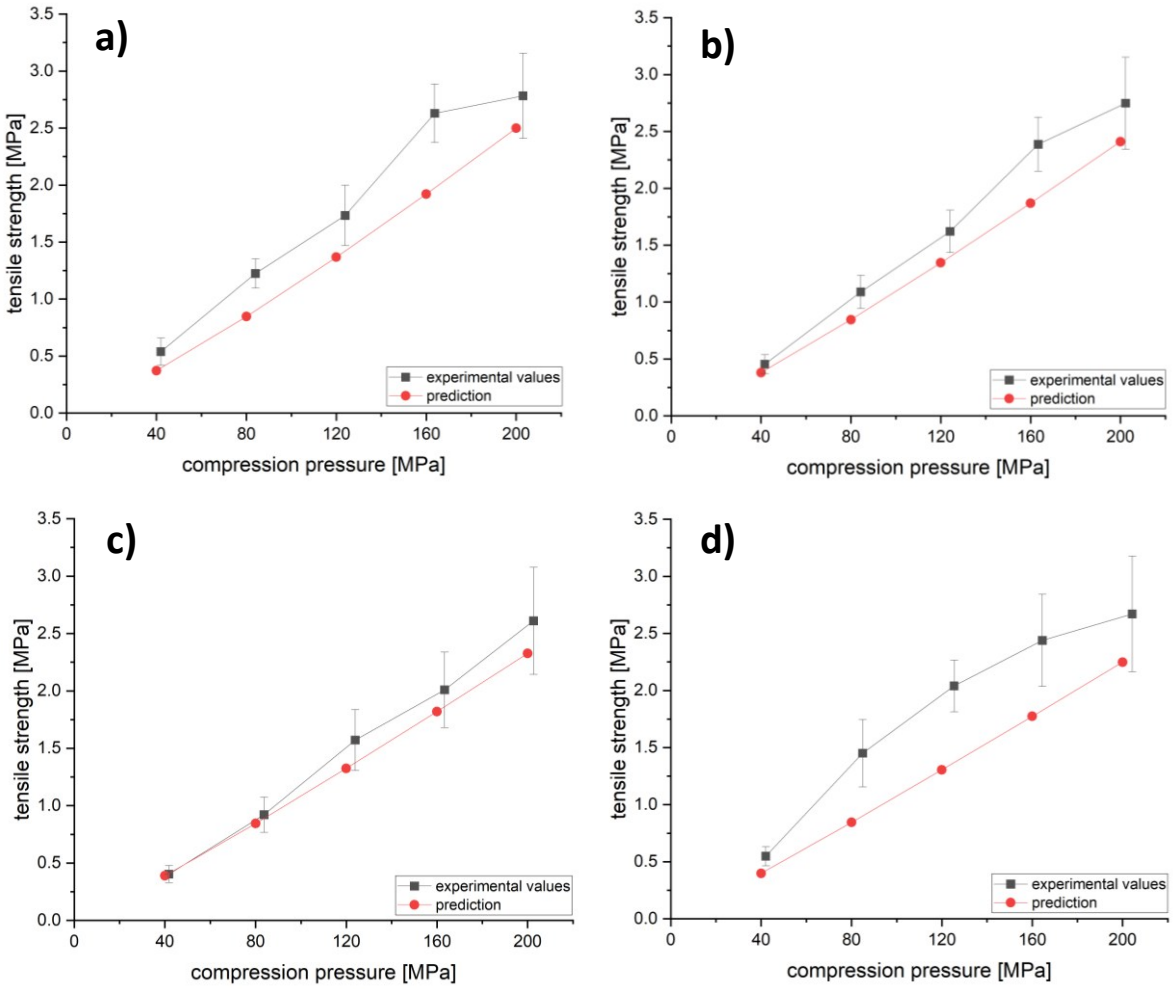


Figure 81: Tabletability of ibuprofen ODMTs with Kollitab™ and their predictions for 2 mm minitablets, a) 5% drug load, b) 10% drug load, c) 15% drug load, d) 20% drug load, tableted on Styl'One compaction simulator, n = 10, mean ± SD

First experiments on the accuracy of the predictions were performed in a previous master thesis [297] and confirmed that the predictions did not match the experimental data and underestimated the actual tabletability, which was attributed to the insufficient characterization of the raw materials. Wünsch et al. [305] elucidated that the Reynolds model, which is used for the Zoomlab® algorithm, is not suitable for a prediction of tensile strength of API mixtures as they do not follow a linear mixing rule. For more accurate predictions, the influence of the API on the deformation behavior of the mixture has to be studied more detailed. Furthermore, the Reynolds model assumes that the particle size distribution is similar for all components of the mixture, which is mostly not the case for API-excipient blends.

The percolation theory, which was first applied in pharmaceutical technology in 1987 by Leuenberger et al. [307], might present an adaptation of the SeDeM system and was already shown to provide more accurate data in literature [308]. Queiroz et al. [306] studied different ibuprofen-MCC blends and found percolation thresholds between 15-20% drug load. However, the percolation threshold has to

be determined individually for each used excipient, to identify the optimal amount of drug in a formulation.

To include the lubricant effect in Zoomlab®, the model of Puckhaber et al. [299] could be integrated. Puckhaber et al. also used the model of Ryshkewitch-Duckworth for the description of compactability of the formulation but extended it by the surface ratio of the diluent and the lubricant. This surface ratio can be calculated by the specific surface area (e.g. measured by BET) and the weight fraction of the components. In another publication by Puckhaber et al. [300] the previously described model was applied to extend the model of Reynolds [225] by the aspect of internal lubrication and achieved predictions in good agreement for most of the experimental data. BASF recently launched a new module to predict the lubricant effect on the tabletability of a single excipient [298], but this function is currently not applicable for the entire formulation. Polak et al. [309] published an extension of the Reynolds model by the aspect of the ejection stress and applied it successfully for the prediction of lubricated mannitol powders. However, only binary and ternary mixtures with diluents and a lubricant were used and no API was incorporated, which should be investigated in further studies before it can be employed in the expert system.

In addition, the tablet size is not included in the calculations and leads to differences in the characterization of the individual components, which influenced the accuracy of the predictions. As the change in tablet properties does not follow a systematic relationship [18], the characterization of the excipients currently has to be performed individually for each tablet size.

3.6.3. Summary

At the moment, no expert system for the development of orodispersible minitablets is available. The characterization of the excipients was shown to depend on the used tablet size and the lubrication type and method. The experiments with IBU-ODMTs showed, that the predictions proved to be less inaccurate if the excipients were characterized with a smaller tablet diameter, pronouncing the importance of accurate characterization of the excipients and APIs. Nonetheless, the system could not predict the tabletability sufficiently, which might be attributed to the fact that most APIs do not follow a linear mixing rule or the Reynolds model is not applicable for minitablets as phenomena such as percolation might occur. Possible extensions of the software have been discussed in this chapter.

All tableted formulations were identified as directly compressible. However, a minimum lubricant concentration is required for minitableting and should be also implemented in the system, for example by measuring the ejection force within concept of successful formulation window (SFW) by Polak et al. [309].

Additionally, Zoomlab® is currently lacking a parameter for disintegration time, which is crucial for ODMTs. Rauf-ur-Rehman et. al [214] were successful in the development of minitablets using the SeDeM system but did not aim for orally disintegrating properties. The system should be extended by an additional disintegration parameter, as in the SeDeM-ODT system [217], to develop OD(M)Ts with the specified disintegration time.

4. Summary and outlook

Although the concept of orodispersible minitablets has been introduced in the scientific literature more than ten years ago, their formulation development is still often conducted by a “trial-and-error” approach and the specific needs of minitablets were not fully elucidated in literature. As ODMTs represent a promising dosage form, recently demonstrated by the market authorization of the first ODMT product, this thesis deals with the first rational formulation development with a special focus on the lubrication system, as this factor is especially critical for ODMTs.

In the first part, the influence of the two most commonly used lubricants, MgSt and SSF, on the key properties of drug-free OD(M)Ts was investigated for 2 mm minitablets in comparison to conventionally sized 11.28 mm tablets using five different co-processed excipients. The claimed superiority of SSF for ODMTs in the first publication from Stoltenberg and Breitkreutz [22] was confirmed as SSF provided a better lubrication efficiency. Besides, OD(M)Ts with SSF presented faster disintegration times and higher mechanical stability compared to the same amount of MgSt. The choice of lubricant was identified as an essential factor when formulations should be tableted into minitablets instead of conventionally sized tablets, as much higher concentrations were required to overcome the increased friction between the powder blend and the die-walls due to a higher interfacial area. The area of the cylindrical part of all tablets within a punch can serve as a factor to compare the resulting ejection forces of tablets with different diameters.

External lubrication via atomization of the lubricant in powdered form was successfully applied in literature for conventionally sized tablets without prolonging the disintegration time. For the first time, the feasibility of external lubrication for a 19-tip tooling for minitablets has been studied in the present work as several tips and dies within one punch have to be covered by lubricant. Here, a comparison of MgSt and SSF revealed no superiority of SSF as found in the experiments with internal lubrication system. Different punch positions were chosen and the distribution of MgSt was evaluated by Raman imaging and atomic absorption spectroscopy. Despite varying amounts of MgSt were found at the different positions, spraying at a low spray rate resulted in ODMTs with uniform tablet properties and very fast disintegration times. A study on the rotary press successfully produced ODMTs within the FDA specification using external lubrication and exhibited superior properties compared to internal lubrication. However, numerous questions still have to be answered to enhance the process understanding. The homogeneity of the spraying mechanism, the impact of the active exhaust system and the influence of the external lubrication system on the content uniformity of API-loaded formulations should be investigated in further studies.

Two newly introduced co-processed excipients with an integrated lubricant were studied as they could be a promising alternative for ODMT formulations where problems with overlubrication occur and can save time by skipping the mixing step. Kollitab™ turned out as a promising excipient for ODMTs as fast disintegration could be achieved but still showed an alteration of the TS on a rotary press through shearing in the filling shoe. The low amount of 1% SSF has to be considered as for higher drug loads it could not be sufficient. Parteck® LM did not show overlubrication effects on the rotary press, but represented a deficit for the disintegration time, as it is lacking an incorporated disintegrant. Consequently, a co-processed excipient with an incorporated disintegrant and internal addition of a lubricant still performed better. Further development of the excipient is necessary to provide superior disintegration performance of ODMTs, apart from this, it presents a good alternative to common CPEs. However, the tableting process on a rotary press could not be simulated with both excipients, as the filling process could not be mimicked on the compaction simulator.

In the following part, formulations for two model APIs with different solubility properties were developed with a focus on the lubricant and its impact on the dissolution performance. Several challenges like capping, flowability issues and need for high lubricant amounts arose during the development of ZMT-ODMTs and no significant influence of the lubricant on the dissolution behavior was found. ODMTs with NPX were successfully manufactured with drug loads up to 40% in a 2 mm MT. As already described for the drug-free MTs, lubrication using SSF showed superior performance and less increase of the disintegration time. Additionally, an experimental design plan (DoE) was used in order to create a design space and to identify critical attributes and factors for the development of naproxen ODMTs. Here, the lubricant showed some impact on the ejection force and the disintegration time, while it did not significantly influence the tensile strength and dissolution profile of the ODMTs. The filler also showed a major impact on the ODMT properties, as Ludiflash® showed higher disintegration times and significantly prolonged drug release of NPX-MTs at higher drug loading, which did not follow a first-order kinetic. In contrast, Kollitab™ turned out to be well suited for the ODMT production. External lubrication resulted in acceptable ejection forces, disintegration times and tensile strength but was not superior compared to internal lubrication using SSF. In the future, systematic studies with the influence of external lubrication on the dissolution behavior of OD(M)Ts in different tablet sizes should be conducted, as different amount of lubricants will be deposited on each tablet.

Lastly, the digital expert system Zoomlab® was evaluated for its applicability for the formulation development of ODMTs. As the lubricant is not included in the calculation of the predictions of the tablet properties and API characterization was not feasible for small sized tablets, this system did not provide precise predictions of the tablet properties. It would definitely benefit from improvements as

implementation of lubrication and disintegration parameters to find a suitable excipient-API combination for the manufacturing of ODMTs. Calculating the parameters for the excipients based on the data of 2 mm MTs led to more precise predictions than the data based on conventionally sized tablets and emphasized the importance of the accurate material characterization. The underlying algorithm also seemed not applicable as the API-excipient mixtures did not follow linear mixing rules and high deviations made the interpretation difficult.

This work can contribute to the rational development of the promising dosage form of ODMTs, as the excipients and lubricants were studied regarding their influence on tabletability and disintegration times. In future studies, the findings of this thesis should be verified by alternative disintegration tests, as the used Ph. Eur. test setup does not represent physiological conditions, e.g. regarding the disintegration medium or volumes and the manual endpoint detection was not optimal for some excipients. In addition, the process of external lubrication for ODMTs should be studied more detailed on the rotary press. Further investigations on the compaction behavior of powder blends for minitablets have to be conducted to provide new models which can be implemented into computerized expert systems and other systematic formulation approaches.

5. Materials and methods

5.1. Materials

The used materials for the minitablet production and characterization are summarized in Table 24 and Table 25:

Tradename	Substance	Batch no.	Manufacturer
-	Naproxen	2007051788	Divis Laboratories Limited, Hyderabad, India
-	Zolmitriptan	22004413	Matrix Laboratories Limited, Hyderabad, India
-	Naproxen-sodium	2-SN-1310808	Divis Laboratories Limited, Hyderabad, India
Ac-Di-Sol® SD 711	Croscarmellose	T1825C	DuPont Nutrition, Wilmington, USA
Aerosil® 200	Fumed silica	157032716	Evonik, Darmstadt, Germany
FlowLac® 100	Lactose	101502420A537D164	Meggle, Wasserburg am Inn, Germany
galenIQ™ 721	Isomalt	L1215923U1	BENEO-Palatinit, Mannheim, Germany
Ibuprofen 50	Ibuprofen	IB5C0005	BASF, Ludwigshafen, Germany
Kollicoat® IR	PVA - PEG - copolymer	70638336W0	BASF, Ludwigshafen, Germany
Kollidon® CL-F	Crospovidone	9450034760	BASF, Ludwigshafen, Germany
Kollidon® CL-SF	Crospovidone	50324145	BASF, Ludwigshafen, Germany
Kollitab™ DC 87 L	Co-processed lactose	38411736W0	BASF, Ludwigshafen, Germany
Ludiflash®	Co-processed mannitol	78295888Q0/44804009T0	BASF, Ludwigshafen, Germany
Parteck® LM high	Mannitol + MgSt	F2229809250	Merck, Darmstadt, Germany
Parteck® LM low	Mannitol + MgSt	F2230129248	Merck, Darmstadt, Germany
Parteck® LUB MST	Magnesium stearate (MgSt)	K4201756311/K53044863113	Merck, Darmstadt, Germany
Parteck® ODT	Co-processed mannitol	F2014390820/F2061190928	Merck, Darmstadt, Germany
Prosolv® ODT G2	Co-processed mannitol	Q2D6L18	JRS Pharma, Rosenberg, Germany

Pruv®	Sodium stearyl fumarate (SSF)	1136/ 1943	JRS Pharma, Rosenberg, Germany
SuperTab® 50 ODT	Lactose	106CP18	DFE Pharma, Goch, Germany

Table 24: Used substances for the (mini-)tablet formulations

Substance	Type	Batch no.	Manufacturer
Acetonitrile	HPLC grade	Various batches	VWR International, Radnor, USA/ CARLO EBRA Reagents, Val de Reuil, France
Demineralized water	-	-	In-house-production using Barnstead™ MicroPure™ UV system (Thermo Fisher Scientific, Waltham, USA)
Dipotassium hydrogen phosphate trihydrate	p.a.	78267955/ 0001778367	Carl Roth, Karlsruhe, Germany/ AppliChem, Darmstadt, Germany
Hydrochloric acid, 1N	p.a.	1264 22K214010	Grüssing, Filsum, Germany VWR International, Radnor, USA
Hydrochlorid acid, concentrated (37% w/w)	p.a.	22D154046	VWR International, Radnor, USA
Methanol	HPLC grade	Various batches	VWR International, Radnor, USA
Nitric acid, concentrated (65% w/w)	p.a.	2230451	Thermo Fisher Scientific, Waltham, USA
Phosphoric acid, concentrated (85% w/w)	p.a.	STBG9936	Sigma Aldrich, Steinheim, Germany
Potassium dihydrogen phosphate	p.a.	3R009612/ 30.1580605	AppliChem, Darmstadt, Germany/ Th. Geyer, Renningen, Germany

Table 25: Used substances for analytical methods

5.2. Methods

5.2.1. Manufacturing techniques

5.2.1.1. Blending

For blending of powder mixtures, the substances were sieved through a sieve with 315 µm mesh size to remove agglomerates (except Aerosil®, mesh size: 710 µm). Afterwards they were weighted in an appropriate vessel to provide enough headspace to ensure appropriate mixing and mixed for 10 min in the Turbula mixer T2C (Willy A. Bachofen, Muttenz, Switzerland). The lubricant was added on the day of tableting and mixed for 2 min after the mixing time of the other components.

5.2.1.2. Direct compression on the Styl'One compaction simulator

The Styl'One Evo compaction simulator (Korsch, Berlin, Germany) was used for the production of tablet batches in a smaller scale. For the analysis of the tableting data, the corresponding Analis software (v2.08.6, Korsch, Berlin, Germany) was used. All tableting experiments were performed in a controlled environment (21 °C, 45% r.h.).

Different punches were used for tableting and are summarized in Table 26:

Punch	Geometry	Manufacturer	Used for
2 mm multi-tip (EuB)	Concave (1.4 mm curvature radius)	Ritter Pharma, Stapelfeld, Germany	Standard tableting (Default cycle 1 compression)
2 mm multi-tip (EuD)	Concave (1.4 mm curvature radius)	Ritter Pharma, Stapelfeld, Germany	Simulation of Korsch XM 12 compaction profile
11.28 mm single tip (EuB)	Flat-faced	Natoli Engineering, Saint Charles, USA	Standard tableting (Default cycle 1 compression)

Table 26: Used punches for the production of (mini-)tablets

Die filling was performed manually for the minitablets as well as for normal tablets to eliminate influencing factors by the feed shoe. The filling height of the API containing tablets was adjusted to a target mass (6.25 mg for ZMT-MTs and 6.5 mg for NPX-MTs), while for the pure excipients (chapter 3.1), a constant filling height was kept.

If not described otherwise, the default cycle 1 compression profile was used with a tableting speed of 10%. Only for the transfer experiments on the Korsch rotary press, the compression profile, which simulates the Korsch XM 12, was applied with different tableting speeds varying from 10 – 30 rpm. Tableting was performed at five different compression pressures (40, 80, 120, 160 and 200 MPa).

For experiments with external lubrication, the associated external lubrication system for the Styl'One compaction simulator was utilized (Korsch, Berlin, Germany), which was explained in detail in a publication by de Backere et al. [91]. For this procedure, the lubricant (MgSt, if not stated otherwise) is filled into a vessel ((A) in Figure 82) before being dispersed by a pulsed air flow cabinet. The spraying nozzle is located directly next to the feed shoe ((B) in Figure 83) and sprays the lubricant on the upper and lower punch surface. Any excessive lubricant is immediately eliminated by an exhaust system ((C) in Figure 84) connected to a vacuum cleaner. Unless specified otherwise, the air pressure was set to 5 bar and the die was sprayed for 500 ms.

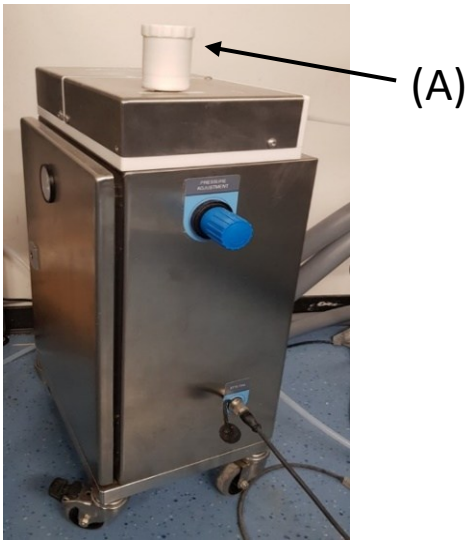


Figure 82: External lubrication pack for the Styl'One compaction simulator with storage container for MgSt on top (A)

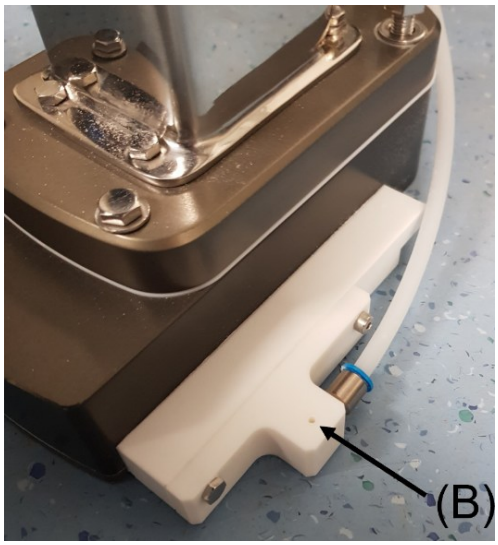


Figure 83: Force feed shoe of the Styl'One compaction simulator with spraying outlet for the lubricant (B)

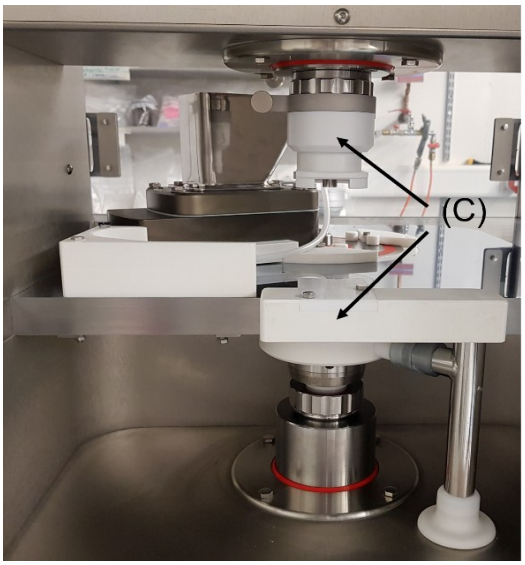


Figure 84: Set-up of the compaction simulator with feed shoe and exhaust system (C) for the external lubrication

5.2.1.3. Direct compression by the rotary press Korsch XM 12

The rotary press Korsch XM 12 (Korsch, Berlin, Germany) was used for the transfer experiments from the Styl'One compaction simulator. The machine can be operated with either EuB or EuD punch sets, the production of minitablets was conducted using two pairs of 2 mm multi-tip EuD punches (Ritter Pharma, Stapelfeld, Germany). The process data during tableting was recorded with the corresponding PharmaResearch software (Korsch, Berlin, Germany). These trials took place in a climatized room with a constant temperature of 21 °C and 45% relative humidity. The feed shoe comprises of two paddles, which were operated with a speed of 15 and 25 rpm. At the beginning of tableting, the filling height was adjusted to reach a target weight of approx. 7 mg per minitablet. After reaching the steady-state of the process, filling height was kept constant and samples were drawn within a time interval of 30 s.

The external lubrication system used in chapter 3.2.4 and already described by Lura et al. [250], consisted of a twin-screw feeder (type K-PH-CL-KT20, Coperion K-TRON, Niederlenz, Switzerland) for MgSt. It was operated in volumetric mode after calibration. The applied spraying pressure was approx. 0.8 bar, and the dosing unit was attached to the rotary press ((B) in Figure 85), facilitating the dispersion of MgSt onto the dies before the filling process. The precompression force was set to 0.5 - 1 kN and, whenever feasible, five different tableting pressures were applied for the main compression (see 5.2.1.2.). The excessive MgSt was removed from the tablet press by the exhaust system, attached to a vacuum cleaner ((A) in Figure 85).

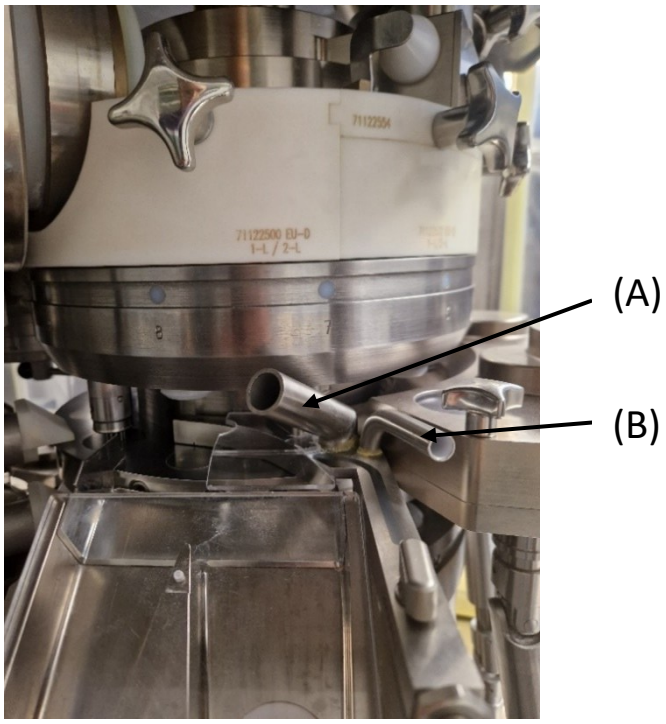


Figure 85: Picture of the interior of the Korsch XM 12 rotary press with connections for the exhaust system (A) and the external lubrication (B), connected with the MgSt dosing unit

5.2.2. Design of Experiments (DoE)

The Design of Experiments (DoE) concept was conducted to investigate the influence of different concentrations of the used excipients. A full-factorial 2^3-plan was designed and evaluated using the Modde® 13 software (version 13.0.2, Sartorius, Göttingen, Germany). The factors selected for this study were the filler type, the lubricant concentration (lub conc) and the drug load (DL). Ludiflash® (-1) and Kollitab™ (+1) served as fillers, with a 50:50 (w/w) mixture of both fillers used for the center point. For Kollitab™, the lubricant amount included in the excipient was taken into account when adapting the lubricant concentration. Following variables were chosen as responses: tensile strength, disintegration time, ejection force, mass variation and drug release (%) after 15 min. The order of experiments was randomized by the software and conducted in following order (Table 27):

Experiment No.	Run Order	Lub conc	DL	filler
N1	10	2	10	-1
N2	7	5	10	-1
N3	8	2	40	-1
N4	3	5	40	-1
N5	2	2	10	+1
N6	5	5	10	+1
N7	4	2	40	+1
N8	6	5	40	+1
N9	11	3.5	25	0
N10	1	3.5	25	0
N11	9	3.5	25	0

Table 27: Design of Experiments for the development of naproxen ODMTs

5.2.3. Storage conditions

All tablets were stored in a climatized environment at 21°C and 45% r.h. for min. 24h before characterization.

5.2.4. Statistical evaluation

Statistical evaluation was performed with a two-sided t-test at a significance level of $\alpha = 0.05$. For statistical approaches such as linear regression and ANOVA, OriginPro (version 2020b, OriginLab, USA) was used. Post hoc comparison of means was performed with the Tukey-test ($\alpha = 0.05$).

5.2.5. Prediction of tablet properties with Zoomlab®

For the prediction and modeling of tablet formulations, the Zoomlab® software (version 4.0, BASF, Ludwigshafen, Germany) was used. The modules “Formulation Wizard”, “Tabletability” and “Processability” of either the active ingredient or the powder blend were applied to the model API formulations.

As the prediction algorithms of Zoomlab® are proprietary and not disclosed completely, the predictions were manually performed according to the model of Reynolds et al. [225], which also serves as the basis of the Zoomlab® algorithm. The Reynolds model relies on the equations of Gurnham and Ryshkewitch-Duckworth to determine the compressibility and compactability. The modified Gurnham equation [310] describes the relationship between the porosity (ε) and the applied pressure (P) (Equation (1)) and derives the two constants P_0 (pressure at $\varepsilon = 0$) and k_C (compressibility resistance).

$$\varepsilon(P) = -\frac{1}{k_c} * \ln(\frac{P}{P_0}) \quad (1)$$

The equation of Ryshkewitch-Duckworth [311] (Equation (2)) illustrates the relationship between the tensile strength of a tablet in dependency of the porosity, where T_0 presents the tensile strength of the tablet at ε = 0 and k_B is the bonding capacity constant.

$$T = T_0 * e^{-k_B * \varepsilon} \quad (2)$$

The Reynolds model calculates the data of a substance mixture not by the weight fraction, but the volumetric fraction by equation (3), as a study by Busignies et al. [312] found an excellent predictability of mixtures with this model.

$$y_i = \frac{\frac{x_i}{(1 - e(P)_i * \rho_{true,i})}}{\frac{\sum x_j}{(1 - e(P)_j * \rho_{true,j}}} \quad (3)$$

Subsequently, the porosity of the mixture is calculated with equation (4) and the tensile strength with equation (5):

$$\varepsilon(P)_{mix} = \sum_i y_i * \varepsilon(P)_i \quad (4)$$

$$\ln T_{mix} = \sum_i y_i * \ln[T_i(\varepsilon(P)_i)] \quad (5)$$

The Reynolds model is based on the assumption that the particle sizes of all mixture components are similar.

For the evaluation of the predictions, the root mean square error of prediction (RMSEP) was calculated according to equation (6), where y_i is the experimental data point, $\hat{y}_i$ is the corresponding predicted data and n the number of data points:

$$RMSEP = \sqrt{\frac{\sum_{i=1}^{n}(y_i - \hat{y}_i)^2}{n}} \quad (6)$$

5.2.6. Characterization of the powders

5.2.6.1. Determination of flowability

Flowability of powders was determined according to Ph. Eur. 2.9.36 with a trickle tester according to Dr. Pfrengle (Typ 3102, Hans W. Schmidt, Mainz, Germany) and a jolting volumeter (J. Engelsmann,

Ludwigshafen, Germany). The powder flow properties were evaluated using the angle of repose, Hausner factor and Carr's index and classified according to Carr [313].

5.2.6.2. Determination of true density

For the determination of the true density of the excipients, the helium pycnometer AccuPyc 1330 (Micromeritics, Norcross, USA) with a 3.5 cm^3 chamber was used at 25 ± 0.1 °C. Each material was measured in triplicate and mean and standard deviation were calculated. For the true density of powder blends, following equation (7) was used [314]:

$$\rho_{blend} = \frac{1}{(\frac{\omega_a}{\rho_a} + \frac{\omega_b}{\rho_b} + \cdots + \frac{\omega_i}{\rho_i})} \quad (7)$$

ρ = true density of the powder blend (ρ_{blend}) or its single components ($\rho_{a/b/i}$)[g/ml]

ω = weight fraction of component a/ b/ i [%]

5.2.6.3. Determination of specific surface area

The specific powder surface area was determined by gas adsorption method according to Brunauer, Emmett and Teller (BET). Sample preparation was performed using the VacPrep™ 061 (Micromeritics, Norcross, USA) at 40°C. Vacuum was applied for minimum 30 min, followed by gassing the samples with nitrogen for 30 min. Afterwards the samples were dried under vacuum for at least 24 h before the measurement. The measurement itself took place using the TriStar 3000 (Micromeritics, Norcross, USA) and the samples were cooled to a temperature of -196°C using liquid nitrogen. The non-adsorbable volume was determined by the introduction of helium into the samples. Afterwards, the amount of adsorbed gas (nitrogen) was recorded at eleven different relative pressures between 0.05 and 0.3. With these values, the specific surface area was calculated according to the BET theory [315] using the software Win3000 (Micromeritics, Norcross, USA). The surface area of each substance was measured in triplicate and the mean value and standard deviation were calculated.

5.2.6.4. Determination of particle size distribution

The particle sizes of all APIs and excipients were determined by laser diffraction using the Mastersizer 3000 system (Malvern Panalytical, Malvern, United Kingdom). Before each measurement, a background measurement was conducted. The dry dispersion unit Aero S (Malvern Panalytical, Malvern, United Kingdom) was used and an air pressure of 0.8 bar was applied for dispersion of the powder particles. In case of zolmitriptan, a higher air pressure of 4 bar was used as the substance was very cohesive. The feed rate was adjusted case-by-case to maintain an obscuration range of 0.5 – 6%. The resulting diffraction patterns were evaluated by the corresponding software using the Fraunhofer

approximation. To evaluate the particle size distribution, samples were measured three times (n = 3) and the d_{10}, d_{50} and d_{90} values and the distribution span (Equation (8)) were calculated.

$$distribution\ span = \frac{d_{90} - d_{10}}{d_{50}} \quad (8)$$

5.2.7. Characterization of the tablets

5.2.7.1. Determination of the wettability

The Drop Shape Analyzer DSA 100 (KRÜSS, Hamburg, Germany) was used for the contact angle determination on the tablet surface. A 11.28 mm tablet composed of the pure excipients/ API was compressed using the Styl'One compaction simulator. If lubrication was necessary, only the lower part of the die was lubricated with MgSt via a swab, ensuring a lubricant-free area on the top of the tablet. The tablet was wetted with one drop of demineralized water (8 - 10 µl) and the contact angle of the drop was calculated with the height-width method. This evaluation was immediately conducted after wetting the tablet (CA_0s) and after 30 s (CA_30s), provided that the drop remained observable on the tablet surface and was not completely absorbed by the tablet. The measurement was performed in triplicate in order to calculate the mean and the standard deviation.

5.2.7.2. Calculation of energies during tableting

During tableting with the Styl'One compaction simulator, forces were recorded with a frequency of min. 2000 Hz and the energies were evaluated with the corresponding Analis software (v2.08.6, Korsch, Berlin, Germany). Figure 86 depicts an exemplary force-displacement diagram, providing a

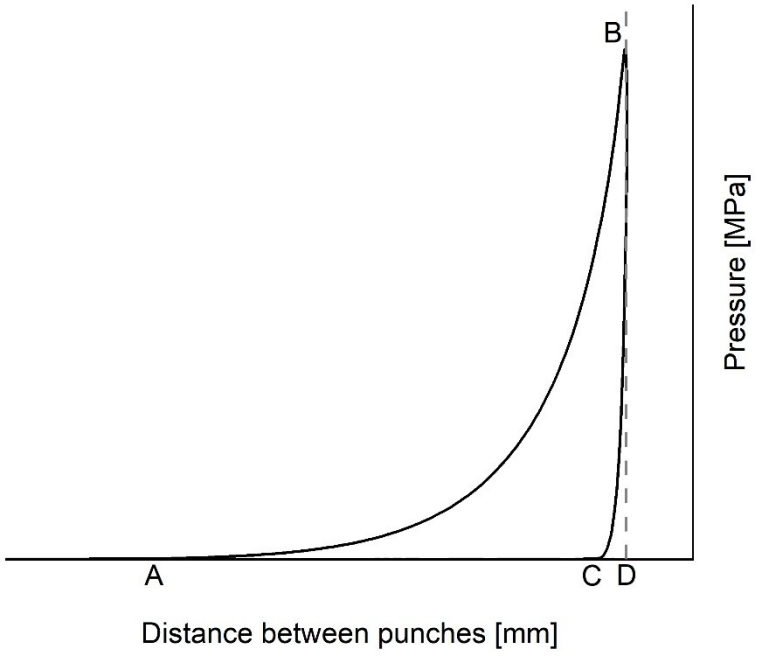


Figure 86: Exemplary force-displacement diagram for the visualization of the calculated energies

visualization of the calculated energies. In this work, the plastic and elastic energy were values of

interest. The elastic energy is described by the area between the points B, C and D in the force-displacement graph. The plastic energy (area ABC) depicts the net work of compaction, while the area ABD is the compression energy. These energy values were used to calculate the elasticity and specific plastic energy using equation (9) and (10) [91]:

$$Elasticity\ [\%] = \frac{elastic\ energy\ [J]}{compression\ energy\ [J]} * 100 \tag{9}$$

$$Specific\ plastic\ energy\ [\frac{J}{g}] = \frac{plastic\ energy\ [J]}{weight\ of\ all\ tablets\ compressed\ in\ one\ cycle\ [g]} \tag{10}$$

5.2.7.3. Calculation of porosity

The porosity is the reciprocal value of the solid fraction (SF) and describes the relative amount of gaseous cavities in a solid compact. It is required for the creation of compactability and compressibility plots and was calculated by the following equation (11):

$$\varepsilon = 1 - SF = 1 - \frac{\rho_{tablet}\left[\frac{mg}{mm^3}\right]}{\rho_{true}\left[\frac{mg}{mm^3}\right]} = 1 - \frac{\frac{mass\ [mg]}{volume\ \ [mm^3]}}{\rho_{true}[\frac{mg}{mm^3}]} \tag{11}$$

The volume (V) of conventionally sized flat-faced tablets can be described as the volume of a cylinder using equation (12):

$$V = \pi * r^2 * h \tag{12}$$

with *r* = radius of the tablet and *h* = height of the tablet.

The minitablets have a biconvex form and the volume can be calculated by dividing the minitablet in a cylindrical part (Equation (13)) and two caps (Equation (14)):

Volume of the cylindrical part (V_{cyl}):

$$V_{cyl} = \pi * r^2 * h \tag{13}$$

Volume of the cap (V_{cap}):

$$V_{cap} = \frac{\pi}{6} * h_{cap} * \left(3 * r^2 + h_{cap}^2\right) \tag{14}$$

Hence, the total volume of the minitablet is calculated with equation (15):

$$V_{tablet} = V_{cyl} + 2 * V_{cap} \tag{15}$$

5.2.7.4. Determination of height, diameter and weight

The height, diameter and weight of normally sized tablets was measured using the SmartTest ST50 (Sotax, Aesch, Switzerland). Since this device is incapable of characterizing minitablets with a diameter of 2 mm, the digital calliper Absolute Digimatic (Mitutoyo, Kawasaki, Japan) was used for the determination of the height and diameter for the ODMTs. The minitablets were weighed on the analytical balance Sartorius Cubis MCE 225P (Sartorius, Göttingen, Germany) with an accuracy of five digits. Each minitablet batch was measured ten times and the mean and standard deviation were calculated.

5.2.7.5. Determination of tensile strength

The breaking force of normally sized tablets was determined with the SmartTest ST50 (Sotax, Aesch, Switzerland) according to Ph. Eur. 2.9.8., whereas the diametral breaking force of minitablets was determined using the Texture Analyser (TA.XT*plus*, Stable Micro Systems, Godalming, United Kingdom). A 5 mm aluminum punch was used, moving down with a speed of 0.1 mm/s. The maximum force of the force-time graph was considered as the hardness of the minitablet. The breaking force was determined for ten tablets of each batch and mean and standard deviation were calculated.

Several publications already used this or a similar device for the determination of the breaking force [17, 22, 35, 202, 304]. For the comparison of different tablet sizes and geometries, the tensile strength is calculated from the hardness data according to equation (16):

$$Tensile\ strength = \frac{2 * F}{\pi * d * h} \tag{16}$$

where *F* is the breaking force [N], *d* the diameter of the tablet [mm] and *h* the thickness of the tablet [mm]. Equation (16) defines the TS according to Fell and Newton [316] and was originally developed for flat-faced tablets. However, also minitablets can be appropriately characterized by the equation of Fell and Newton [11, 17, 317] as they exhibit a cylinder thickness to diameter ratio of > 0.3 and a nearly spherical shape [18].

5.2.7.6. Determination of disintegration time

The disintegration time of ODTs and ODMTs was determined using the PTZ Auto 1EZ (Pharma Test, Hainburg, Germany) or the Z32 disintegration tester (Erweka, Langen, Germany), both complying with Ph. Eur. 2.9.1. Demineralized water was used as the disintegration medium and kept at a temperature of 37 ± 2 °C. The endpoint of the disintegration process was determined visually when no residuals were visible on the mesh.

Despite the availability of various tests for the determination of the disintegration time of minitablets, the modified disintegration test according to Kleinebudde [165] was used in this work. This method was implemented in the literature as a disintegration method for minitablets [35, 79, 83, 168], as the normal disintegration test is not feasible for minitablets as the mesh already has a size of 1.8 – 2.2 mm and the minitablets would immediately pass the openings. This method was chosen because it is only a minor modification of the Ph. Eur. test, ensuring compliance with the pharmacopeial requirements. The objective of the disintegration testing was the assessment of the composition of the tablet formulation and the process parameters rather than an accurate prediction of physiological data.

For the minitablets, small basket inserts with a mesh size of 710 µm were used and a hollow metal cylinder was placed on top to keep the baskets under the water surface. Each measurement was performed six times, afterwards the mean and standard deviation were calculated.

The disintegration times are displayed as box plots with the single data points and the mean, median, and 1.5 IQR are presented with following symbols (Figure 87):

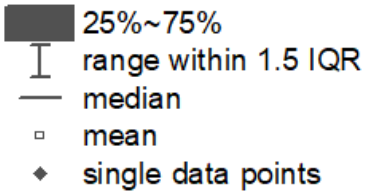


Figure 87: Legend for the box plots of the disintegration time

5.2.7.7. Calculation of the normalized ejection force

For a comparison of the ejection force of minitablets and 11.28 mm tablets, the normalized ejection force was calculated according to equation (17). The dosing height h_D was considered as the height for the radial area (Equation (18)) of the cylinder, which had to be overcome by the ejection force. For the minitablets, the radial area of 19 tips was accounted as the total area for the normalized ejection force as the number of tips has an influence on the ejection force [45].

$$normalized\ ejection\ force\ \left[\frac{N}{cm^2}\right] = \frac{ejection\ force\ [N]}{radial\ area\ \ [mm^2]} * 100 \quad (17)$$

$$radial\ area\ [mm^2] = 2 * \pi * r * h_D \quad (18)$$

5.2.7.8. Determination of the MgSt content via Atomic Absorption Spectroscopy

For the determination of the MgSt content on the individual minitablets, Atomic Absorption Spectroscopy was used. The preparation of the samples was performed following the method

developed by de Backere et al. [91] with adjusted volumes for the acid digestion. One minitablet was placed in the sample tube and 0.5 ml of concentrated hydrochloric acid (37% w/w) and 3.5 ml concentrated nitric acid (65% w/w) were added. The samples were heated up to 180 °C within 10 min with the MARS 6 microwave digestion system (CEM, Matthews, NC, USA), followed by a holding time of 20 min at this temperature. Subsequently, the obtained solution was diluted to a volume of 20 ml with water and analyzed by atomic absorption spectroscopy using the PinAAcle 900T (Perkin-Elmer, Waltham, MA, USA). The measurement was conducted at a wavelength of 285.2 nm with a slit width of 0.7 nm and a flame consisting of an acetylene-air-mix. A multi-element hollow cathode lamp served as a light source for the measurement. The calibration curve was determined using three known concentrations of $MgCl_2$ and the MgSt quantity in the minitablets was calculated based the molar mass of magnesium. For each tablet position within the die, three minitablets were randomly chosen for the measurements and the mean and standard deviations were calculated.

5.2.8. HPLC assay

The samples were analyzed by high performance liquid chromatography (HPLC), using a Hitachi VWR system consisting of a pump (L-2130), an autosampler (L-2200), a column oven (L-2300) and an UV detector (L-2400) with the corresponding OpenLab CDS software (Version 2.6, Agilent, Santa Clara, USA). An Eurospher II C18A column (150 mm x 4.6 mm) with a particle size of 5 µm, a pore size of 100 Å and an integrated precolumn (Knauer, Berlin, Germany), served as the stationary phase for both APIs. Calibration curves for each API were created for every measurement series and measured in triplicate.

5.2.8.1. Zolmitriptan

The quantification of zolmitriptan was carried out with a mobile phase consisting of a mixture of 20% phosphate buffer (pH = 3.5) and 80% ACN. It was pumped at a flow rate of 0.8 ml/min and controlled at a temperature of 30 °C. The analyte peak was detected as a wavelength of 225 nm and eluted at a retention time of about 4.3 min, shown in Figure 88.

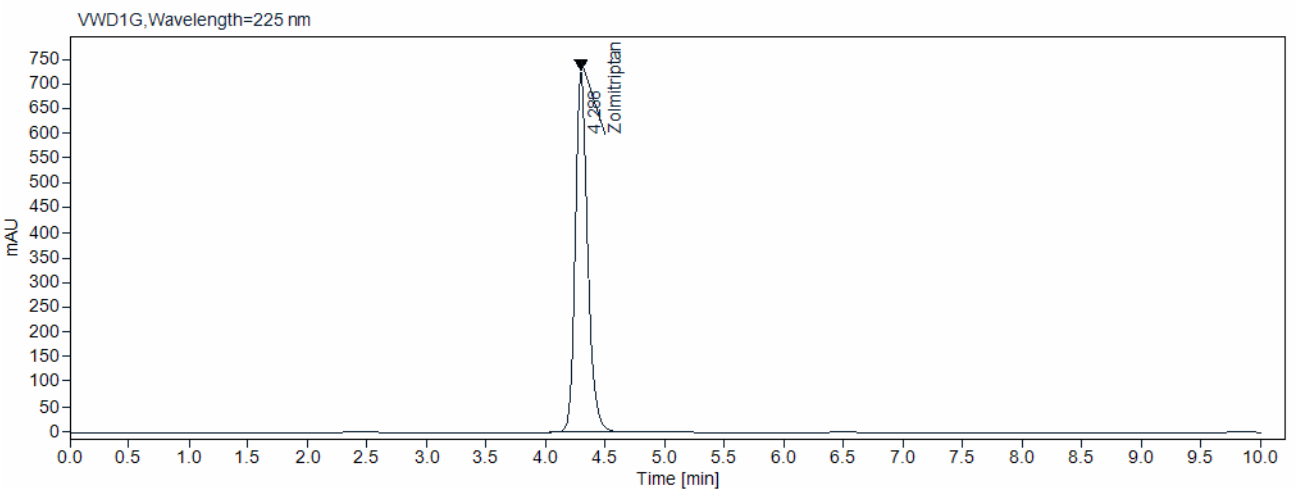


Figure 88: Exemplary chromatogram of zolmitriptan

5.2.8.2. Naproxen

For naproxen, following method was used for the analysis: A mixture of 65 % phosphate buffer (pH = 2.8) and 35 % ACN served as the mobile phase. A flow rate of 1.2 ml/min and a temperature of 25 °C were used. The analyte was detected at a wavelength of 232 nm. The retention time was about 7.6 min, also visible in an exemplary chromatogram in Figure 89.

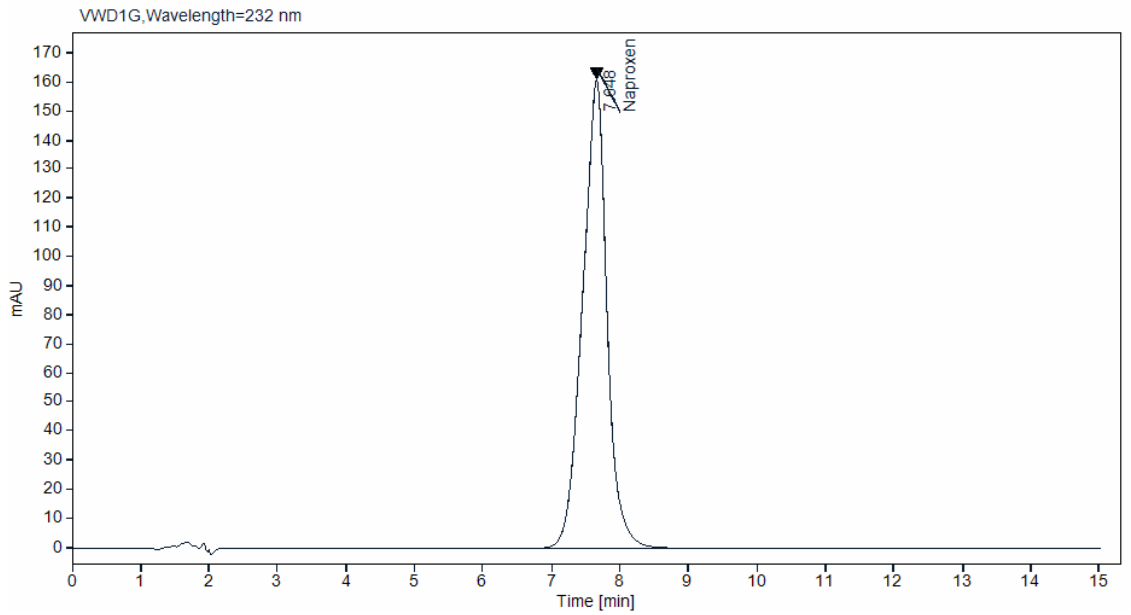


Figure 89: Exemplary chromatogram of naproxen

5.2.9. Dissolution experiments

5.2.9.1. Determination of saturation solubility

In literature, the solubility is often only specified for water. In practice, the solubility in the chosen dissolution media is much more relevant. Thus, the saturation solubility in the used dissolution media was determined experimentally. For this purpose, a sufficient amount of the API to ensure a saturated solution was placed in a vessel and 50 ml of dissolution liquid were added. The over-satured solution

was stirred on a stirring plate with 1200 rpm at 37 °C for at least 48 hours to make sure that the equilibrium solubility was reached. For separation of the sediment formed by the excess of the API, the samples were filtered through a cellulose filter paper (MN 615, Macherey-Nagel, Düren, Germany). Afterwards the samples were filtered through a polyamide syringe filter (Chromafil® Xtra PA-45/25, Macherey-Nagel, Düren, Germany) and analyzed by HPLC analysis, using the methods described in 5.2.8.

If necessary, the solutions were diluted appropriately to obtain absorptions in the suitable range and the injection volume varied between 3 and 10 µl depending on the concentration of the solution. For each API-media combination, three over-saturated solutions were created to calculate the mean and standard deviation.

5.2.9.2. Dissolution set-up

5.2.9.2.1. Zolmitriptan minitablets

The dissolution of zolmitriptan minitablets was performed in a USP I basket apparatus (according to Ph. Eur. 2.9.3.) to prevent floating of the minitablets. Four minitablets were placed in the basket to obtain the therapeutic dose of 2.5 mg. Two different media were used as dissolution media (37 ± 0.5 °C): 0.1 N HCl according to USP monograph "Zolmitriptan Orally Disintegrating Tablets" [282] to imitate the gastric fluid and phosphate buffer pH = 7.35 as a simulation of the human saliva [164], both stirred with 50 rpm. 5 ml samples were drawn in predefined time points with a 10 ml Eppendorf pipette (Eppendorf, Hamburg, Germany). Release testing of the MTs was conducted over a period of 60 min with more frequent sampling in the beginning. The removed volume was not replaced but taken into account in the calculation of the released API amount.

After filtration of the samples through an 0.45 µm PA filter (Chromafil® Xtra PA-45/25, Macherey-Nagel, Düren, Germany) the released API amount was determined by UV-spectroscopy (UV-1800, Shimadzu, Kyoto, Japan) at a wavelength of 226 nm using calibration curves measured in triplicate. For better comparability of the dissolution profiles, the amount of API released was calculated as percentage of the maximum concentration achieved.

For each tablet batch, three dissolution tests were performed to calculate the mean and standard deviation. The developed ODMTs were compared to a commercially available ZMT-ODT product (Zolmitriptan 2.5 mg 1A Pharma, Ch.B. LU6569, 1 A Pharma, Oberhaching, Germany).

5.2.9.2.2. Naproxen minitablets

The dissolution of naproxen minitablets was also tested in a USP I basket apparatus over 60 min. The dissolution test for each batch of minitablets was performed in triplicate with 10 minitablets per

basket. As dissolution medium, 500 ml of a 25 mM phosphate buffer with a pH = 7.35 (37 ± 0.5 °C), corresponding to the pH and the osmolality of the human saliva described by Hermes [164], was used and stirred with 50 rpm. On defined timepoints, a sample of 5 ml was drawn with a syringe and filtered through a prefixed polyethylene cannula filter with a pore size of 1 µm. The removed volume was not replaced but considered in the calculation of the released amount of API. The samples were analyzed by the HPLC method described in 5.2.8.2, injecting a sample volume of 20 µl. The amount of released NPX was expressed as percentage of the theoretical API content of the ODMTs and determined in triplicate to calculate mean and standard deviation.

5.2.9.2.3. Plots for the evaluation of the dissolution kinetics

Dissolution takes place mainly after three different kinetics: zero-order kinetic, first-order kinetic or square-root kinetic.

The first-order kinetic describes an exponential dissolution behavior for immediate release dosage forms where the release rate decreases over the time (Equation (19)).

$$c_t = c_0 * (1 - e^{-k*t}) \quad (19)$$

For the Sigma-Minus-plot, the difference between the complete release (100%) and the released amount for the timepoint t is calculated, logarithmized and plotted on the y-axis against the time. A coefficient of determination close to 1 indicates a dissolution profile according to a first order kinetic. For this work, the first 5 min of the dissolution data were used as the majority of the API was released within this time for the Kollitab™ minitablets.

For the description of the √t-kinetic, the Higuchi plot can be used [318]. Here, the released API amount is plotted against the root of time, and a R^2 close to 1 indicates a √t-kinetic, as the dissolution is proportional to √t (Equation (20)).

$$c_t = k * \sqrt{t} \quad (20)$$

5.2.10. Imaging techniques

5.2.10.1. Scanning electron microscopy

For the evaluation of the particle morphology of the excipients in chapter 263.1.1, SEM images were taken using the Phenom G2 Pro (Phenom World, Eindhoven, Netherlands) under vacuum. For the APIs, Kollitab™ and both Parteck® LM grades, the Zeiss Supra 55VP was used, after gold sputtering for 2 min under vacuum conditions.

5.2.10.2. Confocal Raman spectroscopy

Raman images were captured using the confocal Raman microscope alpha300 R (WITec, Ulm, Germany) with an excitation wavelength of 532 nm, a laser power of 20mW and a Zeiss EC Epiplan-Neofluar Dic 50x/0.8 objective (Zeiss, Oberkochen, Germany). The microscope was equipped with an Andor iDus Deep Depletion charged coupled device (CCD) camera, which was cooled down to -60°C,and a WITec UHTS 300 spectrometer. The mean spectral resolution was 3.8 cm^{-1}/pixel and was obtained by the use of a reflection grating with 600 lines/mm. After removal of cosmic rays and a baseline correction, the Raman intensities were normalized and images were created with the software WITec FIVE (version 5.3.18.110, WITec, Ulm, Germany).

Pictures were taken from different sides of the minitablets which were directly marked after the tableting process. For the bottom side of the minitablet, two different image sizes were recorded: A section with a size of 600 x 600 µm (spatial resolution 4 µm) to obtain an overview of the tablet surface and a section of 150 x 150 µm (spatial resolution 1 µm) for an evaluation of details and smaller particles which were not captured with the lower spatial resolution. Pictures of the side band of the minitablet were taken with a size of 1000 x 400 µm, pictures of the top were also taken with a 600 x 600 µm size. If possible, the images were taken from the center of either the top, the bottom or the side of the minitablet, shown exemplarily in Figure 90 and Figure 91. Additionally, light microscopic pictures were taken of the minitablet, recorded with a Zeiss EC Epiplan HD 10x/0.25 objective.

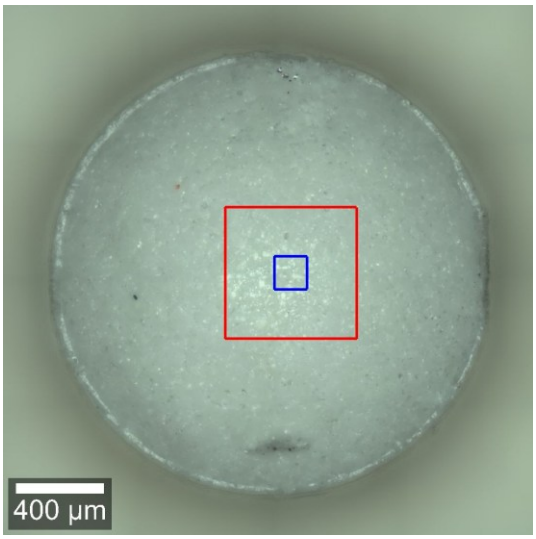


Figure 90: Microscopic image of a minitablet with marked sections used for Raman imaging, red: 600 x 600 µm, blue: 150 x 150 µm

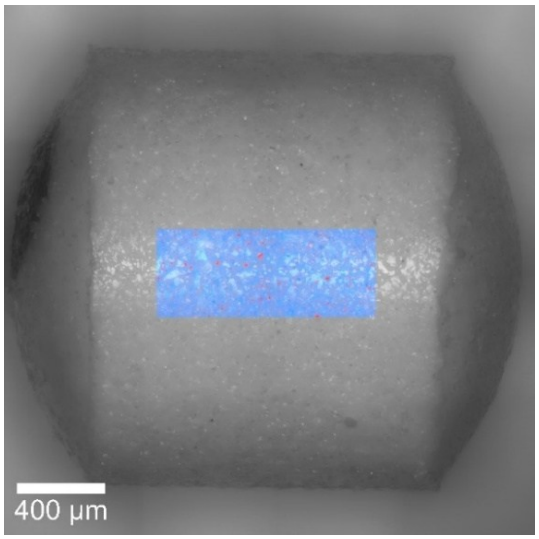


Figure 91: Microscopic image of a minitablet with marked side band area used for Raman imaging (blue = Prosolv® ODT, red = MgSt)

MgSt was distinguished from the remaining components by a characteristic peak at 2850 cm^{-1}. An exemplary spectrum of MgSt is depicted in Figure 92.

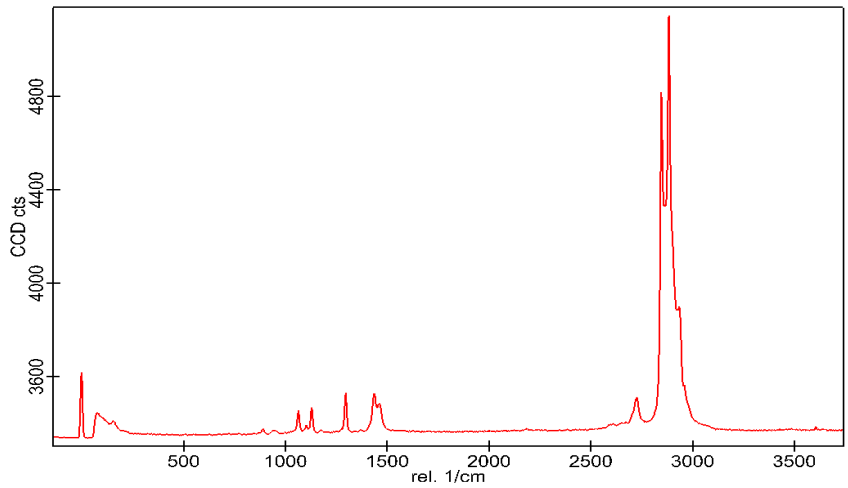


Figure 92: Raman spectrum of magnesium stearate

5.2.10.3. Evaluation of the Raman images

For a semi-quantitative evaluation of the surface coverage with the lubricant, the Raman images were processed with the open-access software Fiji [319] in Image J (version v1.53n). The assembled Raman images were converted into a two-colored picture using the Otsu thresholding method with a brightness adaptation to a range of 100 – 255 for each picture. The lubricant particles were marked and displayed in red colors whereas the other tablet excipients were depicted in black. The MgSt surface coverage was calculated with equation (21):

$$Surface\ coverage\ [\%] = \frac{number\ of\ marked\ lubricant\ pixels}{total\ number\ of\ pixels} * 100 \qquad (21)$$

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8. Eidesstattliche Erklärung

Hiermit versichere ich an Eides Statt gemäß § 5 Abs. 1 der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Heinrich-Heine-Universität Düsseldorf, 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. Die vorliegende Arbeit wurde in dieser oder ähnlicher Form noch bei keiner anderen Fakultät eingereicht.

Düsseldorf, den _____ _____

Jennifer Kuck