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Development and analytical characterization of oral film preparations for controlled drug delivery

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List of Abbreviations

API	Active Pharmaceutical Ingredient
AR	Aspect Ratio
AV	Acceptance Value
c	Concentration
CE	Conveying Elements
CHMP	Committee for Medicinal Products for Human Use
CMC	Carboxymethyl Cellulose, Carmellose (Ph.Eur.)
CR	Controlled Release
CV	Coefficient of Variation
CW	Clockwise
d	Diameter
DL	Double Layer
DS	Diclofenac Sodium
DSC	Differential Scanning Calorimetry
DT	Disintegration Time
EC	Ethyl Cellulose
EFSA	European Food and Drug Safety Authority
GE	Gastric Emptying
GI	Gastrointestinal
EMA	European Medicines Agency
ENDIC	European Network on Drug Investigation in Children
ETB	Elongation to Break
EU	European Union
EUPFI	European Paediatric Formulation Initiative
FDA	United States Food and Drug Administration
FH	Film Sample Holder
FH3D	3D Printed Film Sample Holder
FHB	Film Sample Holder with Backing Plate
FTC	Flow-through Cell

HME	Hot-melt Extrusion
HPC	Hydroxypropyl Cellulose, Hyprolose (Ph.Eur.)
HPMC	Hydroxypropyl Methylcellulose, Hypromellose (Ph.Eur.)
IR	Immediate Release
KB	Kneading Block
L/D	Length to Diameter Ratio
L1	Inspection Level 1
MBF	Mucoadhesive Buccal Film
MCC	Microcrystalline Cellulose
MCC-CMC	Coprocessed MCC and CMC
MDT	Mean Dissolution Time
mg	Milligram
MM, MMs	Micro-Matrix, Micro-Matrices
MP, MPs	Micropellet, Micropellets
n	Sample Size
n_{KP}	Korsmeyer -Peppas Exponent
ODF	Orodispersible Film
ORP	Oromucosal Patch
PAF	Punch and Filter
PE	Polyethylene
PDCO	Paediatric Committee
PGD	Paddle and Glass Disc
Ph.Eur.	European Pharmacopoeia
PIP	Paediatric Investigation Plan
PR	Prolonged Release
PS	Puncture Strength
PSD	Particle Size Distribution
PUMA	Paediatric Use Marketing Authorisation
PVC	Polyvinylchloride
QC	Quality Control
qPMMA	Ammonio Methacrylate Copolymer Type B (Eudragit® RS)

r	Radius
R&D	Research and Development
R^2	Correlation Coefficient
RH	Relative Humidity
RT	Room Temperature
RX	Prescription Drug
s	Second
sd	Standard Deviation
SEM	Scanning Electron Microscopy
SFaB & insert	Slide Frame and Ball plus Insert
SFaB	Slide Frame and Ball
SPC	Supplementary Protection Certificate
STEP	Safety and Toxicity of Excipients for Paediatrics
t	Time
TEC	Triethyl Citrate
TH	Thickness
US	United States of America
USP	United States Pharmacopeia
USPFI	United States Pediatric Formulation Initiative
WHO	World Health Organization
XµCT	X-ray Micro-Computed Tomography
x50	Median Particle Size
XRPD	X-ray Powder Diffraction
µm	Micrometer
ρ	Density
√t	Square Root of Time

Section A. Introduction

A.1 Oral controlled drug delivery

Oral drug delivery is the most widely used route of drug administration. It offers crucial advantages compared to other routes such as the ease of ingestion and non-invasiveness, which supports convenience and may improve the patient's compliance (Sastry et al., 2000). Moreover, oral solid dosage forms provide accurate dosing, high chemical and mechanical stability as well as a cost-effective production (Verma et al., 2002). However, the acceptance is limited to people without swallowing deficiencies. Children and elderly as well as patients suffering from dysphagia as a result of certain medical preconditions are often not able to swallow oral solid dosage forms (Stegemann et al., 2012). The drug effect after oral application is often unpredictable due to intra- and interindividual variation in the physiology of the human gastrointestinal (GI) transit (Mudie et al., 2010).

Biological, clinical or patients specific needs can require the application of controlled (or modified) drug delivery. By controlling and/ or directing the drug release, the dosage form performance can be improved in terms of therapeutic safety and efficiency, compared to immediate release (IR) formulations (Uhrich et al., 1999). Different approaches are described to control the rate and/ or the place of drug release including delayed, pulsatile, and prolonged drug delivery (EMA, 2014).

A.1.1 Prolonged release drug delivery systems

Prolonged drug release (PR) may enable constant blood plasma concentrations within the therapeutic window for a prolonged period of time. Especially for drugs revealing a short half-life or a narrow therapeutic range, these dosage forms are considered to be highly beneficial (Sorin, 2012). Plasma level fluctuations and toxic plasma levels are prevented, which reduces the incidence of adverse drug reactions. Furthermore, the dosage frequency and the risk of drug accumulation within chronic therapy can be reduced to improve the drug's effectiveness and accomplish patient compliance and safety (Hirayama and Uekama, 1999). For some drugs improved bioavailability is obtained by spatial control of the dose at the absorption site (Bhowmik et al., 2012). However, unintended rapid drug release, also termed as dose dumping, or unforeseen events may occur as consequence of poorly formulated dosage forms (Huang and Brazel, 2001). Moreover, PR dosage forms often show a slower onset of drug action and a greater dependence of the therapeutic effect on the GI transit compared to IR formulations (Wilson and Crowley, 2011).

PR dosage forms can either be formulated as single-unit (monolithical) or as multiple-unit (multiparticulate) dosage forms.

Whereas, the single-unit dosage form consists of one undivided, drug-loaded unit, the multiple-unit dosage form usually contains a large number of individual drug-loaded sub-units. PR single-unit dosage forms, such as matrix tablets and coated tablets, tend to release the drug over large parts of the GI tract. Afterwards, they are often discharged as empty cores/ shells or eroded residuals. To retain a reliable CR depot effect, swallowing the intact single-unit dosage form is mandatory, since damage or dividing may result in dose dumping (Bechgaard and Nielsen, 1978; Dey et al., 2008).

Multiple-unit dosage forms consist of large numbers of individual sub-units such as granules, microencapsulated crystals, minitablets or pellets contained in a sachet, capsule or tablet. After administration, the multiple-unit dosage form (tablet or capsule) disintegrates and the individual sub-units are being dispensed and distributed throughout the gastrointestinal tract (Bechgaard and Nielsen, 1978; Cram et al., 2009; Krause and Breitkreutz, 2008). Multiple-unit tablets or capsules can usually be divided or opened without losing the depot effect. Further, a formulation failure of an individual sub-unit does not result in dose dumping, which increases the therapeutic safety of the dosage form. The individual sub-units (multiparticulates) can be swallowed directly, dispensed in a liquid, sprinkled on food or administered via gastric tubes, to accomplish patient convenience and to overcome potential swallowing issues in children, elderly or patients with dysphagia (Gonzalez and Golub, 1983; Pöllinger, 2016). By incorporating different amounts, or mixing various species of multiparticulates, multiple dose strengths and tailored release profiles can be obtained with reduced effort in the formulation development (Dey et al., 2008; Qiu, 2009). Most of the aforementioned multiparticulates can be produced using conventional manufacturing equipment. Disadvantages associated with multiparticulates concern the limited drug load resulting in increased tablet or capsule sizes and the volume of multiparticulates, which have to be ingested to administer a therapeutic drug dose. Furthermore, the formulation and/ or process complexity is increased for tailored drug release products making the process development and the scale up approaches more challenging (Qiu, 2009).

After administration multiparticulates are assumed to perform more consistently regarding GI transit (Sorin, 2012). Thus, the predictability and reproducibility of the

therapeutic effect is increased, whereas the risk of adverse drug reactions is usually reduced (Bechgaard and Nielsen, 1978; Mudie et al., 2010). Differences in the GI transit of multiple-unit compared to single-unit formulations and the resulting clinical effects are discussed in Section A.1.2.

A.1.2 Anatomic and physiological properties of the gastrointestinal tract

To successfully design controlled release (CR) drug delivery systems, knowledge of the technologies, the materials as well as the underlying release mechanisms, and comprehensive understanding of the GI physiology is essential (Dressman et al., 1993). Since CR dosage forms are designed to transit through various regions of the GI tract and to remain there for a substantially longer period of time, compared to IR formulations, the physiological characteristics of the most important phases of GI transit, displayed in Figure A.1.2-1, are highlighted within this section.

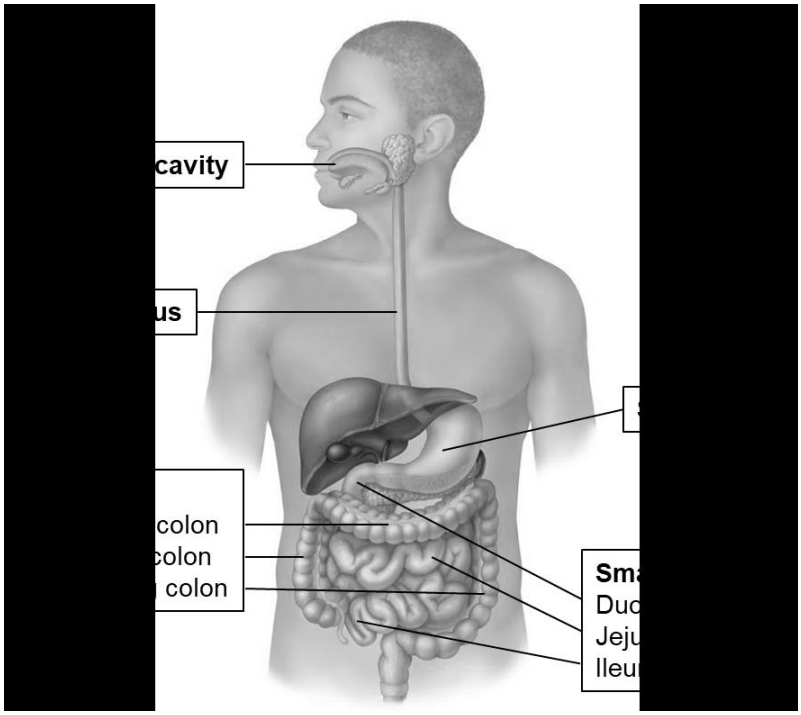

Figure A.1.2-1 Regions of the gastrointestinal transit © Pearson Education, Inc.

A.1.2.1 The oral cavity as application site

The oral cavity represents the first segment of the GI tract and consists of two regions, the vestibule and the oral cavity proper. The human oral cavity is lined by different types of oral mucosa with a total surface area of approximately 200 cm^2 for adult subjects (Collins and Dawes, 1987). While the gingiva, the hard palate and the dorsum of the tongue is lined by masticatory mucosa, which is characterized by keratinized epithelium, the soft palate, the buccal region, and the sublingual region

consist of non-keratinized mucosa, which is assumed to be more permeable than keratinized mucosa (Rathbone and Hadgraft, 1991). The thickness of the oral mucosa ranges from 100 to 300 µm, except for the buccal mucosa revealing an increased thickness of 500 to 800 µm. In general, the thickness of non-keratinized tissue is moderately increased, compared to keratinized epithelium (Squier, 1991). The sublingual mucous membrane is non-keratinized, about 100 µm thin and highly perfused providing ideal conditions for systemic drug absorption (Shojaei, 1998). Further factors affecting the oromucosal absorption include the molecular weight, the pKa value and the hydrophilic-lipophilic balance of the drug as well as the residence time, the pH value, the volume and the flow of saliva in the oral cavity. It is supposed, that most of the drugs administered by sublingual route are absorbed by simple diffusion (Harris and Robinson, 1992). The tongue is lined by specialized mucosa consisting of partially keratinized epithelium and lingual papillae, containing the taste receptor cells. Except the filiform papillae, all other types (vallate, fungiform and foliate papillae) are associated with taste buds carrying groups of taste receptor cells (Yarmolinsky et al., 2009). The oral mucosa is covered with a thin salivary film of approximately 70 to 100 µm (Collins and Dawes, 1987). The saliva is produced by three paired major salivary glands namely the parotid, submandibular and sublingual gland as well as a multitude of minor salivary glands (Edgar, 1992). The salivary glands continuously secrete between 1 and 1.5 l saliva per day, with flow rates of 0.25 to 0.6 ml/min unstimulated and up to a maximum of 7 ml/min stimulated (Chicharro et al., 1998). The saliva is a complex mixture of serous and mucous secretions from the salivary glands, gingival crevicular fluid, oral mucosal transudate, mucous of the nasal cavity and pharynx as well as other components associated with the oral bacteria or the intake of food and medication. The saliva consists of 99.5% water and 0.5% dissolved substances such as the proteins α-amylase and mucin secreted by the salivary glands as well as the osmotically active electrolytes Na^+, K^+, Ca^{2+}, Cl^- and HCO_3^-, just to mention a few of them. The density ranges from 1002 to 1012 kg/m^3. The salivary pH value is linked to the blood CO_2 level, unstimulated usually around 6.5 and stimulated up to 7.2 (De Almeida et al., 2008; Humphrey and Williamson, 2001).

A.1.2.2 Esophageal transit

The esophagus is a fibromuscular tube of 18 to 26 cm in length in adults and reaches from the upper to the lower sphincter. From the pharynx to the stomach swallowed

ingestions are passed through by peristaltic contractions. The esophagus is lined with esophageal mucosa, consisting of non-keratinized epithelium as in the oral cavity. An irregular zig-zag line indicates the transition between esophageal and gastric epithelium (Kuo and Urma, 2006).

The esophageal transit highly depends on the volume of co-administered liquid. If a sufficient amount of fluid is available, it usually takes about 10 s to pass through a dosage form into the stomach. However, influencing factors are the surface structure of the dosage form (Perkins et al., 2001), the age (Stegemann et al., 2012) and the coordination skills (Ren et al., 1993) of the patient as well as medical preconditions such as erosive esophagitis (Vakil et al., 2004), Alzheimer´s disease (Eggenberger and Nelms, 2004), acute stroke (Gordon et al., 1987) and diabetes type 1 (Holloway et al., 1999).

With increasing age, all three phases of deglutition (oral, pharyngeal and esophageal phase) are affected, increasing the prevalence of dysphagia in elderly (Aslam and Vaezi, 2013; Robbins et al., 1992; Shaw et al., 1995). Swallowing deficiencies in elderly are mainly attributed to structural abnormalities such as neoplasm, peptic stricture and diverticula or motor dysfunction, including esophageal spasm, scleroderma and achalasia (Firth and Prather, 2002; Robbins et al., 1995; Shaker and Staff, 2001). In this context, size, shape and color of the dosage form have a high impact on the swallowability (Channer and Virjee, 1986). With increasing size, swallowability decreases (Overgaard et al., 2001). Co-administration of water and the position of the patient further influence the transit time and swallowability. The more water and the more upright the patients position, the faster is the esophageal transit (Hey et al., 1982).

A.1.2.3 Release and absorption in the stomach and the intestine

Physiological conditions of the GI tract clearly show inter- and intraindividual differences. Depending on the physical capabilities, medical preconditions as well as the type and amount of ingested food, GI parameters widely vary (Dressman et al., 1993). Table A.1.2-1 compares physiological characteristics of the stomach and the intestine under fasted and fed conditions.

Table A.1.2-1 Physiological parameters of the different regions during gastrointestinal transit; adapted from Mudie et al. (2010)

	Stomach		Small intestine	
	Fasted state	Fed state	Fasted state	Fed state
Fluid volume [ml]	45[1]	800-900[10]*	105[1]	900-1000[10]*
Flow rate [ml/min]	1[12]	10-50[12]	0.33-0.73[14]	2.35-3.0[14]
Transit time [h]	1-2[2-3]	1.4-4.0[3]	3.6[3]	3.8[3]
pH value	1.5-1.9[3-7]	3-7[2,4#]	6.5-7.2[3]	5.1-7.5[2,11]
Osmolality [mOsm/kg]	98-140[4]	217-559[4]	178-271[4,8]	390[4]
Buffer Capacity [mmol/L*ΔpH]	7-18[4]	14-28[4]	2.4-5.6[4,9]	18-30[4,9]

* including the volume of meal
\# changes with time
[1] Schiller et al. (2005)
[2] Dressman et al. (1998)
[3] Ibekwe et al. (2008)
[4] Kalantzi et al. (2006)
[5] Dressman et al. (1990)
[6] Evans et al. (1988)
[7] Vertzoni et al. (2005)
[8] Lindahl et al. (1997)
[9] Persson et al. (2005)
[10] Custodio et al. (2008)
[11] Hörter and Dressman (2001)
[12] Versantvoort et al. (2004)
[13] Whalen et al. (1966)
[14] Kerlin et al. (1982)

The stomach enables food digestion by peristalsis as well as secretion of digestive enzymes and gastric acid promoting the chyme formation. The gastric mucosa consists of secretory epithelium and is covered by a mucus layer. The gastric intercellular junctions are tight and the permeability of the mucus is low, preventing passive diffusion even for small molecules, well-absorbed at different sites (Wilson and Crowley, 2011).

Three types of gastric glands (cardiac, fundic and pyloric glands) are contained in the gastric mucosa, located beneath the gastric pits within the mucosa. It secrets compounds of the gastric acid such as mucus, pepsinogen, intrinsic factor, gastrin as well as chloride and hydrogen ions for the production of hydrochloric acid (Schubert and Peura, 2008). The pH value of the gastric acid determines the dissolution of ionizable drugs and affects their systemic exposure (Li et al., 2005; Sheng et al., 2006; Vertzoni et al., 2005). The gastric pH value differs depending on age and gender. The basal pH value was found to be elevated for elderly with atrophic gastritis (Farinati et al., 1993; Jaskiewicz et al., 1990) and for female compared to male subjects (Feldman and Barnett, 1991) which might be linked to reduced sensitivity of gastrin-induced simulation of acid secretion (Feldman et al., 1983). The ingestion of food strongly affects the gastric pH value and additionally the gastric emptying (GE) time. The GE time complies with the time which is needed to transport a dosage form through the stomach into the small intestine, which exhibits the major absorption site for most drugs (Dressman et al., 1998; Kalantzi et al., 2006; Welling,

1996). Therefore, physiological conditions in the stomach as well as the GE time determine the extent of dissolved drug to be absorbed from the small intestine and thus the onset of drug action (Kong and Singh, 2008). The GE time strongly differs between fasted and fed state due to differences in the contraction pattern. In fasted state, a regular cycle of peristaltic contractions occurs every 90 to 120 min, inducing GE (Code, 1979). The different phases of the interdigestive motility complex are displayed in Figure A.1.2-2.

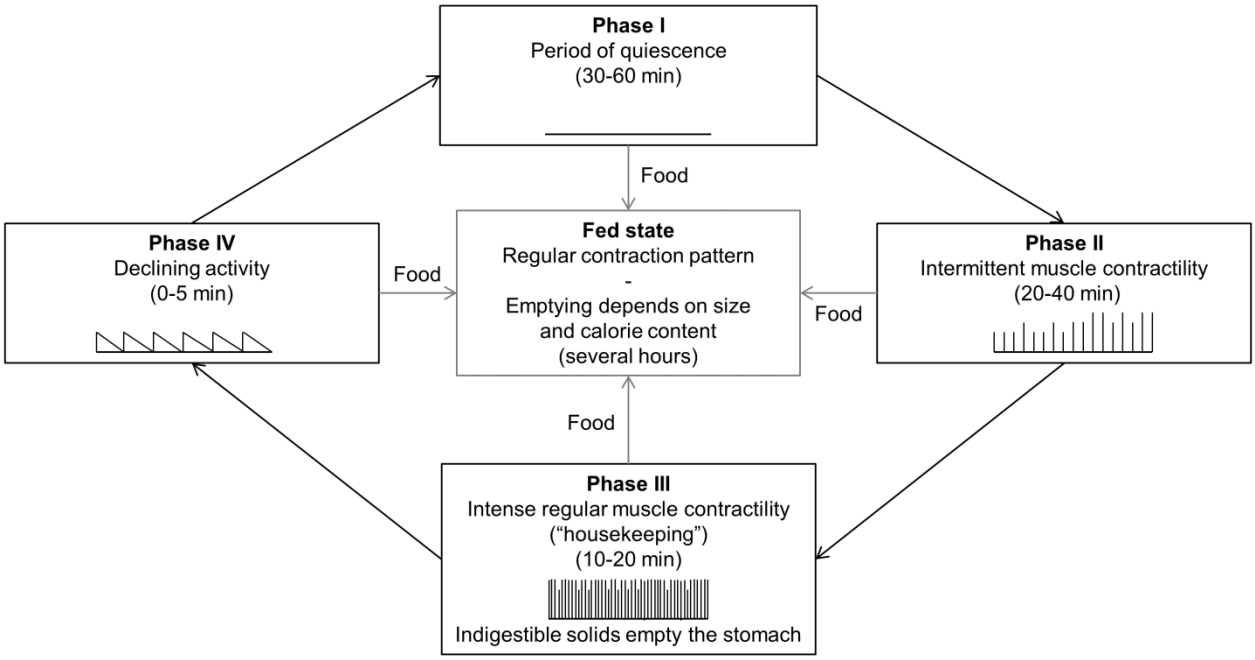

Figure A.1.2-2 Schematic illustration of the gastric motility pattern, adapted from Prajapati et al. (2013)

GE time of an ingested solid ranges therefore from a few minutes up to 2 h, depending on the motility phase at ingestion time and the co-administered fluid volume (Dressman et al., 1998; Oberle et al., 1990). Non-disintegrating solids such as CR single-unit tablets larger 1 mm empty late in phase III of the interdigestive motility complex and show high variability in emptying times. However, further increasing tablet sizes may have no impact on the average emptying time, themselves (Hunter et al., 1982; Park et al., 1984). Compared to non-disintegrating solids, disintegrating solids such as multiparticulates empty gradually and more readily during both, fasted and fed state. The GE time thereby depends on the dispersabilty of the remaining particles in the emptying fluid (Digenis et al., 1990; O'Reilly et al., 1987; Rhie et al., 1998). In fed state a more regular motility pattern is prevalent, which can take several hours. Postprandial GE time of non-digestible

solids widely varies and is strongly affected by the size of the ingested solid as well as the amount and composition (caloric content) of co-administered food (Davis et al., 1984a). For small-sized multiparticulates Meyer et al. (1988) found the influence of the size to be superior compared to co-administered food. They observed 1 mm spheres emptied consistently faster from the stomach than 2.4 or 3.2 mm spheres. GE of larger-sized single-units in fed subjects was investigated by Khosla and Davis (1990) using γ-scintigraphy. With increasing tablet size (7 to 13 mm), the GE time increases (116 to 210 min), whereas the variability decreases. Considering the findings from Hinder and Kelly (1977), it is assumed that the size of non-digestible solids, which empty from the stomach in postprandial state, is limited to 1-2 mm as a consequence of specialized antral and pyloric contraction pattern. While the co-administered food is already cleared from the stomach, larger sized non-digestible solids can retain in the stomach for several hours (Coupe et al., 1991a) and first empty in phase III after the stomach returns to the fasted motility pattern (Dressman et al., 1998).

In contrast, Weitschies and coworkers recently found out that the GE time of ingested solids in postprandial state can be highly variable, depending on the volume of co-administered liquid. The co-administered liquid can move from the fundus along a short path through the center of the antrum directly to the duodenum within 10 min, which is called the Magenstrasse or stomach road (Grimm et al., 2017). In contrast to postprandial GE times of more than 2 h for ingested solids, which are dispersed in the chyme, the GE times of ingested solids, which are moved through the stomach by the Magenstrasse can be very fast with around 10 min (Pal et al.,2007).

Furthermore, Mojaverian et al. (1985) identified GE time to be additionally affected by gender, posture and age of the human subject.

The small intestine consists of three regions, namely the duodenum, jejunum and the ileum. The duodenum is the shortest part with a length of 20 to 25 cm, whereas the length of the jejunum and ileum is considerably longer with 2.5 and 3 m, respectively (Washington et al., 2000). The surface structure of the intestinal mucosa is convoluted including the Kerckring folds, villi and microvilli, which leads to a 600-fold higher intestine surface area, complying with a total area of up to 200 m^2 in an adult subject (Mudie et al., 2010). The intestinal mucosa comprises secretory and absorptive endothelium for digestion of food and absorption of food compounds such as fats, proteins and carbohydrates. Furthermore, the small intestine represents the

major site of absorption for drugs, which were mostly absorbed by passive trans- and paracellular diffusion (Dressman et al., 1998; Kalantzi et al., 2006; Lacombe et al., 2004). Some drugs as well as essential amino acids and vitamins were assimilated by active transport mechanisms such as carrier-mediated transcellular and vesicular transport. In contrast, drug absorption may be reduced by efflux transporters and drug degradation or metabolism. Drug absorption is therefore directly linked to the intestinal surface area and the residence time of the drug in the small intestine (DeSesso and Jacobson, 2001). The intestinal residence time was found to be approximately 3 h (Davis et al., 1984b; Hardy et al., 1987) and highly, intra- and interindividually variable (McConnell et al., 2008; Weitschies et al., 2005). The transit time is not affected by type or size of the dosage form (Coupe et al., 1991b; Davis et al., 1986; Gruber et al., 1987). For drugs which are not fully absorbed during GI transit, the intestinal residence time represents a crucial parameter, since it is directly correlated to the total fraction of absorbed drug. In contrast, an extended residence time in the stomach may be beneficial for drugs, using the upper windows of absorption. Since duodenal transit is rapid (less than 5 min), continuous transport of dissolved drugs from the stomach into the duodenum is assumed to increase drug absorption (Burke and Wilson, 2006).

A.1.2.4 The colon

The three major regions of the colon are the ascending, the transverse and the descending colon. Compared to the small intestine, the lumen of the colon is wider, whereas the length (approximately 1.5 m) and the mucosal surface area are reduced. The residence time varies in the different regions of the colon between 3 to 5 h within the ascending, 0.2 to 4 h within the transverse and up to a maximum of 72 h in the descending colon region (Amidon et al., 2015; Van den Mooter, 2006). The colonic transit time is assumed not to be affected by co-administered food. Edsbäcker et al. (2002) showed that the time of food consumption relative to dose intake had no effect on the absorption of controlled-release budesonide capsules at the ileum and colon. However, Adkin et al. (1993) observed increased residence time in the ascending colon for smaller tablets (3 and 6 mm) compared to larger tablets (9 and 12 mm). For multiparticulates this effect is even more pronounced. Additionally, the drug is exposed to the colon more rapidly, using multiparticulate drug carrier (Asghar and Chandran, 2006; Hardy et al., 1985).

Generally, the reduced mucosal surface area of the colon is linked to a reduced absorptive capacity compared to the small intestine, but may be balanced by the increased residence time. Here only the conditions in the ascending region are suitable for drug absorption after oral drug administration. Drug absorption in the transverse colon is reduced due to a limited water volume (Wilson, 2010). The fluid volume in the ascending and transverse colon is estimated to be about 20 to 30 ml (Diakidou et al., 2009; Schiller et al., 2005). In the descending colon drug dissolution and absorption may be inhibited by fecal solidification. Hebden et al. (1999) observed increased drug dispersion and dissolution in the transverse colon, when the fluid volume is increased such as the result of diarrhea. Moreover, targeted delivery of drugs to the colon has gained high interest in pharmaceutical research and development (R&D), to be beneficial in the treatment of diseases of the distal gut. By colon targeting, increased local concentrations should be provided at the desired region, or at the appropriate time of the day (Gazzaniga et al., 2006). For example, the enzyme azo-reductase represents one of the target structures of colonic drug delivery. The azo-reductase is secreted by the colonic microflora and catalyzes the scission reaction of the 5-ASA prodrugs balsalazide and olsalazine into the active form, targeted within colon (Sousa et al., 2008).

A.1.3 Diffusional drug release mechanisms

Oral controlled drug delivery is usually obtained using polymeric systems controlling the drug release via diffusion, osmotic pressure or ion-exchange processes.

The dosage form design of diffusion-controlled drug delivery systems can be matrix-based or reservoir-based. A matrix-based drug delivery system contains the drug homogeneously embedded in a polymeric matrix. In contrast, a reservoir-based dosage form is characterized by a drug depot, which is surrounded by a rate-controlling polymeric membrane (Verma et al., 2002). The drug release from non-degradable matrix- and reservoir-based systems is schematically displayed in Figure A.1.3-1.

To describe the drug release from polymeric systems (reservoirs and matrices), the semi-empirical power law equation displayed as Equation (1), introduced by Peppas and coworkers, can be used. M_t and M_∞ represent the absolute cumulative amount of drug released at time t and at infinite time; k is a constant, which considers geometric dosage form characteristics, and n represents the release exponent, indicative of the

drug release mechanism (Peppas, 1985; Peppas and Korsmeyer, 1987; Ritger and Peppas, 1987b).

$$\frac{M_t}{M_\infty} = k * t^{n_{KP}} \quad (1)$$

A value of 1 for the diffusional exponent n_{KP} indicates zero-order kinetics (Case-II-transport), whereas square root of time (√t) kinetics according to Higuchi (1961) is associated to a diffusional exponent of 0.5. If the value for the diffusional exponent is between 0.5 and 1, the drug release is determined by diffusion and relaxation processes and is defined as non-Fickian transport. The limits for the diffusional exponent to classify the underlying transport mechanism change depending on the dosage form geometry (Ritger and Peppas, 1987a).

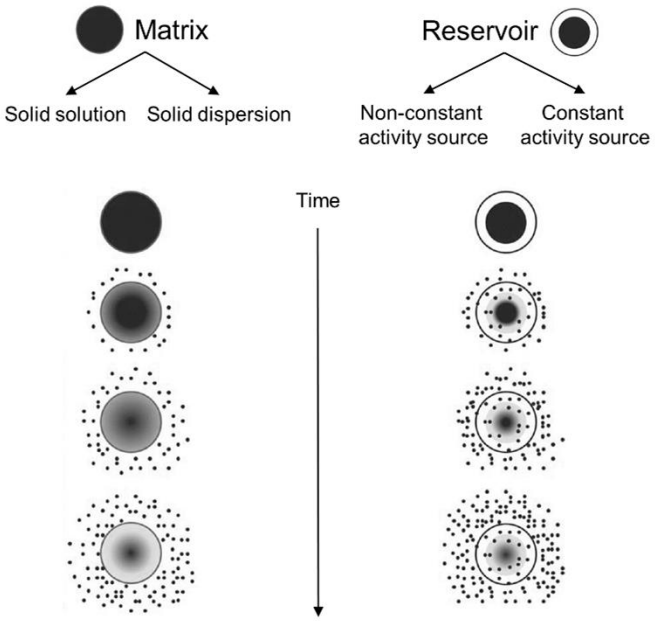

Figure A.1.3-1 Drug release from matrix-based and reservoir-based dosage forms adapted from Coelho et al. (2010) and Siepmann & Siepmann (2008)

Depending on whether the initial drug concentration is either below or above the drug solubility in the (wetted) carrier, the underlying release mechanism for reservoir- and matrix-based systems differs (Siepmann and Siepmann, 2008).

A.1.3.1 Reservoir-based drug delivery systems

The main factors affecting the release profiles of single reservoir-based drug delivery systems are the size, the drug load, and the coating thickness of the dosage form as well as the solubility of the drug within the core and the diffusion coefficient of the drug in the coating material (Marucci et al., 2011).

Drug particles released from a reservoir-based dosage form with a drug load below the drug solubility are not replaced. Thus, the concentration at the inner membrane surface decreases with time, which represents a non-constant activity source. In this case water penetration into the carrier and drug dissolution is much faster than drug diffusion through the polymeric membrane. Assuming perfect sink conditions, constant permeability of the drug through the membrane and that the drug release is sole diffusion-controlled (no swelling or dissolution of the membrane), Fick's law of diffusion can be applied. The drug release is then proportional to the concentration at the inner surface of the membrane resulting in first-order kinetics independently from the dosage form geometry (Siepmann and Siepmann, 2008; Siepmann and Siepmann, 2012).

For reservoir-based drug delivery systems with a drug concentration exceeding the solubility of the drug within the (wetted) carrier, all released drug molecules are rapidly replaced by dissolution of drug particles from the saturated solution within the carrier, representing a constant activity source. The drug concentration at the inner membrane´s surface remains constant as long as the drug excess provides replacement of drug molecules. Under the abovementioned assumptions and, that the system is in steady state, also the drug release is constant following zero-order kinetics, irrespective of the dosage form geometry (Kaunisto et al., 2011; Siepmann and Siepmann, 2012).

In practice, drug release in early phase deviates from steady state conditions due to lag-time or burst effects. Burst release describes an initial huge bolus of dissolved drug, released from the dosage form before reaching the steady state of drug release (Siepmann and Siepmann, 2012). The burst release is mainly attributed to storage effects. Thereby, the rate-controlling membrane is saturated with drug molecules and/ or drug molecules are recrystallized on the dosage form surface (blooming) during storage, which are released rapidly when placed in the release medium (Huang and Brazel, 2001; Khan and Craig, 2004). Modeling the drug release, burst effects can lead to underestimated release rates in early phase (Siepmann and Siepmann, 2012). In contrast, the lag-time represents an initial time-interval, which is necessary to reach a steady state (Higuchi, 1961). The lag-time is characterized by a strongly reduced amount of drug released from the dosage form and is attributed to the time, which is needed for the dissolved drug molecules to diffuse from the core through the membrane into the ambient release medium. Initial lag-time phases can

cause overestimated release rates applying mathematic drug release models (Siepmann and Siepmann, 2012). The formation of ruptures, linked to hydrostatic pressure built up in the core, exerting mechanical stress on the coating material is another phenomenon influencing the drug release from reservoir-based systems (Frenning and Strømme, 2003; Marucci et al., 2008). The drug release is assumed to be not only diffusion-controlled, but also affected by convection processes, making the mathematic modeling much more complex (Siepmann and Siepmann, 2012). When the drug delivery system is formulated as multiple-unit dosage form, knowledge of the subunit properties is important to understand the overall release mechanism (Kaunisto et al., 2011). To assess the release mechanism, experiments on the single-unit level are recommended and described in the literature (Borgquist et al., 2004; Borgquist et al., 2002; Kaunisto et al., 2011; Marucci et al., 2010; Marucci et al., 2008; Schultz and Kleinebudde, 1997).

A.1.3.2 Matrix-based drug delivery systems

The dissolution kinetics of matrix-based systems however is strongly influenced by the geometry of the dosage form.

For matrix-based systems containing the drug molecular dispersed within the polymeric matrix (solid solution), Fick´s second law of diffusion can be used to calculate the drug release, applying specific parameters depending on the dosage form geometry. Requirements for the validity are an initial homogeneous drug distribution within the matrix as well as the assumptions described for reservoir-based systems (Siepmann and Siepmann, 2008; Siepmann and Siepmann, 2012).

In case of matrix-based systems, where the initial drug concentration significantly exceeds the drug solubility within the matrix, the square root of time relationship according to Equation (2) has been postulated (Higuchi, 1961), where M_t represents the cumulative absolute amount of drug released at time t; A the total surface area exposed to the release medium; D the diffusion coefficient of the drug within the polymeric matrix; c_s the drug solubility, and c_0 the initial drug concentration within the (wetted) matrix system (Siepmann and Siepmann, 2012).

$$\frac{M_t}{A} = \sqrt{D * (2 * c_0 - c_s) * c_s * t} \quad (2)$$

However, Higuchi (1961) implemented this relationship for thin films with negligible edge effects. Further requirements for the validity are a pseudo-steady-state, a particle size of drug particles smaller than the film thickness as well as the

assumptions mentioned for reservoir-based systems (Siepmann and Peppas, 2011). Since the geometry of most CR drug delivery systems deviates from thin films, further approaches considering different dosage form geometries have been made (Desai et al., 1966; Higuchi, 1963; Lapidus and Lordi, 1968; Lapidus and Lordi, 1966; Siepmann and Siepmann, 2008). Figure A.1.3-2 exemplarily displays principles to manufacture reservoir-based and matrix-based drug delivery systems.

[1] GSK (2017)
[2] Watano et al. (2004)
[3] Ishida et al. (2008)
[4] Tomuta and Leucuta (2007)
[5] Krogars et al. (2000)
[6] Dashevsky et al.
[7] Lee et al. (1999)
[8] Quinten et al. (2009)
[9] Moorman-Li et al.
[10] Burness and Keating (2014)
[11] Flanders et al. (1987)
[12] De Brabander et al.
[13] Goskonda et al. (1994)
[14] Young et al. (2002)
[15] Jenquin and McGinity
[16] Glaessl et al. (2009)

Figure A.1.3-2 Different types of CR drug delivery systems

A.1.4 In vitro dissolution testing of oral solid dosage forms

In vitro dissolution testing is an experimental methodology, which supports characterization of the drug release properties of oral solid dosage forms to evaluate the underlying release mechanism and to enable an estimation of the dosage form performance.

Dissolution testing guides the formulation design and the optimization of processes within pharmaceutical R&D and is routinely performed for quality control (QC) (Anand et al., 2011; Siewert et al., 2003). Furthermore, in vitro dissolution testing can be used to assess the biopharmaceutical properties of oral solid dosage forms. Adequate oral bioavailability of the drug is essential for the effectiveness of these dosage forms. If the drug release from the dosage form represents the rate limiting step for the drug absorption, it can influence the bioavailability of the drug significantly (Amidon et al., 1995). Thus, in vitro dissolution testing represents a valuable tool to predict the in vivo performance. However, in vitro-in vivo correlation needs to be demonstrated for the applied dissolution method (Dressman et al., 1998). A more detailed overview of the applications of in vitro dissolution testing is given in Section C.2 and C.3.

A meaningful dissolution test method should be discriminative and sensitive to variations in the product quality, but robust enough to detect effects on the dissolution rate only when they are biologically relevant (Azarmi et al., 2007). In vitro dissolution testing needs to be conducted under precisely defined conditions and in standardized apparatuses, as hydrodynamic properties as well as the composition, temperature and pH of the medium strongly influence the drug release behavior (Baxter et al., 2005; Shiko et al., 2011). The United States Pharmacopeia (USP; USP, 2018) as well as the European Pharmacopoeia (Ph.Eur., Ph.Eur., 2018b) refers to seven dissolution apparatuses. Four of them are intended to characterize oral solid dosage forms such as the basket (apparatus 1), paddle (apparatus 2), reciprocating cylinder (apparatus 3) and flow-through apparatus (apparatus 4). The different dissolution apparatuses are defined in chapter <711> of the USP and <2.9.3> of the Ph.Eur.. The most widely used dissolution apparatuses are the basket and paddle apparatus, due to their simple, robust and well standardized test setup. Other apparatuses are defined in chapter <724> of the USP and <2.9.4> of the Ph.Eur. to investigate the drug release from transdermal patches. A chewing apparatus for medicinal chewing gums is described in chapter <2.9.25> of the Ph.Eur..

Furthermore, dissolution-related guidelines are published by the US Food and Drug Administration (FDA; FDA, 1997; FDA, 2000), in which for instance recommendations on the procedure development, setting of specifications and the establishment of an in vivo-in vitro correlation procedure for IR and CR dosage forms are provided (Shah et al., 1997). For dissolution testing of novel dosage forms or the development of physiologically relevant test procedures the application of non-compendial equipment may be necessary (Siewert et al., 2003). The applications of a mini or mega paddle, peak vessel, a punch and filter device and special flow-through cell designs are only some examples of non-compendial dissolution equipment (Gray et al., 2009; Klein and Shah, 2008; Krampe et al., 2016a).

The development of a suitable test procedure for CR dosage forms has to be performed on a case-by-case basis as the underlying drug release mechanism is more complex, compared to IR formulations, including diffusion, dissolution, erosion and swelling processes or combinations of those (Crison, 1999). In order to assess the dissolution behavior of CR dosage forms, evaluation of a prolonged test period as well as multiple time points may be necessary (FDA, 1997). Moreover, biorelevant dissolution media (Klein, 2010), novel mechanistic tools (Chen et al., 2010; Coutant et al., 2010; van der Weerd and Kazarian, 2004) or dissolution systems considering relevant dynamic and digestive features of the GI tract (Blanquet et al., 2004; Gu et al., 2005; Souliman et al., 2007; Vardakou et al., 2011) can be used to obtain a better in vivo-in vitro correlation.

A.2 Patient centered dosage form design

Patient-centered dosage form design describes all activities related to increased therapeutic success by enhancing patient acceptance and compliance. The acceptance of an oral dosage form is contributed to both, the ability and the willingness of a patient taking the prescribed medication as intended (Stegemann et al., 2010). Swallowing deficiencies or refusal of oral medication due to limited physical or cognitive capabilities are major challenges in the pharmacotherapy of pediatric and geriatric patients (Liu et al., 2014; Stegemann et al., 2012). As dysphagia in elderly is attributed to a variety of pathophysiological disorders, discussed in Section A.1.2.2, a prevalence of more than 16% of over 87-year-olds and even up to 50% of residents in care homes is not surprising (Bloem et al., 1990; Rofes et al., 2011). Polypharmacy, anxiety and bad experiences further decrease the acceptance of oral medication in elderly (Schiele et al., 2013). In contrast, the prevalence of dysphagia in children has not yet been sufficiently investigated. However, it is known that swallowing problems are typically linked to the developmental stage of the children. The ability to swallow matures between 6 month and 3 years (Arvedson, 2006). Although it is assumed that the swallowing reflex is fully developed with at least 6 years of age, Hansen et al. (2007) reported that more than 33% of adolescents between 11 and 20 years had problems taking oral medication. Children with history of prematurity, low birth weight, and complex medical conditions suffer significantly more often from swallowing disorders (Arvedson, 2008; Miller, 2009).

A.2.1 Acceptability of oral formulations in children

The acceptability of taking oral medication is based on the ability to swallow, as mentioned above, and on the willingness of the patient. The ability of swallowing oral solid dosage forms was found to be directly linked to the size of the dosage form. It could be demonstrated that 91% of 6- to 11-year-old-children as well as 80% of 1- to 9-year-old-children were able to swallow 7 mm tablets, complying with the age of conversion from liquid to solid formulations (Kokki et al., 2000; Kreeftmeijer-Vegter et al., 2013). And although, Klingmann et al. (2015) showed the acceptance and safety of 2 mm minitablets administered to neonates, liquid drug formulations are often considered to be most appropriate (“gold standard”) for children as swallowing of large particles is avoided. Disadvantages of liquid formulations are related to issues in stability, handling and dosage accuracy (Zajicek et al., 2013). Using liquid

formulations in children, special attention must be paid to taste-masking approaches to accomplish palatability. Many drugs and excipients used in liquid formulations such as preservatives in multiple-dose containers have a bitter taste. Furthermore, excipients, which are not appropriate for all pediatric patients such as propylene glycol, benzyl alcohol or ethanol have often been used in liquid formulations, creating a potential health risk (Standing and Tuleu, 2005). Therefore, the World Health Organization (WHO) expert forum proposed a paradigm shift concerning medicines for children towards oral solid dosage forms already in 2008 (WHO, 2008; Ivanovska et al., 2014).

However, a huge number of licensed drugs are not available in child-appropriate dose strengths and/ or dosage forms. As consequence, conventional oral solid dosage forms are often manipulated including the unintended crushing of tablets or opening of capsules to enable age-appropriate dosage regimen and/ or to facilitate the administration to patients with swallowing deficiencies (Paradiso et al., 2002; Stubbs et al., 2008; Wright, 2002). Medicines administered in this way are used off-label or unlicensed and could cause adverse drug reactions and stability issues due to severe changes of the pharmacological profile (Bellis et al., 2013). Moreover, some drugs used in niche markets are not at all available due to the cumbersome drug legislation in the European Union (EU) (Breitkreutz, 2008). Thus, the administration of approximately 50% of prescribed drugs in hospitalized children in the EU has been reported to be off-label or unlicensed by the European Network on Drug Investigation in Children (ENDIC) in 2000 (Conroy et al., 2000). To overcome these problems, the EU passed the *Regulation on Medicinal Products for Paediatric Use* in 2007 to promote the R&D of medicines for children by issuing rewards or incentives (Breitkreutz, 2008; Council of Europe, 2006). Pharmaceutical companies are required to consider children in early phase of drug product development and to submit a *Paediatric Investigation Plan* (PIP) to the expert Committee on Pediatric Medicines (PDCO) of the European Medicines Agency (EMA) (van Riet-Nales et al., 2017). Guidance for PIP preparation is provided in the *Guideline on Pharmaceutical Development of Medicines for Pediatric Use* of the EMA and the E 11 Guideline of the International Council for Harmonisation (ICH) (ICH, 1999; EMA, 2013a). A Supplementary Protection Certificate (SPC) for new drug products, which grants an exclusivity extension for 6 month, is only issued, if the development process completely adhered to the PIP negotiated with the PDCO. For orphan drugs, the SPC

could grant an exclusivity extension of even 24 month in addition to the 10 years, obtained by the EU Orphan Drug Act. For PIPs related to the development of child-appropriate products using off-patent drugs, funding can be provided by the EU Seventh Framework Program to obtain a *Paediatric Use Marketing Authorisation* (PUMA). Once a PUMA is accepted, 10 years of exclusivity for the use of the drug in children is granted (Breitkreutz, 2008; van Riet-Nales et al., 2017).

Points to consider in the development of medicines for children proposed by the EMA Guideline (EMA, 2014), WHO Guideline (WHO, 2011) and the reflection paper of the Committee for Medicinal Products for Human Use (CHMP) (CHMP, 2006) regarding oral formulations are described below. The dosage form design should be appropriate to use in the targeted age group. Thereby, the intended route of administration, the safety of excipients, the miscibility with food and drinks, the dosing frequency and flexibility, the container closure system as well as the application of an administration device has to be evaluated. Generally, dosage forms enabling the administration of variable dosages to be applicable to different age groups are to be preferred. The administration should be reliable, convenient and practicable to be performed even by caregivers. Multiple step administration should be avoided to reduce dosing errors. Thus, CR dosage forms may be reasonable. The reduced dosing frequency of once or twice daily may enable the participation in age associated activities and affect the daily life as little as possible. The manufacturing should be commercially feasible and cost and time effective. Solely, non-toxic and a limited number of excipients should be used for the production. Information about the safety of excipients for pediatrics is provided within the *Safety and Toxicity of Excipients for Paediatrics* (STEP) database developed by the US and the EU Paediatric Formulation Initiatives (USPFI/ EUPFI). Within this database, non-clinical, clinical and in vitro data as well as regulatory references e.g. of the WHO, the FDA or the EU Food Safety Authority (EFSA) are compiled to guide the selection of excipients. Table A.2.1-1 compares the applicability of different oral dosage forms in relation to the age of the patient.

Table A.2.1-1 Applicability of oral dosage forms related to the age adapted from Committee for Medicinal Products for Human Use (CHMP, 2006)

Dosage form	preterm newborn infants	0-28d	1m-2y	2-6y	6-11y	12-16/18y
Solution/ Drops	2	4	5	5	4	4
Emulsion/ Suspension	2	3	4	5	4	4
Effervescent dosage forms	2	4	5	5	4	4
Powders/ Multiparticulates	1	2	2	4	4	5
Tablets	1	1	1	3	4	5
Capsules	1	1	1	2	4	5
Orodispersibles dosage forms	1	2	3	4	5	5
Chewable tablets	1	1	1	3	5	5

Preterm newborn infants	Early ages (preterm newborn infants-6y)	Higher ages (6-16/18y)
Term newborn infants (0-28d)	1 not applicable	1 not accepted
Infants and Toddlers (1m-2y)	2 applicable with problems	2 accepted under reserve
Children (pre-school) (2-6y)	3 probably applicable, but not preferred	3 acceptable
Children (school) (6-11y)	4 good applicability	4 preferred acceptability
Adolescents (12-16/18y)	5 best and preferred applicability	5 dosage form of choice

While for young children the applicability of most of the dosage forms is limited by safety issues, principally all listed dosage forms are applicable for older children. The rating numbers are displayed in Table A.2.1-1 and refer either to the applicability for children of early ages or the acceptability, preferences and experiences with oral formulations of older children (CHMP, 2006).

In the therapy of preterm newborn infants, none of the listed oral formulations are applicable. The formulation with the best applicability for this age group is the parenteral intravenous injection of solutions. For term newborn infants, infants and toddlers, predominantly liquids and oral effervescent dosage forms are used due to the highest clinical evidence for administration of liquid formulations. However, the palatability of liquid formulations considerably impacts the acceptability in children and mainly depends on the taste, smell and volume. Whereas preferences regarding taste and smell subjectively vary, the volume of administered liquid should optimally be in the range of 3.3 to 4.5 ml. This value complies with the average volume of one swallow, found for children with dysphagia from 5 month up to 13 years (Rommel et al., 2014) or for healthy children from 15 month up to 3.5 years (Liu et al., 2015), respectively. Minitablets, multiparticulates and orodispersible dosage forms are typically used in children from an age of 2 years, since swallowability is facilitated due to the small size of these dosage forms. The adaption of the dose strength to the age of the patient offers high flexibility. Furthermore, the stability as well as the dose accuracy is increased compared to liquid formulations. The administration of minitablets to neonates and infants has recently been explored and indicated suitability (Klingmann et al., 2015; Klingmann et al., 2013; Spomer et al., 2012). For the other formulations acceptability studies are scarce, ongoing or still need to be

performed (Lopez et al., 2018; Metz et al., 2009; Orlu et al., 2017). Chewable tablets and chewable gums are assumed to be valuable for children from an age of 6 years, when the swallowing reflex is fully developed. However, a literature review including literature from 1966 to 1999 performed by Michele et al. (2002) indicated safety and acceptability for children from an age of 2 years.

A.2.2 Acceptability of oral solid dosage forms in elderly

In developed countries the percentage of people older than 65 years is estimated to grow from 17% in 2008 up to 30% until 2050 (EMA, 2017; Stegemann et al., 2010). Moreover, the geriatric population represents the most heterogeneous group due to normal physiological changes as well as increased probability of pathophysiological disorders with age. As a result, geriatric patients are often treated with several concurrent medications (polypharmacy) for various diseases. Polypharmacy was found to be directly linked to an increased number of adverse drug reactions impairing the general condition of the patient and inducing substantial medicinal costs (Hajjar et al., 2007; Nguyen et al., 2006). Swanlund (2010) observed that over-74-year-olds received 2 to 9 different medicines representing 30% to 50% of all the prescriptions within this study. Further, patient compliance was found to decrease with an increasing number of drugs and complexity of the therapy (Miller, 2008; Swanlund, 2010).

As well as for children, a variety of drugs is not available in dosage forms or dose strengths, appropriate for elderly. This results in off-label and unlicensed drug use with effects on the safety and efficacy of the therapy. Although similar considerations for the dosage form design can be applied for both patient populations, factors affecting the acceptability widely vary between these two age groups. Similar to children, low dose strengths are required to allow dose titration, covering the declining metabolic capacity in geriatric patients. The use of fixed-dose combinations and CR formulations may be beneficial to reduce the total number of medication and to improve the adherence of the patient. A dosage form design comprising small-sized multiparticulates, which allows co-administration with food and drinks may be valuable to overcome swallowing problems. However, further aspects of dosage forms appropriate for elderly should include easy identification, e.g. by using specific color schemes and/ or shapes, a simple drug product information supported by pictograms and adequate packaging materials, matching the motoric capabilities of

elderly such as screw cap openings and push-through blisters (Drumond et al., 2017; Stegemann et al., 2010).

Guidance in the development and approval of medicines for geriatric patients is provided by the ICH E7 Guideline (ICH, 2011) and the draft of the EMA *Reflection Paper on the Pharmaceutical Development of Medicines for Use in the Older Population*. The aforementioned Reflection Paper has been issued after the EMA published the *Geriatric Medicines Strategy* (EMA, 2011), the *Concept Paper on the Need for a Reflection Paper on Quality Aspects of Medicines for Older People* (EMA, 2013b) and the draft of *Points to Consider on Frailty* (EMA, 2016). A major aspect addressed in these documents is the inclusion of geriatric patients into clinical trials as they often represent the majority of the target group treated with the drug. Thereupon, the inclusion of geriatric patients into clinical trials has been introduced to article 6 of the EU Regulation in 2014 (Council of Europe, 2014).

Many efforts have already been made to focus on specific needs and to consider the geriatric population in the pharmaceutical development of drug products as shown by the aforementioned documents and the installation of a Geriatric Expert Group of the EMA. However, incentives supporting the development of geriatric medicines such as PIP and PUMA within pediatric formulation development are not yet established (van Riet-Nales et al., 2016) but would be beneficial to enforce the development of dosage forms, which fulfil the needs of older patients.

A.2.3 Development of oromucosal film preparations to accomplish patient centricity

Oromucosal film preparations represent a viable alternative in oral drug delivery to accomplish patient centricity. Since they provide a number of application features such as the ease of administration without water, applicability for patients with swallowing deficiencies and dosing flexibility, the acceptability and compliance of pediatric and geriatric patients may be improved by fulfilling their specific needs.

A.2.3.1 General aspects

In 2012, oral film preparations have been integrated into the monograph O*romucosal Preparations* of the Ph.Eur.(2018a), where they are defined as thin, drug-loaded polymeric sheets to be administered to the mouth of the patient. Depending on the residence time in the oral cavity and the site of drug action or absorption, the Ph.Eur. differentiates between orodispersible films (ODFs), and mucoadhesive buccal films

(MBFs). Since the monograph does not clearly define critical quality attributes and specifications, together with the given information, distinction between MBFs and ODFs is not officially possible. However, MBFs are usually characterized by an increased residence time in the oral cavity and adhesion to the oromucosal epithelium to obtain a local or a systemic effect by drug absorption through the oral mucosa. Drug absorption through the oral mucosa may increase the drugs bioavailability and shorten the onset of action by avoidance of the hepatic first pass metabolism. However, the speed and extent of oromucosal drug absorption widely varies, depending on physicochemical properties of the substance as well as physiological properties of the patient (Dixit and Puthli, 2009; Morales and McConville, 2011). The application site within the oral cavity serves possibilities to control oromucosal absorption as discussed in Section A.1.2.1. MBFs usually show PR profiles, as the polymeric matrix is slowly disintegrating or insoluble and has to be removed after use. In contrast, ODFs are rapidly disintegrating in the oral cavity. They are intended to obtain either a local or a systemic effect, usually after swallowing the dissolved or dispensed drug along with the saliva followed by absorption from the GI tract. The rapid disintegration of ODFs is often linked to immediate drug release. Whereas ODFs most frequently own a single-layer structure, MBFs are usually designed as multilayer sheets (Hoffmann et al., 2011). The application of a second film layer can be used to generate multilayer films with different release rates of the layers or to implement a shielding layer for facilitated unidirectional drug release and oromucosal absorption such as for the design of MBFs and non-dissolvable oromucosal patches (ORP) (Preis et al., 2013; Preis et al., 2014b).

In comparison to liquid and semi-solid oral and oromucosal preparations, oromucosal films show increased stability and dose accuracy while maintaining the advantages of dose flexibility, swallowability and rapid onset of drug action, if intended (Barnhart, 2008). Compared to conventional solid oromucosal preparations such as buccal tablets and lyophilisates, increased robustness and flexibility is observed, considering oromucosal film preparations as suitable for personalized use (Borsadia et al., 2003). However, the drug load of oromucosal films is limited to a maximum of approximately 30% (w:w), reducing their applicability to highly potent drugs (Hariharan and Bogue, 2009). Since the residence time in the oral cavity is usually increased for oromucosal film preparations compared to conventional oral solid dosage forms, a variety of

additional critical quality attributes has to be considered to accomplish patient acceptability such as taste, mouthfeel, irritation of the mucosa and mucoadhesion (Krampe et al., 2016b). An overview of taste masking approaches performed in the development of oromucosal film preparations is given in Table A.2.3-1.

Table A.2.3-1 Taste masking approaches used for oromucosal film preparations adapted from Krampe et al. (2016b).

Taste overlay		
Addition of sweeteners	Safety, efficacy, caloric intake, cariogenic risk for different types of sweetener (nutritive, artificial, sugar alcohols) has to be evaluated	1, 2, 3, 4
Addition of flavors	Selection according to patient preferences	5
Inactivation of bitter receptor		
Addition of bitter blocker (G-protein antagonists)	Bitter taste of drug substances and the after taste sensation of artificial sweeteners are reduced	6
Interruption of drug-receptor interaction		
Particle coating/ encapsulation	Use of saliva insoluble or enteric/ PR coatings Note: Difficulties due to potential dissolution during production; gritty mouthfeel due to enlargement of particles, changes in the dissolution profiles may be possible	7
Incorporation in complexes/ structures	Complexation of drug substances using cyclodextrins and maltodextrins	8, 9, 10
Ion exchange resins (Colestyramin)	Binding of ionic drug molecules to charged moieties may reduce the amount of dissolved drug in the saliva and thus the interaction with the taste receptors	11
Application of backing layers	Use of insoluble or slowly erodible polymers for the second layer to cover the drug-loaded layer	9
Chemical modification of the drug substance		
Salt or prodrug formation	Formation of insoluble salts or prodrugs or faster absorption of the prodrug in relation to the conversion into its active form Note: Not always applicable, changes in the dissolution profiles are possible	12

[1] Wiet and Beyts (1992)
[2] Liew et al. (2012)
[3] Dinge and Nagarsenker (2008)
[4] Cilurzo et al. (2011)
[5] Mishra and Amin (2009)
[6] Slack et al. (2010)
[7] Krampe et al. (2016b)
[8] Joshi et al. (2012)
[9] Preis et al. (2012)
[10] Mahesh et al. (2010)
[11] Li and Krumme (2017)
[12] Hussain et al. (1988)

The mouthfeel is a highly subjective perception and mainly depends on the size and texture of the preparation (Krampe et al., 2016b). The mouthfeel has to be evaluated and adjusted individually for different film formulations according to the needs of the targeted patient population. But generally, a size of 2 x 2 to 2 x 3 cm and a thickness of 100 to 350 µm was found to be accepted in human volunteer studies (ElMeshad and El Hagrasy, 2011; Nishigaki et al., 2012). The mouthfeel may further be affected by remaining particles after film disintegration as grittiness is correlated to increasing particle sizes (ElMeshad and El Hagrasy, 2011; Liew et al., 2013). Possible irritation of the mucosa is linked to the pH value and the buffer capacity of the formulation, which should generally comply with the physiological pH value of the saliva of approximately 7 ± 1.5 to be non-irritant for the patient (Patel et al., 2006). Mucosal irritation can result in pain, increased risk of infection and uncontrolled permeability. Nevertheless, the addition of pH modifiers or buffer substances can be necessary in special cases to support the biopharmaceutical efficacy.

A.2.3.2 Excipients used in oromucosal film preparations

As oromucosal films are considered as child-appropriate dosage form, the number of excipients used for the formulations should be reduced to a minimum. The type and the amount of excipients have to be evaluated thoroughly in terms of safety and the acceptable daily intake for the targeted age group. Apart from that, oromucosal film preparations usually consist of a film-forming polymer, which serves as carrier matrix for the drug substance and if necessary, a plasticizer to ensure sufficient film flexibility. Most commonly hydrophilic cellulose derivates (hypromellose (HPMC), hyprolose (HPC) and carmellose (CMC)), polyvinyl alcohols and pullulan are used as film-forming polymers for disintegrating oromucosal films (Garsuch and Breitkreutz, 2010). Water-insoluble ethyl cellulose or the aforementioned cellulose derivates in high-molecular-mass grades are usually used to prepare backing or shielding layers, which are not disintegrating or slowly erodible (Lindert and Breitkreutz, 2017; Preis et al., 2014b). An overview of excipients used for oromucosal film preparations is provided by Hoffmann et al. (2011) and Preis et al. (2013).

Additional excipients may be beneficial to increase patient acceptability such as saliva stimulating agents, fillers, sweeteners, flavors, and coloring agents (Krampe et al., 2016b). Further additives are used to support the dosage form safety and efficacy including pH modifier (Dixit and Puthli, 2009), permeation (Nicolazzo et al., 2005) and solubility enhancers (ElMeshad and El Hagrasy, 2011), preservatives (Hariharan and

Bogue, 2009; Patel, 2010), stabilizers (Arya et al., 2010; Dinge and Nagarsenker, 2008) and inhibitors of salivary enzymes (Hao and Heng, 2003).

A.2.3.3 Manufacturing of oromucosal film preparations

Manufacturing methods for oromucosal films have been derived from established technologies such as pharmaceutical coating and extrusion processes. The most commonly used manufacturing methods for oromucosal films are the solvent casting method and hot-melt extrusion (HME) through laminar dies. In both cases a primary film is produced to be cut up into individual dosage units.

For the solvent casting method, a film-forming casting mass is produced by dispersing or dissolving the components of the oromucosal film (at least the drug and the film-forming polymer) in a suitable solvent and stirring until homogeneity. Thereby, the film-forming polymer has to be dissolved in the solvent. Most commonly water or ethanol or mixtures thereof are used as solvents. The addition of a cosolvent can be valuable to improve the drug solubility and to reduce the drying time of the films. After degassing by vacuum or constant stirring, the viscous casting mass is poured into glass moulds (Kumar et al., 2010), petri dishes (Murata et al., 2010), teflon-coated trays (Kunte and Tandale, 2010; Perumal et al., 2008), or cast onto a release liner using a film applicator equipped with a casting knife. To avoid scratching and defective primary films, casting width has to be adjusted carefully according to the particle size of insoluble particles and considered in the formulation development as it determines the drug load (Barnhart, 2008; Corniello, 2006). After casting, the primary film is dried at room temperature or in an oven, may be rolled up for intermediate storage or transport and is finally cut into the film size, before the pharmaceutical product is individually packaged. As the volume of the film determines the drug load, adjusting the wet-film thickness (casting width) as well as the size of the final film can be used to control and individualize the dosage of the single unit films. Accordingly, a suitable viscosity range for the casting mass has to be determined and adjusted for processing. A too low viscosity may lead to sedimentation of suspended particles and variations from the targeted film thickness and thus to poor content uniformity (Woertz and Kleinebudde, 2015), whereas a too high viscosity may result into hindrance of the coating process as the time to degas the casting mass is prolonged and the casting mass itself may block the casting gap (Wong et al., 1999). Air bubbles within the film casting mass lead to irregularities and failures decreasing the mechanical stability of the films (Kianfar et al., 2012).

Depending on the equipment, a viscosity range from 0.3 to 6.2 Pa*s was found to be sufficient for film production via solvent casting method (Krampe et al., 2016b; Preis et al., 2014b; Thabet and Breitkreutz, 2018). Critical process parameters further include the casting speed as well as the drying temperature and time. The drying conditions affect the residual moisture of the films. Using water as solvent for the film production the residual moisture is correlated to the flexibility of the films. In terms of organic solvents used for the film production, the regulations for residual solvents according to the Ph.Eur. and ICH have to be respected (Goel, 2008; Thabet and Breitkreutz, 2018).

However, the list of critical quality attributes and process parameters has to be evaluated and extended case-by-case depending on the formulation. An overview is provided by Thabet and Breitkreutz (2018) and displayed as Ishikawa diagram (Figure A.2.3-1).

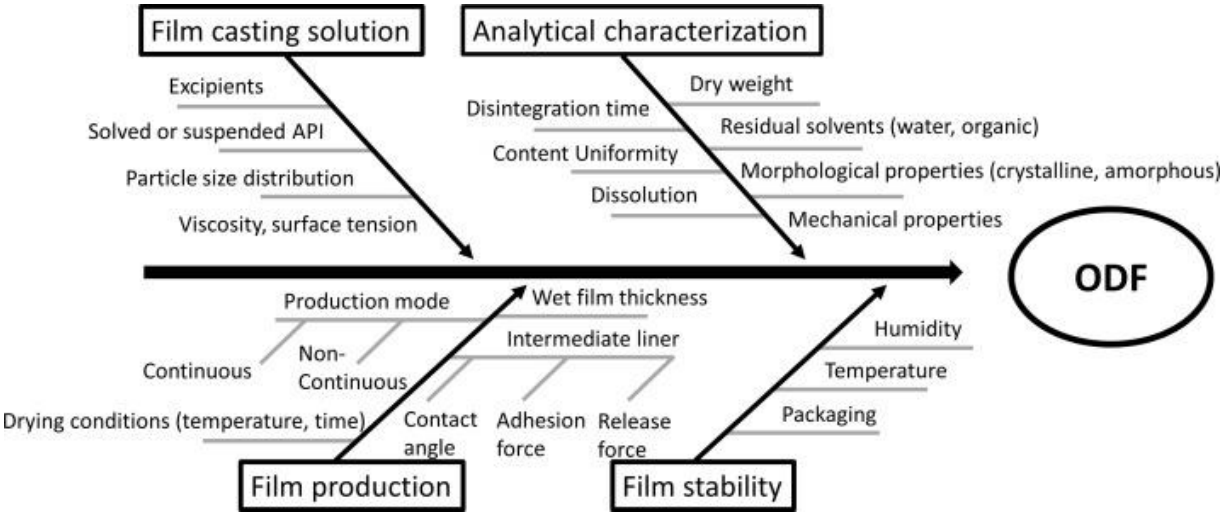

Figure A.2.3-1 Ishikawa diagram for the formulation development of orodispersible films according to Thabet and Breitkreutz (2018)

Nevertheless, the solvent casting method is not suitable to produce films containing moisture-sensitive drugs or volatile excipients.

For these drugs, HME may be an applicable production technique. HME of oromucosal films is considered as a solvent-free and continuous method for film production as a powder mixture is processed under heat and pressure without using solvents. Therefore, a pre-blended powder mixture is fed into the extruder, compounded, molten and finally pressed through a die. Whereas extrusion through a spherical die requires an additional roll out step to produce a primary film (Koster and Thommes, 2010; Low et al., 2013), the use of a laminar die directly results in a thin

primary film (Cilurzo et al., 2008; Repka et al., 2003). However, the application of HME is limited to thermally stable drugs and excipients, as the input of thermal energy is required to soften the mass and enable extrusion. By application of HME, films with increased densities and thicknesses are usually obtained, which impacts the mechanical stability as well as the disintegration and dissolution behavior. Thus, HME may be a suitable technique to produce oromucosal films with PR properties. As hot-melt extruded oromucosal films usually reveal increased film thicknesses and disintegration times compared to solvent casting films, safety and acceptability have to be evaluated.

Further production methods for oromucosal film preparations are described in the literature, including rolling (Arya et al., 2010; Yang et al., 2008) and compression methods. More sophisticated production methods for oromucosal film preparations are the application of freeze-drying (Boateng et al., 2010; Boateng et al., 2009a), electrospinning (Nagy et al., 2010; Taepaiboon et al., 2006; Yu et al., 2010) as well as 2D and 3D printing methods for film production. 2D printing describes printing a drug-loaded ink onto a drug-free or drug-loaded base film layer, which is usually derived from a previous solvent-casting approach (Janßen et al., 2013; Sandler et al., 2011; Thabet et al., 2018). In contrast, 3D film printing includes the application of a semisolid 3D printed structure onto a drug-free or drug-loaded base film layer or that the entire oromucosal film is produced by 3D printing technique (Ehtezazi et al., 2018). A general overview of manufacturing methods of oromucosal film preparations is given by Preis et al. (2013). Moreover, the review article of Preis et al. (2015) elucidates the film production via 2D and 3D printing technologies.

A.2.3.4 Analytical characterization of oromucosal film preparations

The Ph.Eur. requires oromucosal film preparations to possess suitable mechanical stability and to demonstrate appropriate drug release. Moreover, ODFs should rapidly disperse, when placed in the mouth (Ph.Eur, 2018a). However, specification and suitable test methods to determine and evaluate mechanical properties, dissolution profiles and disintegration times are not referred.

In the literature, several methods are described to characterize mechanical properties of oromucosal films including the standardized tensile test for foil materials according to DIN EN ISO 527 and modifications thereof (Boateng et al., 2009b; DIN, 2003; Garsuch and Breitkreutz, 2009). Furthermore, the puncture test using the Texture Analyzer equipped with hemispherical (Bodmeier and Paeratakul, 1993; Radebaugh

et al., 1988) or flat-faced cylindrical probes (Preis et al., 2014a) has been conducted. As the tensile test according to DIN EN ISO 527 requires bone shaped specimen of 80 mm length, which does not match the commonly used rectangular geometry and size of oromucosal films, suitability to use rectangular specimens has been investigated and successfully applied for characterization (Niese and Quodbach, 2019). Within this study, the secant modulus and the yield stress were evaluated as these parameters provide detailed information about the deformation behavior of continuously manufactured ODFs. For the puncture test, using the Texture Analyzer, application of a flat-faced cylindrical probe was considered to reveal increased suitability for film characterization as the contact area of the probe is clearly defined (Preis et al., 2014a). The puncture strength and the elongation to break are usually derived from the puncture test to assess the mechanical stability in terms of industrial production and handling by the consumer. Accordingly, the folding endurance of oromucosal films is investigated by repeatedly folding the film sample in the center until breakage. The folding endurance is performed to estimate the resistance during handling and administration without being damaged.

Dissolution and disintegration behavior constitute valuable estimates for the biopharmaceutical performance of oromucosal film preparations. If the drug is freely water-soluble and molecularly dispersed in the film, determination of the disintegration time may be sufficient as the film disintegration represents the rate limiting step for dissolution. An analogous procedure was proposed for orodispersible tablets by the FIP/AAPS guidelines and may be transferred to ODFs (Siewert et al., 2003). For MBFs and ODFs containing dispersed drug particles, solubility as well as the dissolution rate strongly affect the biopharmaceutical performance and thus necessitate the conduction of dissolution studies (Hoffmann et al., 2011). An overview of dissolution test methods for oromucosal film preparations and advanced methods, developed within this work are provided in Section C.2 and C.3.

As mentioned above, determination of the disintegration behavior of ODFs is mandatory as it is linked to the biopharmaceutical performance. Moreover, the disintegration time of ODFs affects their patient acceptability and safety during administration since non-disintegration within a set time frame can result in choking or aspiration of the whole or parts of the ODF (Low et al., 2015). A compendial test method or a time frame for ODF disintegration has not yet been provided. While analytical methods to characterize film disintegration clearly differ throughout the

published studies, the disintegration time limit for orodispersible tablets of 180 s required by the Ph.Eur. (2018b) or 30 s required by the FDA (2008) is commonly used for specification. In Section C.1, analytical test methods used to determine the disintegration time of ODFs are described and evaluated.

Imaging techniques such as light microscopy, polarized light microscopy and scanning electron microscopy (SEM) are useful tools to visualize surface structures (microstructures, porous film surfaces), the presence and distribution of crystalline particles as well as connections between two layers of multilayer films (Garsuch and Breitkreutz, 2009). Solid state characterization such as X-ray powder diffraction (XRPD) or differential scanning calorimetry (DSC) enables identification of substances by crystallographic “finger print”, identification of polymorphic forms, differentiation between amorphous and crystalline structures as well as glass transition of excipients and drug particles indicating miscibility.

In combination, explanatory information for instance on the dissolution behavior and the storage stability can be obtained (Boateng et al., 2009a). Since aqueous solutions are most commonly used for the production of oromucosal films, they usually reveal a certain amount of residual water, which also affects the solid state properties, the dissolution and disintegration behavior as well as the film flexibility. Karl Fischer titration, loss on drying and infrared light balances are used to determine the residual water content of films, whereas water vapor sorption is performed to receive information about the behavior of films, when exposed to different ambient conditions (Preis et al., 2013).

Since MBFs are characterized by an increased residence time in the oral cavity and adhesion to the oral mucosa, to obtain a systemic effect via oromucosal absorption, the mucoadhesive strength and permeation behavior should further be investigated. Methods to evaluate the mucoadhesive strength between the oromucosal film formulation and the mucin layer are comprehensively described by Woertz et al. (2013). They include the use of the texture analyzer, modified balances or surface tensiometer to assess for instance the detachment force or work of mucoadhesion (Duchěne et al., 1988; Jones et al., 1997; Smart et al., 1984).

In vitro permeability studies have been performed, using donor- and acceptor compartment models separated by isolated animal mucosal tissue (Lindert and Breitkreutz, 2017). The instrumental setup can either be horizontal (Franz and Kerski diffusion cell) or vertical (Ussing chamber). Most commonly esophageal

porcine mucosa is used due to the similarity to the human oral mucosa. In special cases reconstructed human epidermis models of the oral mucosa or the commercially available EpiOral^{TM} tissue models are used (Rossi et al., 2015; Teubl et al., 2013; Walle et al., 2006). In order to standardize the test procedure and to reduce variability, the use of artificial membrane materials such as agar and gelatin gel layers has been explored (Giovino et al., 2013).

Process analytical technologies to monitor the continuous film production process have been introduced by Hammes et al. (2014), exploring the potential of an infrared sensor for inline measuring the drug content. Moreover, Raman spectroscopy and Raman chemical imaging have been used as non-destructive technologies to inline monitor the API quantity and distribution by Edinger et al. (2017). More recently Niese and Quodbach (2019) successfully applied an optical probe to determine the wet-film thickness of a continuously manufactured ODF containing warfarin sodium for individualized dosing inline by chromatic confocal measurements.

The ongoing efforts made by academia and pharmaceutical industry to explore the dosage form of oromucosal film preparations reflect the continuous interest and indicate the high potential for drug formulations respecting patient centricity.

A.3 Aims of the thesis

Most commonly, oral solid dosage forms such as tablets and capsules are used for oral drug delivery due to their high stability and dose accuracy as well as a cost and time effective production. However, the inability of swallowing oral solid dosage forms is still a major issue in the pharmacotherapy of patients suffering from swallowing deficiencies. As consequence, their medication is often manipulated before administration, which bears the risk of dose inaccuracy, contamination and hygiene problems. Moreover, severe changes in the pharmacological profile such as dose dumping of CR dosage forms are likely to occur. Orodispersible films represent a promising approach in oral drug delivery to overcome the problems of common oral solid dosage forms, as they provide a number of special application features. Due to the rapid disintegration of ODFs in the mouth of the patient, swallowing of large particles and additional intake of water is avoided. Until now the application of ODFs is limited to immediate release formulations. Controlled release formulations have not been reported so far.

Test methods to characterize ODFs are described in the literature, but neither relevant pharmacopoeias nor regulatory authorities refer to generally accepted test methods and specifications.

The general aims of the thesis therefore include the development as well as the analytical characterization of rapidly disintegrating ODFs, which exhibit controlled drug release.

In particular, the aims of the thesis are:

To explore extrusion and coating techniques for the production of matrix as well as reservoir type multiparticulate drug carriers to be incorporated into ODFs. Based on these findings, to determine the potentials and the limitations in terms of feasibility and to assess the applicability with respect to the pharmaceutical industry.

To explore test methods for analytical ODF characterization from the literature and to adapt the methods for investigation of ODFs with CR properties. Particularly, to systemically evaluate disintegration and dissolution test methods regarding their suitability to investigate particle-free as well as particle-loaded ODFs and oral film preparations with IR as well as CR properties, respectively.

To develop a dissolution test method, which is suitable to characterize the dissolution profiles of oral film preparations with IR and CR properties. Moreover, within the development of the test method, compendial definitions and standards in the technical setup and the procedure, but also the ability to reflect physiological conditions should be considered. The dissolution test method should further be applied to oral film formulations developed within the scope of this thesis and the obtained results should critically be assessed.

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Section B. Formulation development and analytical characterization of oral film preparations with prolonged release properties

B.1 Prolonged drug release properties for orodispersible films by combining hot-melt extrusion and solvent casting methods

This section examines the development and characterization of orodispersible films with prolonged release properties. These films were designed to contain multiple units of incorporated small-sized and drug-loaded micro-matrices to provide prolonged drug release and to accomplish patient compliance and safety. The dissolution behavior and the underlying release kinetics of micro-matrices produced via hot-melt extrusion as well as orodispersible films containing these micro-matrices has been investigated. Furthermore, the influence of different sizes of micro-matrices on the content uniformity, the dissolution and disintegration behavior as well as on physical and mechanical film properties has been studied extensively.

The following research paper has been published by the European Journal of Pharmaceutics and Biopharmaceutics in 2018 (Impact factor 2017: 4.491). In divergence from the original publication, the wording "matrix particle (MP)" was replaced by "micro-matrix (MM)", to preserve clarity in terms of the used abbreviations within this thesis. The first author, Isabell Speer, is responsible for the concept, the experimental work and data evaluation as well as writing of the manuscript. Dr. Maren Preis is responsible for the concept and revision of the manuscript. Prof. Dr. Jörg Breitkreutz, listed as senior author, is responsible for the idea and the concept as well as revision of the manuscript.

Prolonged drug release properties for orodispersible films by combining hot-melt extrusion and solvent casting methods

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B.2 Prolonged release from orodispersible films by incorporation of diclofenac-loaded micropellets

A further approach for prolonged drug release from orodispersible films is highlighted in this section. The incorporation of drug-loaded micropellets into a solvent casting film has been investigated. The micropellets were produced via extrusion and spheronization technique, and coated in fluidized bed to prolong the drug release even for freely water-soluble drugs. X-ray micro-computed tomography has been performed to display internal and external surface structures of the micropellets before and after release studies in order to evaluate the underlying drug release mechanism. Moreover, dissolution studies have been performed over a storage period of up to 12 weeks at different climate conditions to assess the coating stability. Mechanical strength and disintegration time has routinely been explored for quality control purposes.

The following research paper has been published by the International Journal of Pharmaceutics in 2019 (Impact factor 2017: 3.862). The first author, Isabell Speer, is responsible for the concept, the experimental work and the data evaluation as well as writing of the manuscript. Vincent Lenhart participated in the experimental work and data evaluation due to his expertise in pelletization techniques. Dr. Maren Preis is responsible for the concept and revision of the manuscript. Prof. Dr. Jörg Breitkreutz, listed as senior author, is responsible for the idea and the concept as well as revision of the manuscript.

Prolonged release from orodispersible films by incorporation of diclofenac-loaded micropellets

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Section C. Development and evaluation of analytical methods to characterize oral film preparations

C.1 Comparative study on disintegration methods for oral film preparations

In this section, four different disintegration methods for oral film preparations described in the literature have been examined to characterize different types of oral films. The influence of different film thicknesses and amounts of incorporated, water-insoluble particles has systematically been investigated. Moreover, the suitability for oral film preparations as well as the handling has comprehensively been described and evaluated. Finally, guidance for the choice of disintegration method has been provided considering special needs of different pharmaceutical disciplines such as quality control or research and development purposes.

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Comparative study on disintegration methods for oral film preparations

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C.2 Novel dissolution method for oral film preparations with modified release properties

The development of a dissolution method for oral film preparations with immediate as well as modified release properties is described within this section.

The suitability of the method to characterize different types of films, such as orodispersible films revealing immediate and prolonged drug release as well as double-layer films has been studied and evaluated. The study design further allows the examination of unidirectional drug release by application of a second film layer, which is often used to facilitate buccal absorption. Moreover, the influence of different pH values and flow rates on the drug release has been studied with respect to the in vivo application of oral films.

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Novel dissolution method for oral film preparations with modified release properties

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C.3 Dissolution testing of oral film preparations: experimental comparison of compendial and non-compendial methods

Four different compendial and non-compendial dissolution test methods have been applied to investigate oral film preparations with immediate and modified release properties. A comprehensive study comparing the suitability for oral films with different release behavior, the setup and handling as well as the feasibility to reflect physiological conditions has been conducted and is displayed within this section. As dissolution testing is required for oral film preparations, but suitable test methods or specifications are not referred to by the Ph.Eur., this study should further provide guidance for the selection of an appropriate dissolution test method in pharmaceutical industry.

The following research paper has been published by the International Journal of Pharmaceutics in 2019 (Impact factor 2017: 3.862). In divergence from the original publication, the wording "matrix particle (MP)" was replaced by "micro-matrix (MM)", to preserve clarity in terms of the used abbreviations within this thesis. The first author, Isabell Speer, is responsible for the concept, the experimental work and data evaluation as well as writing of the manuscript. Dr. Maren Preis is responsible for the concept and revision of the manuscript. Prof. Dr. Jörg Breitkreutz, listed as senior author, is responsible for the idea and the concept as well as revision of the manuscript.

Dissolution testing of oral film preparations: experimental comparison of compendial and non-compendial methods

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Section D. Conclusions and Perspectives

Orodispersible films (ODFs), providing prolonged drug release (PR), while rapidly disintegrating, have successfully been developed and comprehensively characterized within the present thesis. They represent a promising approach for patient centered pharmacotherapy and enable the controlled drug delivery to patients, not being able to swallow common oral solid dosage forms. The need of an appropriate dosage form, which has not to be manipulated prior to the administration, has been addressed to improve the therapy safety and efficacy. Moreover, critical quality attributes of the dosage form have been identified and systematically investigated. Analytical methods to characterize the disintegration and dissolution behavior have been evaluated or newly developed, specifically for this purpose. Since standardized test procedures and specifications are still lacking even for common oral film preparations, the underlying work of this thesis may contribute to close this gap and further enable the experimental investigation of an innovative oral film for controlled drug delivery.

Formulation development and analytical characterization of oral film preparations with prolonged release properties

In Section B.1 micro-matrices (MMs) have been produced and incorporated, which enable prolonged theophylline release, following square root of time kinetics, controlled by diffusion through the water-insoluble matrix. The initial burst release, which is a typical characteristic for matrix controlled drug release, depends on the specific surface area of the drug-matrix system and thus on the size of MMs. Using differently sized MMs combined in an ODF, adjustable dissolution profiles can be obtained, providing initial immediate drug release (IR), followed by prolonged release to maintain the drug action.

Limitations for this principle can be found in a low drug load of MMs and the use of thermo-sensitive or freely water-soluble drugs. Due to short diffusion paths within the MMs, prolonged release could not be obtained for highly drug-loaded MMs and for freely-water soluble drugs. Metoprolol tartrate was used as model drug in a failed study. Immediate metoprolol release was observed for MMs produced using water-insoluble polymers in combination with a minimal amount of pore-former as well as polymers containing minimal numbers of functional groups to increase their permeability. The use of completely water-insoluble polymers, such as ethyl cellulose, as matrix former only led to the release of an initial small portion of

metoprolol within the first minutes. The rest of the metoprolol has not at all been released within the explored period of 48 h. Verhoeven et al. (2008) showed prolonged metoprolol release, using cylindrical mini-matrices with a length of 2 mm and a diameter of 3 mm. However, the size of matrix systems to be incorporated into ODFs is limited by the acceptance of the patient as well as the manufacturing process, as sedimentation and scratching may occur, when large-sized matrices are incorporated. Since the acceptance by the patient highly depends on the size of incorporated matrices, the use of large-sized matrices can further reduce the patient compliance. Thus, the acceptability of ODFs containing particulate drug-carrier systems has to be explored in future in vivo studies. For highly active drugs, or drug substances revealing a bitter taste, the incorporation of MMs to prolong the drug release from ODFs can further bear the risk of taste issues and adverse drug effects as a result of the burst release.

Therefore, the incorporation of micropellets (MPs) into ODFs for prolonged drug delivery, even of freely water soluble drugs, has been explored in Section B.2. Drug-loaded MPs were produced by extrusion and spheronization technique to realize an increased drug load of up to 60% diclofenac sodium. They were subsequently film-coated to obtain a reservoir type drug delivery system. Drug release is controlled by diffusion through the rate-controlling membrane, which aids constant plasma concentrations and reduces the occurrence of adverse drug reactions. As the dosage form design comprises multiple units to be incorporated into the ODF, defects in the coating of an individual MP, will not lead to dose dumping, which improves the safety of the dosage form. The lag time, observed in the dissolution profiles of MPs and corresponding ODFs, may be beneficial in terms of taste issues of the drug substance. Due to the uniform pellet size distribution as well as the spherical shape, increased amounts of MPs could be incorporated homogeneously. Adjustable dissolution profiles and dose strengths can be obtained, using MPs, revealing different coating thicknesses, and mixing drug-loaded and drug-free MPs, respectively. The production of fixed-dose combinations of drugs with different release profiles has been explored in preliminary studies, which have not been published. Thereby, the incorporation of zolmitriptan, dispersed within the ODF-forming matrix, in combination with diclofenac sodium, incorporated in form of MPs to provide prolonged release, has been investigated. However, content uniformity for both drugs could not be obtained yet. MPs could be incorporated homogeneously.

Due to the resulting, uneven surface structure, the thickness of the ODF layer and thus the zolmitriptan content varied. In future studies, these problems may be solved by optimizing the physicochemical properties of the ODF-forming casting mass.

However, the production of small-sized MPs to be homogeneously incorporated into ODFs was challenging, but necessary to ensure processability and to potentially increase patient acceptability. Therefore, the co-processed excipient Vivapur® MCG, consisting of MCC and CMC, was used. Furthermore, scale-up issues from lab scale to pilot or production scale are likely to occur. Increased production times, which are necessary for pilot and production scale manufacturing, can cause sedimentation and premature drug release. This will impact the dissolution profile and decrease the content uniformity with effects on the pharmacological safety and efficacy of the dosage form. To enable industrial production, drug-carrier systems could be applied onto a base film layer, subsequently to the film casting process, for instance via electric or magnetic roll-to-roll manufacturing processes. Alternatively, industrial implementation of ODFs for controlled drug delivery could include 3D printing of defined structures onto a base film layer via fused deposition modeling or pressure-assisted microsyringe printing.

A potential approach for the application of poorly water-soluble drugs may be the incorporation of drug-layered micropellets, produced from organic solvents, or hot-melt extruded MMs, comprising the drug in form of an amorphous solid dispersion. If further the hepatic first pass metabolism should be avoided to increase bioavailability, incorporation of these systems into mucoadhesive buccal films may be beneficial. This could also be a promising approach for the oromucosal application of peptide drugs.

Development and evaluation of analytical methods to characterize oral film preparations

Oral film preparations have been integrated into the Ph.Eur. in 2012 and the first prescription drug (RX) product in the EU, Risperidon Hexal® SF, has already been approved in 2010 (Ph.Eur., 2018a; Siebenand, 2010). But until now, standardized test procedures and specifications for quality control purposes are still lacking.

For ODFs with prolonged release properties, the disintegration time and the dissolution behavior were found to be relevant critical quality attributes, which need to

be monitored during the formulation development to ensure sufficient product quality. Therefore, within the second part of this thesis, the disintegration and dissolution behavior of oral film preparations have extensively been employed. In Section C.1 an experimental comparative study of four disintegration test methods from the literature, namely the petri dish, the slide frame, the slide frame and ball (SFaB) as well as the PharmaTest® disintegration test method, is displayed. Based on the results of the study, it was concluded, that the slide frame and the SFaB method are particularly applicable for research and development (R&D) purposes. The PharmaTest® disintegration tester and again the SFaB method fulfil the demands for testing within the pharmaceutical QC.

An experimental comparison of dissolution test methods for oral film preparations is elucidated in Section C.3. Within this study, three test methods, described in the literature, as well as a specifically developed dissolution test method (Section C.2) have been compared and assessed regarding their suitability to investigate oral film preparations with different release characteristics. Additionally, their potential to simulate biorelevant conditions and to potentially predict the in vivo behavior has been evaluated. Generally, all dissolution test methods included in this study were capable to determine the drug release of film preparations. However, not all methods were equally suitable for all types of films. Since the Punch and Filter (PAF) and the flow-through cell equipped with the 3D printed film sample holder (FTC+FH3D) method consider physiological conditions to reflect the in vivo application and the gastrointestinal transit, they have been assessed as valuable for pharmaceutical R&D. However, their instrumental setup is complicated and the preparatory work is time-consuming. In contrast, the basket and the Paddle and Glass Disc (PGD) method comprise a simple and well standardized instrumental setup and showed high robustness, indicating suitability for use in pharmaceutical quality control (QC), to monitor batch-to-batch variations and product changes during storage.

Both studies, the comparative study of disintegration test methods as well as the experimental comparison of dissolution test methods, were performed to provide guidance for the selection of suitable test methods based on scientific investigations and to recall the need of approved and standardized test methods and specifications, on which the pharmaceutical industry can stick to during formulation development and drug product approval.

Finally, the development of a novel dissolution method for oral film preparations with controlled release (CR) properties is displayed in Section C.2. The instrumental setup is based on a commercial USP type 4 flow-through cell (FTC), which has additionally been equipped with three different types of in-house built film sample holders to enable reliable investigations by maintaining the film in a constant position within the cell. The FH3D sample holder has been constructed by means of 3D printing. Applying the FTC in combination with customized film sample holders, successful investigation of oral film preparations with IR as well as CR properties has been enabled. The FTC was chosen due to its ability to run dissolution at different hydrodynamic conditions and in different media. It enabled the simulation of the gastrointestinal transit in terms of pH and hydrodynamic profiles. This information is of high interest for the film formulation development. The decreased release rate, which was found by applying a flow rate, which is comparable to the salivary flow, can directly be linked to a reduced amount of drug, available in the oral cavity. For the application of mucoadhesive buccal films a reduced amount of drug, available in the oral cavity, might be correlated to a reduced clinical efficacy. However, in terms of taste and thus patient acceptability of ODFs a reduced amount of drug might be advantageous due to reduced taste sensation.

Due to operating the FTC apparatus in a closed-loop, dissolution testing using a small volume of dissolution medium, as it is required to consider small physiological fluid volumes and flow rates such as in the human oral cavity, has been realized. By further introducing the FH3D, the operative volume of dissolution medium inside the FTC has been reduced to approximately 3 ml, which better reflects to the physiological saliva volume. Additionally, the sample holders constructed with a backing plate provide a surface, at which ODFs can be attached similar to their in vivo application and further enable investigation of the shielding layer. Often, multi-layer oral films comprise shielding layers to facilitate unidirectional drug release and to enable drug absorption via oral mucosa. The obtained data can therefore help to estimate potential buccal exposure. By lining the backing plate of the film sample holders with artificial or porcine mucosa, simulation of in vivo ODF application could be improved.

Section E. Summary

Most commonly, tablets and capsules are prescribed for oral drug delivery, as they provide a number of advantages in comparison to other dosage forms. However, the inability of swallowing conventional oral solid dosage forms is still a major problem in the pharmacotherapy of patients suffering from swallowing deficiencies such as children and elderly. As consequence, their medication is often manipulated before administration, which bears at least the risk of severe changes in the pharmacological profile, when controlled release (CR) dosage forms are unintendedly crushed.

Up to now the application of orodispersible films (ODFs), which represent a recent promising approach to overcome these issues, is limited to immediate release (IR) formulations. Therefore, the development and the analytical characterization of rapidly disintegrating ODFs with CR properties are the major aims of this thesis.

The underlying experimental work of the present thesis can be structured into two main parts. The first part focuses on the formulation development of rapidly disintegrating ODFs with prolonged drug release (PR) properties, whereas the second part extensively employs the analytical characterization of oral film preparations.

Within the formulation development of ODFs for prolonged drug delivery, the manufacturing and incorporation of micro-matrices (MMs) into ODFs, produced by solvent casting technique, has been explored. MMs were produced by hot-melt extrusion (HME) and subsequent milling, using theophylline anhydrous as model drug. Five size classes of MMs ranging from <315 µm up to >1000 µm as well as drug loads of 10% and 30% theophylline anhydrous within the MMs have been explored within this study.

ODFs containing MMs of all five size classes have been produced by solvent casting technique. ODFs containing MMs of up to 500 µm revealed acceptance values of below 15, indicating content uniformity and homogeneous MM distribution. Dissolution of MMs and corresponding ODFs was found to be matrix controlled, following square root of time (√t-) kinetics with an initial burst release phase. Generally, the dissolution rate and the burst release increase with decreasing size and increasing drug load of MMs. Further, the disintegration behavior has been investigated using the PharmaTest® disintegration tester equipped with film sample holders. Decreasing disintegration times have been observed with increasing size of incorporated MMs. The uneven surface structure and thus the reduced ODF-matrix

layer thicknesses, which have to be dissolved for ODF disintegration, have been proposed as an explanation for this finding. Decreased thickness of the ODF-matrix was observed by scanning electron microscopy for ODFs containing large-sized MMs.

In a second approach, the development of rapidly disintegrating ODFs, providing PR by incorporation of small-sized, drug-loaded micropellets (MPs) has been investigated. Due to its high water-solubility, diclofenac sodium (DS) was used as model drug. MPs were produced by wet extrusion and spheronization technique, using the co-processed excipient, Vivapur® MCG, consisting of MCC and CMC, as pelletizing aid. Thus, the production of small-sized MPs with a drug load of 70% DS was realized. MPs were subsequently film-coated, applying two different coating thicknesses, 2.5 and 5.0 mg/cm^2, of a qPMMA film coating (Eudragit® RS/RL), and incorporated into the ODF-forming casting mass. The ODFs were produced by solvent casting technique. Different proportions of MPs have been incorporated to obtain ODFs with different DS dose strengths of 10, 15 and 20 mg. X-ray micro-computed tomography (XµCT) was used to investigate the inner structure of the core and the structure of the film coating before and after dissolution. XµCT images of MPs after dissolution provide information about the underlying release mechanism and revealed a highly porous core and a film coating, comprising ruptures. Generally, the release behavior of MPs depends on the applied coating thickness. Uncoated MPs showed IR after disintegration, whereas both types of coated MPs remained intact, revealing linearly PR profiles. The release rate clearly decreased with increasing coating thickness. Reduced lag times and slightly increased release rates were found after incorporation of MPs into ODFs. This has been explained by the incorporation of MPs into an aqueous ODF-forming solution and occasional damage of MPs by cutting the ODFs into a size of 20 x 30 mm during manufacturing. The storage stability of ODFs at room temperature (RT), 40 °C and 75% relative humidity (RH) either stored open or individually packaged into aluminum sachets has been investigated. Significant influences of the storage conditions on the drug release profiles were observed. Reduced lag times and increased release rates were found for ODFs stored in polyethylene bags at RT. However, ODFs stored at 40 °C and 75% RH packaged into aluminum sachets revealed dissolution profiles, comprising clearly increased lag times and decreased release rates. Even more prolongation of the drug release was obtained by ODFs, stored unpackaged at 40 °C and 75% RH.

This instability has been explained by coalescence of polymer chains, which is triggered by increasing temperature and humidity, decreasing the permeability of the coating material and thus the release rates. However, all types of ODFs showed rapid disintegration in less than 30 s. The content uniformity of ODFs was found to be improved by incorporating an increasing number of MPs, since the presence or absence of an individual MP does no longer significantly influence the assay value. Content uniformity with an acceptance value below 15 was observed for ODFs with DS dosages of 15 and 20 mg.

The second part of this thesis aimed at the identification, evaluation and development of suitable test methods for the characterization of different ODF types.

An experimental study has been conducted to systematically compare four disintegration test methods from the literature, namely the petri dish, the slide frame, the side frame and ball (SFaB) as well as the PharmaTest® film disintegration test method. Within this multi-laboratory study, 21 different ODF formulations, produced with varying film thicknesses and/ or amount of insoluble particles, have been manufactured and investigated, applying the four different test methods. All methods showed similar tendencies, at which the disintegration time proportionally increased with increasing dry film thickness and decreased, when insoluble microcrystalline cellulose (MCC) particles were contained within the ODF. However, absolute disintegration time values widely vary, depending on the applied method. The longest disintegration times and high variability were observed for the petri dish method, since the whole ODF has to be disintegrated and the endpoint detection was challenging. Almost all of the analyzed formulations showed disintegration times above 180 s. However, the instrumental setup is simple and can be applied independently of the laboratory equipment. The endpoint for the slide frame method, however, is clearly defined. In comparison to the petri dish method, disintegration times were reduced. Prolonged disintegration times and reduced reproducibility were only observed for ODFs with high dry film thicknesses, since the small fluid volume used for this method seems to be incapable to completely soak the film matrix. The SFaB method showed increased suitability to investigate film formulations with increased thicknesses. The application of a stainless steel ball and the slightly increased volume of dissolution medium reduced the disintegration time, while retaining full sensitivity. The PharmaTest® uses the established test setup of the

disintegration tester defined by the Ph.Eur./ USP. All ODFs investigated by PharmaTest® showed rapid disintegration.

Based on the results, the slide frame method and SFaB method have been evaluated as particularly suitable for research and development (R&D) purposes. They were able to precisely discriminate between formulations with slight variations. For pharmaceutical quality control (QC) purposes, a robust and reliable method is needed to monitor the quality within a defined specification range. In the tested area, only the PharmaTest® and the SFaB method fulfilled these demands.

The development of a dissolution test method, which is suitable to investigate the drug release of film preparations with IR as well as CR properties is displayed in the second subsection. The instrumental setup is based on a commercial USP type 4 flow-through cell (FTC), which has additionally been equipped with three different types of in-house built film sample holders such as a sample holder without backing plate (FH), a sample holder with backing plate (FHB) and a 3D printed sample holder (FH3D). Within this study, ODFs with IR (ODR_{IR}) and PR ($ODF_{PR<315}$ and $ODF_{PR500-715}$) properties as well as a double-layer film (ODF_{DL}), comprising of a drug and a water-insoluble shielding layer were produced and investigated. Anhydrous theophylline was used as model drug. The application of film sample holders constructed with backing plates (FH and FH3D) led to decreased release rates for ODF_{IR} and $ODF_{PR<315}$, due to a reduced ODF surface exposed to the dissolution medium. For ODF_{DL} linear prolonged release profiles were observed, applying these sample holders, which indicates the suitability to examine the integrity of the shielding layer.

Different flow rates and media compositions have been applied to simulate conditions within the oral cavity, stomach, and intestine. The application of a low flow rate of 1 ml/min, comparable to the salivary flow within the oral cavity, showed decreased theophylline release, while similar release profiles were obtained by flow rates between 2 and 8 ml/min. Substantial impact on the theophylline release was exerted by varying the composition of the dissolution medium. Since the drug release from ODF_{PR} is controlled by diffusion through the water-insoluble qPMMA matrix, ion species and concentration strongly affected the permeability and thus the release behavior.

By introducing film sample holders for the dissolution testing of oral films, keeping them in a constant position within the cell, reliable investigation has been enabled.

Furthermore, the potential for biorelevant dissolution testing, considering physiological conditions of the gastrointestinal (GI) transit, which is relevant for oral film preparations, has been assessed. In this context, the application of the FH3D showed superior suitability as on the one hand a backing plate, which allows simulation of the in vivo application and investigation of the integrity of the shielding layer has been provided and on the other hand the operative volume has been reduced to approximately 3 ml, which is in a better agreement to physiological saliva volumes. However, further studies need to explore the comparability of the obtained dissolution data to in vivo plasma profiles. Then, the developed dissolution test method would be a valuable analytical instrument to predict the in vivo performance and to enable evaluation of dissolution related issues such as taste sensation and permeation processes.

Finally, an experimental study has been conducted to compare the developed dissolution test method for oral film preparations to three dissolution test methods from the literature. The test methods from the literature were the basket method, the Paddle and Glass Disc (PGD) method and the Punch and Filter (PAF) method. Within this study, the suitability to analyze different ODF types, the instrumental setup, the method practicability and the potential for biologically relevant dissolution testing should be compared and assessed. The FTC + FH3D method, developed within this work, and the PGD method showed increased discriminatory power and were suitable to investigate the integrity of the shielding layer of $ODF_{DL.}$ This could not be achieved by applying the basket and PAF method. These methods did not allow clear discrimination between ODF_{IR} and ODF_{DL}, since IR profiles were found for both, ODF_{IR} and ODF_{DL} respectively. The FTC + FH3D method provided high flexibility, which may be used to simulate gastrointestinal transit. The PAF method reflects physiological conditions of the oral cavity and enables mimicking the in vivo film application. Based on these findings, it has been concluded that the FTC + FH3D and the PAF method are particularly valuable for R&D. Due to the simple and well standardized instrumental setups as well as high robustness, the basket and PGD method are suitable for use in pharmaceutical QC.

ODFs with CR properties represent a promising new dosage form for patient centered drug therapies. The multiparticulate dosage form design might allow the administration of CR dosage forms to patients with swallowing deficiencies, while

complying with safety and efficacy standards for pharmaceutical products, which meet the current state of science.

The development and evaluation of analytical test methods for oral film preparations should emphasize the need of standardized test methods and specifications, which may or may not be based on the proposed methods of the present thesis, to close the gap of lacking regulatory guidance.

Section F. List of Publications

F.1 Original publications

Speer, I., Preis, M., Breitkreutz, J.: Dissolution testing of oral film preparations: experimental comparison of compendial and non-compendial methods. *International Journal of Pharmaceutics,* 561 (2019): 124-134.

*Öblom, H., Zhang, J., Pimparade, M., Speer, I., Preis, M., Repka, M., Sandler, N.: 3D printing of isoniazid tablets for the treatment and prevention of tuberculosis - Personalized dosing and drug release. *AAPS PharmSciTech*, 20.2 (2019): 52.

Speer, I., Preis, M., Breitkreutz, J.: Novel dissolution method for oral film preparations with modified release properties. *AAPS PharmSciTech,* 20.1 (2019): 7.

Speer, I., Lenhart, V., Preis, M., Breitkreutz, J.: Prolonged release from oro-dispersible films by incorporation of diclofenac-loaded micropellets. *International Journal of Pharmaceutics* 554 (2019): 149-160.

Speer, I., Steiner, D., Thabet, Y., Breitkreutz, J., Kwade, A.: Comparative study on disintegration methods for oral film preparations. *European Journal of Pharmaceutics and Biopharmaceutics* 132 (2018): 50-61.

Speer, I., Preis, M., Breitkreutz, J.: Prolonged drug release properties for orodispersible films by combining hot-melt extrusion and solvent casting methods. *European Journal of Pharmaceutics and Biopharmaceutics* 129 (2018): 66-73.

**This publication is not part of the present thesis. The co-author, Isabell Speer, is responsible for some parts of the experimental work (XRPD, DSC and water sorption analysis), writing of the corresponding chapters as well as revision of the manuscript.*

F.2 Contributions to meetings

F.2.1 Oral presentations

Speer, I., Berkenkemper, S., Hüsing, A., Lenhart, V., Preis, M., Breitkreutz, J.: Prolonged release properties realized for orodispersible films by incorporation of drug-loaded micropellets. *World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, Granada 2018.

Speer, I., Löseke, L., Peters, R., Preis, M., Breitkreutz, J.: Novel dissolution method for oral film preparations with modified drug release. *European Conference on Pharmaceutics*, Krakau 2017.

Speer, I., Preis M., Breitkreutz, J.: Prolonged release properties of orodispersible films combining solvent casting and hot-melt extrusion. *World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, Glasgow 2016.

Thabet, Y., Speer, I., Bartscher, K., Wiedey, W., Breitkreutz J.: Flexible dosing of enalapril by orodispersible minitablets: paediatric concept, drug development and PIP approval. *World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology*, Glasgow 2016.

Speer, I., Hahn B., Preis, M., Breitkreutz, J.: Characterization methods for orodispersible films containing matrix theophylline particles. *PSSRC Annual Meeting*, Kopenhagen 2016.

F.2.2 Poster presentations

Adam, A., Speer, I., Breitkreutz, J.: Mini-tablets containing coated diclofenac. *European Conference on Pharmaceutics*, Krakau 2017.

Speer, I., Pápai-Herczeg, K., Preis, M., Breitkreutz, J., Broscheit, J., Roewer, N.: Enhanced oromucosal permeation of midazolam HCl released from mucoadhesive buccal films using methylated β-cyclodextrins. *Conference of European Paediatric Formulation Initiative*, Warschau 2017.

Speer, I., Preis, M., Breitkreutz, J.: Comparison of extrusion methods to produce drug-loaded matrix particles to be incorporated in orodispersible films. *AAPS Annual Meeting*, San Diego 2017.

Adam, A., Lenhart, V., Speer, I., Breitkreutz, J.: Orodispersible mini-tablets with prolonged drug release. *AAPS Annual Meeting*, San Diego, 2017.

Speer, I., Hahn, B., Preis, M., Breitkreutz, J.: Characterization of orodispersible films containing matrix theophylline particles with prolonged release. *AAPS Annual Meeting*, Denver 2016.

Bartscher, K., Speer, I., Breitkreutz, J.: Considerations on process development of low-dosed enalapril orodispersible mini-tablets manufactured by direct compression. *Conference of European Paediatric Formulation Initiative*, Athen 2014.

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