Oromucosal film preparations for pharmaceutical use – formulation development and analytical characterization

Inaugural-Dissertation

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vorgelegt von

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"I think I benefited from being equal parts ambitious and curious. And of the two, curiosity has served me best."

Michael J. Fox

Für Irene

Vorwort

Die vorliegende Doktorarbeit entstand während meiner Tätigkeit als Wissenschaftliche Mitarbeiterin am Institut für Pharmazeutische Technologie und Biopharmazie der Heinrich-Heine-Universität Düsseldorf und später parallel zu meiner Tätigkeit bei der Firma Sapiotec aus Würzburg.

Die in der Arbeit thematisierten filmförmigen Zubereitungen zur Anwendung in der Mundhöhle sind neue Darreichungsformen, für die aufgrund ihrer jüngsten Einführung in das Europäische Arzneibuch bisher keine detaillierten Qualitätsanforderungen definiert sind. Das Ziel dieser Doktorarbeit war es, auf Basis der aktuellsten Erkenntnisse filmförmige Zubereitungen und dazugehörige Methoden zur Charakterisierung zu entwickeln.

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Düsseldorf, im August 2014 Maren Katherina Preis

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List of abbreviations

A	Area
a_i	Activity of the substance
AD	Autistic disorder
ADI	Acceptable daily intake
ADHD	Attention deficit hyperactivity disorder
ANOVA	Analysis of variance
API	Active pharmaceutical ingredient
AUC	Area under the curve
AV	Acceptance value
BUT	Buccal tablet
CHMP	Committee for Medicinal Products for Human Use of the EMA
CB	Caffeine benzoate
CC	Caffeine citrate
CD	Cyclodextrin
CH	Caffeine hydrochloride
chemFET	Chemical field-effect transistor
CI	Confidence interval
CM	Caffeine maleate
COL	Compressed lozenges
Conc	Concentration
CPA	Change of membrane potential caused by absorption
Da	Dalton
DE	Dextrose equivalent
DMH	Dimenhydrinate
DSC	Differential scanning calorimetry
E	Electrode potential
E^O	Standard electrode potential
EDQM	European Directorate for the Quality of Medicines
EFSA	European Food Safety Agency
EHEC	Ethyl (hydroxyethyl) cellulose
EMA	European Medicines Agency
F	Faraday's constant
FCS	Food Standards Committee
FDA	The Food and Drug Administration
GPCR	G protein-coupled receptor
HEC	hydroxyethyl cellulose
HEMC	hydroxyethylmethyl cellulose

HPßCD	Hydroxypropyl-ß-cyclodextrin
HPC	Hydroxypropyl cellulose
HPLC	High performance liquid chromatography
HPMC	Hydroxypropylmethyl cellulose / Hypromellose
HPSP	hydroxypropyl pea starch polymer
ICH	International Conference of Harmonisation
LMS	Labeled magnitude scale
ln	Natural logarithm
LOD	Limit of detection
LOQ	Limit of quantification
MBF	Mucoadhesive buccal film
MBT	Mucoadhesive buccal tablet
MDT	Mouth dissolving tablet
MC	Methyl cellulose
MCC	Microcrystalline cellulose
MD	Maltodextrin
M_r	Relative molecular mass
MT	Mini-tablet
MTPS	Maltotriose polysaccharide
MVDA	Multivariate data analysis
NaCMC	Carboxymethyl cellulose sodium salt
NMR	Nuclear magnetic resonance
ODF	Orodispersible film
ODMT	Orally disintegrating mini-tablet
ODT	Orodispersible tablet
OMCL	Official Medicines Control Laboratories
ORI	Oromucosal (oral) inlay
ORP	Oral patch
OTC	Over-the-counter
OQ	Operational qualification
PAA	Polyacrylic acid
PC(A)	Principal component (analysis)
PDCO	Paediatric Committee of the European Medicines Agency
PDE	Permitted daily intake
PET	Polyethylene therephtalate
Ph.Eur.	European Pharmacopoeia
pK_a	Acid dissociation constant
PP	Polypropylene
PPACP	Polyethylene glycol-poly vinyl alcohol co-polymer
PVC	Polyvinyl chloride

PVPP	Polyvinylpolypyrrolidone (crospovidone)
PQ	Performance qualification
R	Universal gas constant
R^2	Coefficient of determination
(R)SD	(Relative) Standard deviation
SB	Sodium benzoate
SEM	Scanning electron microscopy
SLT	Sublingual tablet
SPR	Surface plasmon resonance
SRT	Sustained release tablet
SSF	Simulated saliva fluid
s_{x0}	Standard deviation of the procedure
s_y	Residual standard deviation
T	Temperature
TM	Taste-masking
TRC	Taste receptor cell
USP	United States Pharmacopoeia
UV	Ultra-violet / Unit-variance
VAS	Visual analog scale
V_{x0}	Relative standard deviation of the procedure
WHO	World Health Organization
z	Ionic valence of the substance

A. Introduction

A.1. Anatomic and physiological properties of the oral mucosa

Different regions are present in the human mouth. The oral mucosa can be separated into keratinized and non-keratinized mucosa. The keratinized sites are involved in mechanical processes like mastication and speech and are called the masticatory mucosa (Collins and Dawes, 1987). Of all oral mucosa, 25% is keratinized epithelium, which is mainly located at the gingiva and the hard palate (Wertz and Squier, 1991). Keratinized mucosa is supposed to be less permeable than that in the non-keratinized sites. Additionally, acylceramides and ceramides are present in considerable amounts. Their presence amongst other lipids can be associated with barrier functions (Harris and Robinson, 1992; Squier et al., 1991). However, even non-keratinized mucosa features a certain amount of keratin, but masticatory mucosa consists of keratins with higher molecular mass (Tseng et al., 1982). The non-keratinized mucosa covers the inner cheeks (buccal mucosa), the bottom side of the tongue, the soft palate and the sublingual area. It is present in approximately 60% of the oral cavity. The tongue is assigned a specialized mucosa; the epithelium is partly keratinized, representing approximately 15% of the total area. The oral mucosa can be histologically divided into three groups: the masticatory, lining and specialized mucosae (Figure 1) (Squier, 1989). The particular attributes of the specialized mucosa of the tongue and its role in taste sensation is discussed in Chapter A.3.

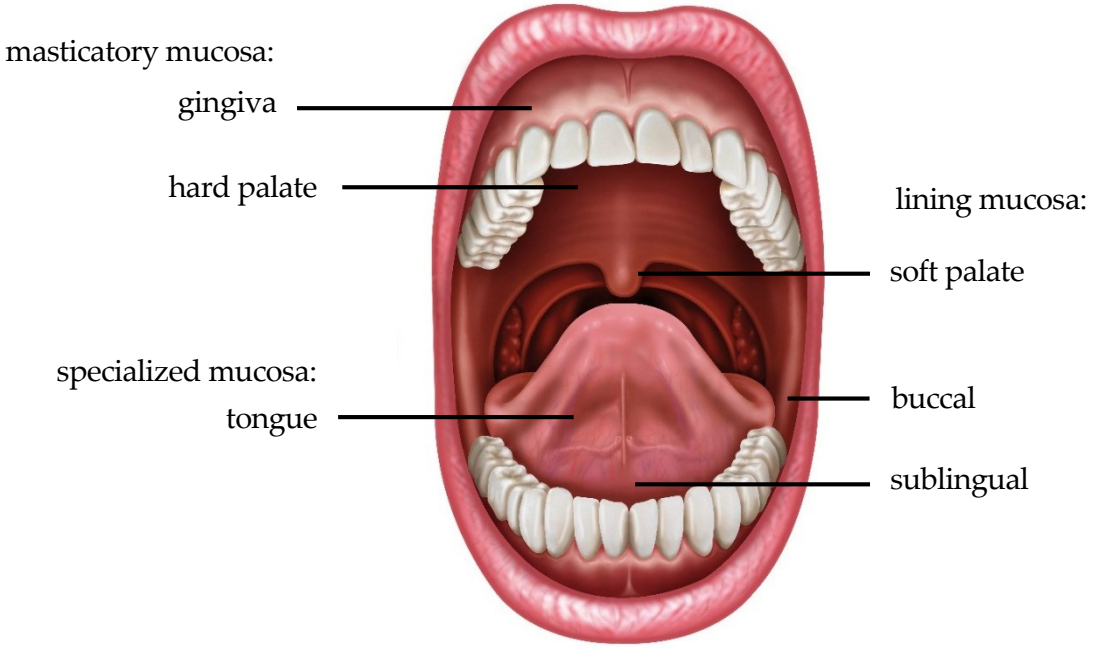

Figure 1. *Types of mucosa in the oral cavity.* © *Depositphotos.com/Alexilus*

The buccal mucosa consists of approximately 40 – 50 cell layers and measures 500 – 800 µm. The thickness of the other lining and masticatory mucosal tissues is much lower (100 – 200 µm). Keratin becomes deposited in the superficial cells resulting in flattening of the cells. The

generally non-keratinized mucosa features less flattened cells on its surface (Harris and Robinson, 1992).

A schematic structure of the oral mucosa is given in Figure 2, adapted according to the literature (Harris and Robinson, 1992; Morales and McConville, 2011). The epithelium is connected to the lamina propria mucosa, a thin layer of loose connective tissue, via an extracellular matrix, the basal lamina. The underlying structure is the submucosa, which consists of connective tissue that assists blood vessel draining into the veins (Smart, 2005).

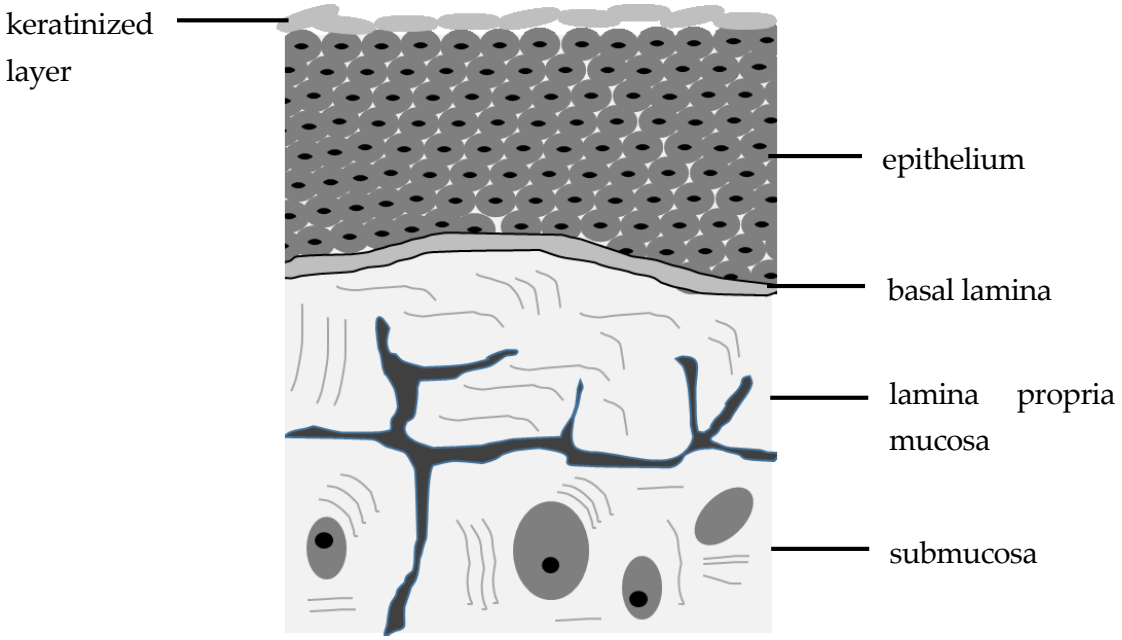

Figure 2. *Cross section of keratinized mucosa (adapted according to Harris and Robinson, 1992 & Morales and McConville, 2011).*

Three major salivary glands (Glandula parotis, Glandula submandibularis and Glandula sublingualis) are situated in the oral cavity (Mutschler et al., 2007a). Saliva serves as a lubricant for oral functions, for instance, to facilitate swallowing and support digestion of carbohydrates by enzymes (Smart, 2005). Saliva can be assigned as a neutral buffer solution, whereby pH and composition may diverge depending on pre- or postprandial secretion; the composition may also be influenced by disease or age (Ben-Aryeh et al., 1990; Chauncey et al., 1962; Larsen et al., 1999; Moreira et al., 2009).

Saliva consists to a large extent of water. The main electrolytes in the secretion are sodium (Na^+), potassium (K^+), chloride (Cl^-), hydrogen phosphate (HPO_4^{2-}) and further hydrogen carbonate (HCO_3^-) electrolytes. Their composition may differ predominately depending on salivary flow rates. Mucins, viscoelastic glycoproteins and enzymes like amylase or lysozyme, but also immunoglobulins, complement the composition of saliva (Nagler and Hershkovich, 2005; Park and Robinson, 1985). The thickness of the salivary film coating the oral mucosa has been estimated to be between 70 to 100 µm (Collins and Dawes, 1987).

A.2. Drug delivery in the oral cavity

Drug delivery in the oral cavity has to be distinguished into the release of an active substance and subsequent swallowing of the dispersed or dissolved components via the saliva, and by drug delivery to and absorption via the oral mucosa. The first option can be described as an alternative per oral drug administration. The disposition of an active substance onto the oral mucosa will provide local action, whereas drug delivery via the oral mucosa represents a local administration, but systemic drug action.

According to Collins and Dawes, the surface area of the adult human oral mucosa is approximately 215 cm^2 (Collins and Dawes, 1987). The majority of this surface is assigned to non-keratinized mucosa, which offers a facilitated opportunity for drug administration to reach the systemic blood flow via the oromucosal route and to avoid the per oral administration. The keratinized mucosa may also be utilized for drug delivery, but its permeability is inferior to the buccal or sublingual site (Pimlott and Addy, 1985a, b).

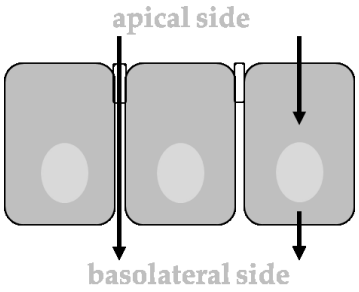

Figure 3. *Paracellular (left) and transcellular (right) transport.*

Lipophilic molecules are preferably transported via the transcellular route, as they are able to permeate the lipid double layer of the cell membrane (Figure 3). Hydrophilic substances that cannot overcome the lipid barrier may pass the cell membrane by being transported paracellularly. To accomplish this route, the so-called "tight junctions" have to be overcome in between the cells, which block the intracellular gaps (Mutschler et al., 2007c).

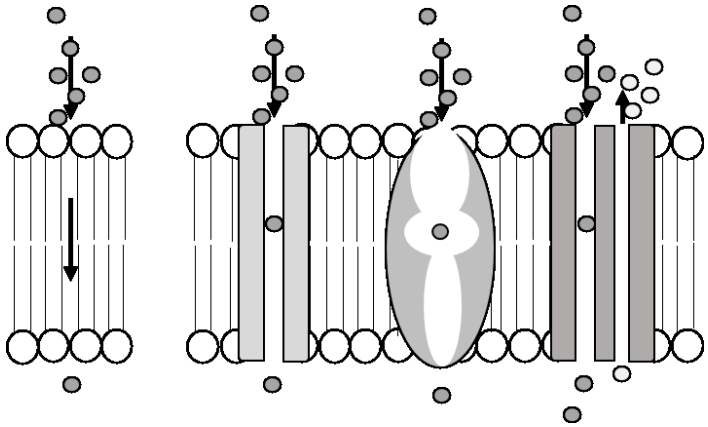

Figure 4. *Transcellular transport mechanism through the lipid double layer: easy diffusion (left), transport via membrane proteins: channel, carrier, pump (right).*

The transcellular transport of drugs requires certain pre-requisites. Drug diffusion offers the most convenient way for overcoming the lipid barrier of the cells. However, more opportunities are given by the proteins presented in the membrane (Figure 4). The cells provide channels, carriers and pumps, which may be helpful in terms of drug absorption and with regard to an active transport (Mutschler et al., 2007c).

The key factors affecting transmucosal absorption are summarized in Table 1. The hydrophilic and lipophilic properties of a drug mainly influence the success of the transport and absorption (Harris and Robinson, 1992). The absorption of hydrophilic substances depends on the size of the molecule, as with increasing molecular size its oromucosal absorption decreases. Furthermore, pH value plays an important role; depending on the acid dissociation constant (pKa) of the drug substance and the pH value of the saliva, altering of the drug ionization may occur.

The saliva volume and flow represents another crucial factor influencing transmucosal absorption, as the active substance may be flushed away by the saliva before being absorbed. Finally, the aforementioned site of administration is important in terms of the properties of the oromucosal tissue and its degree of keratinization (Wertz and Squier, 1991).

Table 1. *Key factors affecting transmucosal absorption according to Franke (2013); Narang and Sharma (2011)*

Influences on transmucosal absorption
pKa
Hydrophilicity – lipophilicity balance
Molecular size
Salivary volume
Salivary flow
Saliva pH
Residence time
Site of application (administration)

To summarize, drug delivery into the oral cavity implies various challenges and opportunities. Nevertheless, there are requirements with respect to the natural barrier function of the mucosal tissue that needs to be overcome to enable drug absorption via the oral mucosa. A main advantage of oromucosal drug absorption is avoiding the gastrointestinal and hepatic first pass effects, which could be beneficial with respect to bioavailability (Hoffmann et al., 2011). Drug delivery in the oral cavity is not limited to mucosal absorption: local action can be achieved by presenting the drug to the mucosal surface and the saliva wetted surfaces, enabling dissolving of active substances and its carrier material prior to swallowing.

A.3. Physiology of taste and taste assessment

The delivery of the drug substance to the oral cavity implies that the active pharmaceutical ingredient (API) may also be in contact with the tongue. As mentioned in Chapter A.1., the mucosa of the tongue is highly specialized. The specialized cells that are responsible for taste perception are predominantly present on the tongue, but may also be situated in the soft palate, cheek or throat (Chandrashekar et al., 2006). The actual taste sensing organs of the tongues, the taste buds, are located in the three different types of papillae, i.e., papillae vallate, fungiformis or filiformis (Figure 5). The taste buds are onion-shaped structures containing up to 100 cells clustered in groups. The taste receptor cells (TRCs) have either ion channel or G protein-coupled receptors (GPCRs) located in their microvilli, which are presented to the aqueous environment. This area is called the taste pore (Sainz et al., 2007). The perception of saltiness or sourness is mediated through ion channels, whereby bitter, sweet and umami tastes are transmitted via GPCRs. The stimulation of a TRC evokes the release of Ca^{2+} ions by depolarization of the cell (ion channels) or second messenger release via GPCRs. The ions stimulate the release of neurotransmitters, which activate an afferent nerve fiber. Subsequently, the signal is transmitted via the cranial nerves to the brain (Mennella et al., 2013). They reach the brain stern and the signal is forwarded to the thalamus, partly to the hypothalamus and the limbic system, respectively. The olfactory sensation is also projected in the limbic system. It is therefore assumed that the affective-emotional taste sensation is mediated by this area. The stimulation of TRCs, which lead to the conscious taste sensation, leads the signals to the thalamus. The thalamus projects the signals over its nuclei to the cerebral cortex, where the primary taste areas are located (Mutschler et al., 2007b).

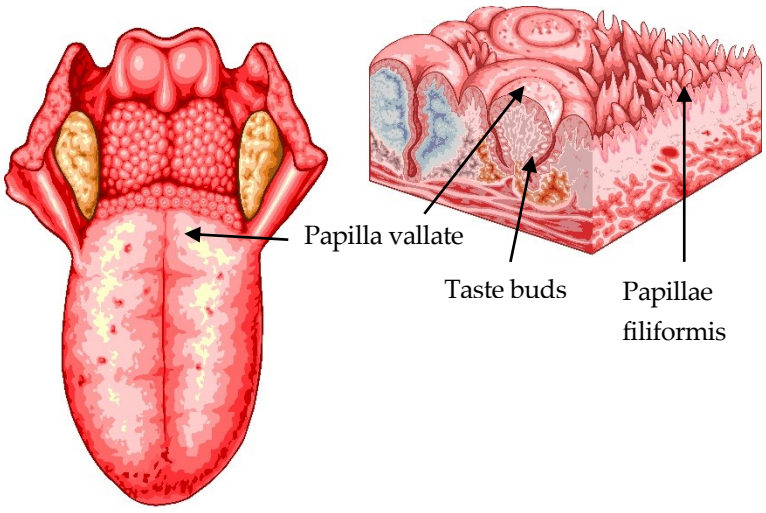

Figure 5. *The human tongue.* © *Depositphotos.com/oguz.aral*

The taste attributes that can be perceived and distinguished by humans are sweet, sour, umami, salty and bitter. Taste is important and may protect the individuum from intoxications, as it is evolutionally derived, for example, toxic plants provide a bitter taste and their intake should be prevented (Behrens and Meyerhof, 2006). The majority of drug

substances provide a bitter taste and in some cases nociceptive action, which can be perceived as a spicy or metallic taste impression. Therefore, it is not surprising that bitter medicines might lead to rejection and influence a patient's therapy coherence (Mennella et al., 2013).

The habituation to certain tastes during early childhood may influence taste perception (Beauchamp and Mennella, 2009). As mentioned previously, taste perception is mediated by different cerebral regions, including the limbic system, processing for example emotions, which may affect individual taste perception. Furthermore, bitter taste perception may vary from one individual to another due to, for example, polymorphism in bitter taste receptor genes (Behrens and Meyerhof, 2006). Known bitter taste receptors have been exposed to a large number of substances and their ability to recognize the substances as bitter tasting was highly depended on the receptor type; some reacted only to a few, others to a wide range of substances (Meyerhof et al., 2010).

Thus, the perception of taste is an individual process and there will not be an overall solution for everyone to overcome bitter taste, e.g. of medicines, in a suitable way. Nevertheless, there is the need to improve pharmaceutical formulations in the best manner possible. Human sensory tests are undoubtedly the most reliable way for assessing the taste of, for example, a pharmaceutical product; however, conducting of studies in humans, especially when active substances are involved, is challenging. This is even more challenging when it comes to children, especially very young ones. Mennella et al. (2013) have provided an overview on psychophysical tools used to assess bitter taste and medication palatability in children.

In the early stages of formulation development, electronic taste sensing systems (electronic tongues) are more likely to be used and be popular, not only in research facilities, but also for health institutions and in the pharmaceutical and food industry for evaluating formulations and to use them as quality control tools (Campbell et al., 2012; Eckert et al., 2011; Sadrieh et al., 2005; Woertz et al., 2011c).

The development of sensory systems can be traced back to the mid-1990s. The main idea was to develop sensor-based electrode systems that could concentration-dependently detect dissolved substances. In 1994, a Japanese research group introduced a multichannel sensory system based on a potentiometric mechanism, where the electrodes were equipped with lipid membranes (Toko et al., 1994). The aim was to design a system that could register changes in electric potential according to the interaction of the substance with the lipid membrane. The lipid membranes were composed to mimic the properties of biological membranes and their ability to interact with dissolved substances in order to assess an electronic signal, which could then be correlated to taste attributes of beverages. This promising approach was further investigated and led to a marketed electronic tongue, the Insent® taste sensing systems (Kobayashi et al., 2010; Takagi et al., 2001; Toko and Habara, 2005). The system is equipped with sensors providing different lipid membranes and is declared as being sensitive to different tasting substances depending on lipid membrane composition. A French company, AlphaMOS, has also designed an electronic tongue. The system is based on the same

measurement mechanism, but provides different sensors with another underlying technology. Both systems have been compared and the Insent® system was qualified according to ICH guidelines (Woertz et al., 2010, 2011a). The performance qualification of the AlphaMOS electronic tongue αAstree is described in Chapter E.2. Furthermore, there are several electronic tongues under development or for in-house use only in various research facilities (Jańczyk et al., 2010; Kumar et al., 2012; Legin et al., 2004), which indicates for potential future improvements in electronic taste sensing.

The membrane-coated systems aim to simulate the molecular interaction of dissolved substances with biological membranes. Commercial systems and systems under development provide multiple sensors with diverging sensitivity for ions or chemical structures. Multivariate data analysis of sensor patterns can be performed to obtain signal patterns. These patterns can then be compared when it comes to experiments with samples of different composition. The electronic tongues are not able to provide overall taste impressions, but could be shown as feasible especially in generic formulation design (Woertz et al., 2011b). The systems are able to distinguish between differently composed formulations and by comparative studies, a first hint of the potentially most suitable formulation can be derived.

The first electronic taste application was applied to food products and beverages, to assess for example uniform quality, which is connected to taste. However, it turns out that the systems are also useful tools in pharmaceutical development avoiding the need for a human sensory panel in the first place (Kobayashi et al., 2010; Woertz et al., 2011c).

A.4. Pharmaceutical development of patient-centered formulations

A.4.1. Medicinal products for geriatric and pediatric use

It is not naturally granted that there is an age-appropriate dosage form available for every medicinal treatment. With respect to certain patient populations such as the elderly or children, medicinal treatment can be challenging (Breitkreutz and Boos, 2007; Cram et al., 2009). Esophageal diseases and swallowing issues may complicate compliance and adherence of geriatric patients, who often face problems regarding the administration of their medicines. Another vulnerable group is children: with respect to physical attributes, children of younger age-groups might not be able to swallow the same sized dosage forms as adults. Thus, the elderly and children form a special patient group, making it worthwhile to further develop dosage forms to facilitate drug administration. Children and the elderly face similar issues regarding drug therapy. The challenges for accomplishing pediatric and geriatric oral/oromucosal drug delivery are summarized in Table 2 and are based on the findings of Breitkreutz and Boos (2007). All aspects should be considered with respect to both patient groups.

Table 2. *Challenges in pediatric and geriatric oral and oromucosal drug therapy (Breitkreutz and Boos, 2007).*

Aspects to consider
Palatability /acceptable taste
Safety of excipients
Handling of packaging
Precise & clear product information
Acceptable dose uniformity
Size of dosage form
Easy and safe administration
Sufficient bioavailability

The logical solution for pediatrics may be to administer liquid formulations (EMA, 2006). Nevertheless, a WHO expert forum proposed a shift of paradigm towards solid dosage forms in 2008 (WHO, 2008). Still, the initial situation has not changed: children are not able to swallow large-sized tablets or capsules and they may even refuse taking and swallowing solid dosage forms. However, a new trend in dosage form development has taken place in recent years: orodispersible tablets, multiparticulates or the administration of powder in sachets have been investigated with respect to appropriateness for children (Stoltenberg et al., 2010).

The further development of orodispersible tablets (ODT) has led to orally disintegrating mini-tablets (ODMT) (Stoltenberg and Breitkreutz, 2011). The use of small-sized tablets (1–2 mm in diameter) has been an emerging success in dosage form development. It combines the convenience of tablets, a solid dosage form, with less issues in stability than liquid formulations, and the opportunity to avoid swallowing a large unit, as the ODMTs are intended to disintegrate rapidly once in contact with the saliva wetted tongue or mucosa (Hermes, 2012; Stoltenberg, 2012). Furthermore, studies revealed an overall positive response of children in investigations on mini-tablet (MT) acceptance (Klingmann et al., 2013; Spomer et al., 2012). The MTs (2mm) have been favored compared to syrup by the children in trials, and these results can also affirmed for children of aged six months. The tendency of children to sympathize with small sized dosage forms has been confirmed in a further study using 4 mm tablets compared to syrup, suspension and powder. Parents were asked to administer placebos to their children of one to four years and rate the acceptability and report about (non-) successful intake. The study again revealed predomination of the tablets in being best accepted by the children (Van Riet-Nales et al., 2013). Furthermore, the number of fully swallowed tablets was higher than for other dosage forms.

The above findings demonstrate that children are willing to accept solid dosage forms; moreover, once convinced by the ease of its administration, they may even favor a certain dosage form.

The use of film preparations as an alternative to liquids or tablets is an upcoming field of interest in drug delivery. It can be proposed that if a film preparation, meaning a thin and flexible polymer sheet at maximum the size of a stamp, can be described as a solid dosage form, as the film is a solid preparation prior to administration. Oromucosal film preparations are placed in the mouth to disperse rapidly (orodispersible film) or are placed on the mucosal tissue and may dissolve (buccal film) (Ph.Eur., 2012b). Where orodispersible films (ODFs) may be described as an alternative per oral dosage form, (mucoadhesive) buccal films (MBFs) offer a variety of possibilities in drug delivery.

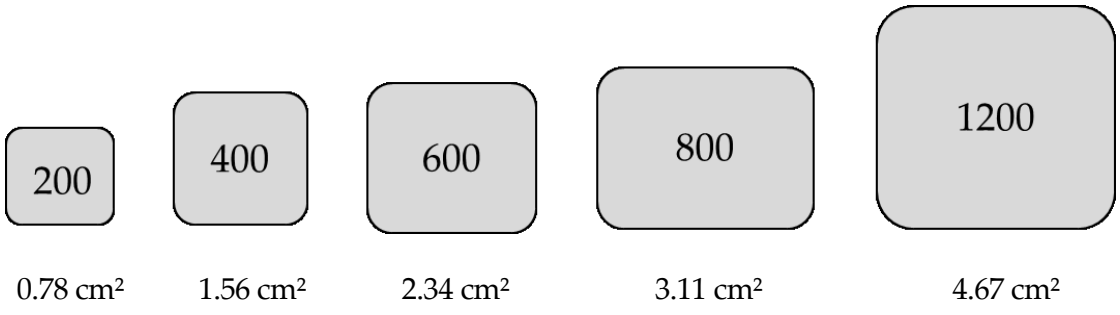

Figure 6. *Sizes of the commercialized MBF Breakyl® Buccalfilm in different strengths (200 µg, 400 µg, 600 µg, 800 µg, 1200 µg (Medicines.org, 2012).*

Detailed information on the classification and different types of oromucosal film preparations according to the European Pharmacopoeia (Ph.Eur.) will be provided in Chapter A.5 and Chapter B.

Table 3. *Overview of licensed orodispersible films in chronological order.*

Approval or launch date	Brand	Supplier	Active substance	Indication
2000	Listerine® Pocket Packs / Breath Strips	Warner-Lambert (Pfizer, Johnson&Johnson)	Essential oil	Mouth refresher
2004	Triaminic Thin Strips®	Novartis Consumer Healthcare	Phenylephrine Diphenhydramine Dextromethorphan	Cold Cough
	Theraflu®			
	Chloraseptic® Relief Strips	Prestige Brands (InnoZen)	Benzocaine	Sore throat
2005	Sudafed® PE quick dissolve strips	Pfizer (Johnson&Johnson)	Phenylephrine	Nasal congestion
2006	Gas-X Thin Strips®	Novartis Consumer Healthcare	Simethicone	Bloating / Abdominal pain
	Benadryl® Allergy quick dissolve strips	McNeill-PPC	Diphenhydramine	Allergy
2008	Pedia-Lax™ Quick Dissolve Strip	C.B.Fleet	Sennosides	Constipation
2010	Suboxone® Sublingual film	Reckitt Benckiser Pharmaceuticals	Buprenorphin Naloxon	Pain
	Risperidon HEXAL® SF	HEXAL	Risperidone	Schizophrenia
	Ondansetron Rapidfilm®	LabTec / Applied Pharma Researchj	Ondansetron	Nausea Vomiting
2011	Breakyl® Buccalfilm	Meda Pharma	Fentanylcitrat	Pain
	Smartstrips™ (several products)	Velox	Flavors, Melatonin, Caffeine, Vitamins, Plant extracts, Amino acids	Appetite curbing Sleeplessness Life style
2012 / 2013	Niquitin®	GlaxoSmithKline	Nicotine	Nicotine withdrawal symptoms
	Zuplenz®	Vestiq Pharmaceuticals	Ondansetron	Nausea Vomiting
	Setofilm®	Norgine	Ondansetron	
	Zolmitriptan Rapidfilm®	LabTec / Applied Pharma Research	Zolmitriptan	Migraine

References: (Breitenbach, 2013; EvaluateLtd., 2008; Franke, 2013; Hoffmann et al., 2011; Siebenand, 2010; Smartstrips, 2011)

Despite the fact that ODFs were only introduced in the monograph on "Oromucosal preparations" in 2012 (Ph.Eur., 2012b), there is over 10 years of market experience in this area (Table 3). The first ODF was not a medicinal product; rather, it was the mouth refresher Listerine® PocketPacks or Breath Strips that began the era of films.

Today, there are several over-the-counter (OTC) and prescription drugs available with ODF as the dosage form. The dose strength of a film can be varied by using different film sizes (Figure 6). This approach is advantageous with regard to the manufacturing of the films, as only one production line is needed and different doses can be achieved by varying the cutting size of the film. Breakyl® is a bilayered mucoadhesive buccal film, where the API is incorporated in one layer that is attached to the buccal mucosa, while the second layer serves as a backing layer to ensure the drug is released only unidirectional, towards the mucosa and is only slightly swallowed (Rathbone et al., 1994).

Drug delivery via the oral mucosa has been described in Chapter A.2. The advantages of a mucoadhesive buccal film with a backing layer compared to a dosage form is given, as swallowing of certain amounts of the active substance can be avoided, which may lead to decreased bioavailability, as the substance may not be absorbed by the mucosa in the first place.

Another advantage of films is their flexibility in dosing. If the expected effect (e.g., pain relief) is not taking place, the dose can easily be increased by applying a second film. With respect to pediatric medicines, the use of very small films may be possible for applying low doses in the first place and to easily adjust the dose e.g. with age or depending on physiological conditions.

A.4.2. Regulatory guidance

A.4.2.1. Medicines for pediatric use

Recently, a novel guideline of the European Medicines Agency (EMA) on pharmaceutical development of medicines for pediatric use was published and comes into effect on February 15, 2014 (EMA, 2013a). From that date onwards, the guideline will be mandatory to adhere to in pharmaceutical development for children between birth and 18 years of age. The aim of the "Paediatric Regulation" is "to facilitate the development and accessibility" of age-appropriate pediatric medicines. The aim should be achieved "without subjecting children to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age populations" (Council of Europe, 2006). The EMA, the Paediatric Committee (PDCO) and the Committee for Medicinal Products for Human Use (CHMP) do not aim to set up restrictions, but to make guidance available.

***Table 3.1**: Points to consider according to the novel guideline on pharmaceutical development of medicines for pediatric use with regard to oral and oromucosal administration: general considerations, active substances and dosage form (EMA, 2013a).*

General considerations	Active substances	Dosage form
„Infants are simply unable to swallow conventionally-sized tablets"	Liquid medicinal product:	"Route of administration should be discussed and justified for children in each of the target age group(s)"
Pharmaceutical design appropriate for use in target group	e.g. improved solubility (use of salt or different salt instead of base)	
Development of dosage forms facilitating the administration of a range of doses and being acceptable to different age groups	or "less soluble form (…) to overcome taste issues, e.g. base instead of salt"	Aspects to consider: condition(s) to be treated, treatment duration, properties of active substances, necessity of particular excipients, measuring and administration devices, stability issues, dosage requirements, risk of dosing errors, ease of administration and acceptance
Consideration of special needs: minimum age, condition-related (e.g. disabilities, fluid restriction, high degree of co-medication, ability to swallow), pharmacodynamics and dose regimen, age associated activities (e.g. school, nursery), duration and frequency of therapy, environment setting, characteristics/behavior (child and caregiver)	Selection of the form of the active substance should "take into consideration the properties affecting development of paediatric medicinal products"	

Table 3.1 summarizes the general considerations and points to consider with regard to the active substances and the dosage form given in the new guideline. It once more points out that the dosage form should enable the administration of variable doses and be suitable for a large range of age groups and their special needs. Furthermore, it becomes evident that the authors of the guideline also kept in mind the competence of the caregivers of children, who are responsible for carrying out the drug administration. The taste of the active substance is discussed at the very beginning of the guideline with regard to the possible overcoming of taste issues by using less soluble forms to avoid the interaction of API molecules with the

taste buds (compare to Chapter A.3). To choose the appropriate dosage form, the properties of the active substance should be taken into account to ensure stability. Most certainly, risks regarding dosing errors or measuring devices should be considered.

***Table 3.2**: Points to consider according to the novel guideline on pharmaceutical development of medicines for pediatric use with regard to oral and oromucosal administration: oral administration, oromucosal preparations, dosing frequency, modified release preparations (EMA, 2013a).*

Oral administration	Oromucosal preparations	Dosing frequency	Modified release preparations
"Main choice (…) between liquids and solid dosage forms" Solids single-unit dosage form: stable and easy dosing approach "Oral powders, granules and liquids normally provide greater dosing flexibility than oral solid single-unit dosage forms" Liquids: avoiding multiple step procedures (risk of dosing errors) Applicants are encouraged to investigate the feasibility of bringing different dosage form (…) to the market	"Correct use and acceptability or oromucosal preparations will depend on the age of the child and the ability to keep the preparation in a specific part of the mouth over a defined period of time" Adhesive properties (if necessary) Suitable applicator needed (e.g. for dental gels, mouthwashes)	Justification according to: active substance; pharmacokinetic profile; indication; convenience; therapeutic adherence "Maximum of twice daily dosing is preferred for out-patient use" Special attention when medicines used more than twice daily (suitability of administration when no trained caregiver is around, e.g. in the kindergarten or school)	"Should not be restricted to the oral route" Prolonged release: reduced dosing frequency may be beneficial Oral solids: "risk of chewing and its impact on the efficacy and safety" Impact of physiological conditions on drug absorption

It is stated in the guideline that the use of either solid or liquid dosage forms reveals advantages (Table 3.2). Solid, single-unit dosage forms represent an easy dosage approach. However, multiparticulates, like powders or granules, and liquid preparations may be dosed even more flexible. An interesting statement in the guideline is the demand for investigating and developing several different dosage forms to serve the diversity of preferences. Depending on their experiences, children might refuse a certain dosage form; for example, the child may have experienced a very poor-tasting medicine liquid and will therefore reject all liquids. Another child may have had the same experience with tablets.

The chapter on oromucosal preparations, which is part of the chapter on oral administration, is brief. It mainly states that a correct use and acceptability of the dosage form should be given, which may depend on the age group concerned and proposes the use of applicators to facilitate administration by a caregiver. The guideline further refers to preparations that are intended to stay in the mouth for a certain time; the ability of the dosage form to adhere to a specific site in the mouth should also be considered.

The use of fast-dissolving orodispersible films will circumvent the challenge of correct use as mentioned in the guideline: simple placing in the mouth and subsequent immediate disintegration of the thin film strip does not require the application of the film to a special

absorption site and the child would have nothing to accomplish other than the natural swallowing of its saliva, where the film is dispersed (compare to Chapter A.2).

The dosing frequency is recommended to be two times daily at a maximum with regard to the background that the medicine shall be taken at home in the morning and in the evening. More doses over the day would imply ease of administration that does not require the help of a trained caregiver.

Modified release preparations are reasonable not only in terms of oral dosage forms. The advantage of prolonged release drug formulation is a reduction of the dosing frequency facilitating the therapy. However, the use of such preparations may entail the risk of varying efficacy, for example, when the dosage form is intended to stay in the mouth (compare to the aforementioned oromucosal preparations), but children may influence the drug release by chewing on the medicinal product.

***Table 3.3**: Points to consider according to the novel guideline on pharmaceutical development of medicines for pediatric use with regard to oral and oromucosal administration: excipients, acceptability, container closure system, measuring device (EMA, 2013a).*

Excipients	Acceptability	Container closure system	Measuring device
"key element of its pharmaceutical development"	Influenced by child's age, individual health status, behavior, disabilities, background and culture	Adolescent children: "discrete and portable, and when reasonable, enable individual doses"	"Specific attention should be given to the ease and accuracy of the administration."
Special safety considerations: function; safety profile (single or daily exposure); duration of treatment; severity of the condition to be treated; acceptability including palatability; allergies and sensitization	Aspects to consider: palatability, swallowability; appearance; complexity; required dose, dosing frequency and duration of treatment; administration device; container closure system; mode of administration and any related pain or discomfort	"Applicants are encouraged to consider novel packaging and administration strategies that improve child acceptability, child adherence and child caregiver convenience while reducing risk of accidental dosing errors"	Oral liquids: oral syringe = "more reliable method (…) in the youngest age groups than a spoon or a cup"
Decision tool to evaluate the safety profile of excipients	"should preferably be studied in children themselves"		
	"should also be assured during the life-cycle of the product" (e.g. changes in composition, packaging)		

The choice of excipients is another crucial factor in the development of medicinal products, especially for pediatric use. The guideline provides a detailed decision tool to evaluate the safety profile of excipients. The easiest way to ensure that an excipient can be used in a pediatric product is given as when there is a European Food Safety Agency scientific opinion (EFSA) available for the excipient supporting its use in children.

According to the guideline, there is no further justification needed to use the particular excipient. Other routes to justify the use of an excipient are given and includes when the excipient is

- included in a CHMP opinion or
- included in a Committee/CHMP/ICH guideline or
- approved in current pediatric medicines or
- included in the EU food legislation

and when the information is still up-to-date, related to the target age group and relevant to the maximum daily exposure/acceptable daily intake (ADI).

If none of this information is available on the particular excipient, additional data is required, for example, juvenile animal studies or clinical studies, or there is simply the need to reformulate and choose other excipients. The acquisition of the required additional data is connected to high costs and is not affordable for most suppliers. Consequently, nobody wants to introduce a novel excipient that has not been described elsewhere previously and will therefore consider reformulation and exclusion of the excipient.

The acceptability of medicinal products by children is highly dependent on individual conditions (compare to Chapter A.4.1). However, some aspects that have already been discussed in this section, like the taste of API, the overall palatability, dose regimen and mode of administration can nonetheless influence acceptability (Table 3.3). It is stated in the guideline that an international harmonized method for assessing acceptability is lacking and that the authorities know about variation in the outcome of acceptability trials even when same target groups are investigated. However, when discussed thoroughly, it becomes evident that reasonable benefit-risk consideration may justify the chosen method. The major focus of the chapter on acceptability is on palatability ("the overall appreciation of an (often oral) medicinal product in relation to its smell, taste, aftertaste and texture") and the ease of mixing medicines with food or drinks. Palatability is mainly influenced by the characteristics of the active substance and excipients. The guidance points out that "Information on the palatability of the active substance should consequently be acquired at an early stage in the development of a medicinal product, e.g. from dedicated adult panels or literature" (EMA, 2013a). The assessment of results from human taste panels and the acquisition of literature on the taste of specific active substances is a major challenge. Furthermore, the taste perceived by adults may significantly differ from the perception of children (Mennella and Beauchamp, 2008; Mennella et al., 2013). However, the guidance states taste assessments in an early stage in development as being important. The use of electronic taste sensing systems is an innovative approach to circumvent taste panels in the first place (compare to Chapters A.3 and E) to investigate formulations and to provide preselection for further trials before having to employ cost-intensive trials in humans.

The mixing of drugs with food and drinks is accepted as reasonable and desirable in terms of masking the taste and insufficient palatability when a formulation does not provide acceptable palatability. Therefore, effects concerning the mixing with food and drinks should be discussed for a novel formulation with regard to feasibility, stability and compatibility.

The main aspect concerning the container closure system is that the medicine can be used appropriately. A discrete and portable system should be provided for adolescent children. The authorities encourage applicants to investigate and develop innovative approaches to facilitate administration and to enhance acceptability. Measuring devices like spoons, cups or syringes should ensure adequate dosing.

The overall impression of the novel guidance is that the authorities possess an immense interest in improving and promoting the development of pediatric medicines by providing detailed considerations on how novel products should be designed. Additionally, the guideline implies that innovations in pediatric medicines are intended and should be encouraged.

A.4.2.2. Medicines for geriatric use

Older patients (> 65 years) represent another patient group with special needs. The Committee for Medicinal Products for Human Use (CHMP) published a concept paper in 2013 claiming "the need for a reflection paper on quality aspects of medicines for older people" (EMA, 2013b). The EMA encouraged the proposal of drafts to be able to provide a legal document on the development of medicines for geriatric use; such as the guideline on pediatric medicines that has recently been pulished (EMA, 2013a). The elderly is the fastest growing population group that faces similar issues in medicinal treatment as children. Geriatric and pediatric patients may be unable to swallow tablets and may need assistance of caregivers. The ease of handling of a medicinal product is an equally important issue, owed to possible physical and cognitive impairments. The physiological changes in organ funtions (e.g. hepatic, renal or gastrointestinal impairments) has to be considered in dosing regimens. Adequate and flexible dosing, adjusted to individual conditions of the patient, has to be taken into account in the pharmaceutical development of medicines.

A.5. A novel dosage form and its regulatory challenges

A.5.1. The work of the European Pharmacopoeia

The European Pharmacopoeia defines its mission as promoting "public health by the provision of recognised common standards [and] to facilitate the free movement of medicinal products in Europe [and to] ensure the quality of medicinal products and their components imported into or exported from Europe" (EDQM, 2013). The main task of the Ph.Eur. is the design of monographs to provide legal guidance for authorities and manufactures to ensure the quality of materials and products.

The European Pharmacopoeia is considered a mandatory necessity according to a convention developed by the Council of Europe in Strasbourg 1964 (Council Of Europe, 1964). Adopted protocols and the adoption of European Union Directives followed (EDQM, 2013).

There are 19 groups of experts assigned to different special fields by the European Pharmacopoeia Commission. The majority of these groups focuses on different types of substances, e.g. biological or chemical substances, sera and vaccines, blood and blood products, or particular drugs like antibiotics (EDQM, 2011). Additionally, there is a high number of working parties with a more detailed focus. Expert group 12 focuses on dosage forms and methods and discusses the elaboration and revision of monographs to ensure up-to-date and high quality guidance in the Ph.Eur. How these procedures take place is discussed in the next chapter.

A.5.2. Elaboration and revision of a monograph by the European Pharmacopoeia

To ensure monographs provide the latest information and requirements, the Ph.Eur. can be described as a constantly growing and updated compendium. The commission of the Ph.Eur. itself may decide to elaborate or revise a monograph, but it also encourages the public (e.g. individuals, manufactures) to submit drafts or to propose revisions. Once a revision or draft is submitted to the commission, it will hand the proposal to the group of experts for evaluation. If a draft is accepted for further evaluation, it is published online for a period of at least three months. During this time, comments and opinions on the draft may be sent to the Technical Secretary of the EDQM. After the modification and considerations of all received comments on the draft, the commission can decide on whether to adopt the monograph.

A.5.3. The monograph on "Oromucosal preparations"

The monograph on "Oromucosal preparations" has been revised following the aforementioned procedure. In 2010, a draft proposal was published (EDQM, 2010) that included buccal films in the chapter of "mucoadhesive preparations" (Figure 7) and a complete novel chapter was proposed on "orodispersible films" (Figure 8). The definition of

oromucosal preparations was not changed, as it complies with the newly introduced film preparations (Figure 9). However, in a future revision, the definition may be refined in more detail to meet the opportunities that are enabled by film preparations.

DEFINITION
Mucoadhesive preparations contain one or more active substances intended for systemic absorption through the buccal mucosa over a prolonged period of time. They may be supplied as mucoadhesive buccal tablets, as buccal films or as other mucoadhesive solid or semi-solid preparations. They usually contain hydrophilic polymers, which on wetting with the saliva produce a hydrogel that adheres to the buccal mucosa; in addition, **buccal films** may dissolve.

Mucoadhesive buccal tablets are prepared by compression and may be single- or multilayer tablets. **Buccal films are single- or multilayer sheets of suitable materials.**

PRODUCTION
In the manufacture of mucoadhesive buccal tablets and of buccal films, measures are taken to ensure that they possess suitable mechanical strength to resist handling without crumbling or breaking. For mucoadhesive buccal tablets this may be demonstrated by examining the Friability of uncoated tablets (2.9.7) and the Resistance to crushing of tablets (2.9.8).

TESTS
Dissolution. Unless otherwise justified and authorised, a suitable test is carried out to demonstrate the appropriate release of the active substance(s).

Figure 7: *Monograph on buccal films in the European Pharmacopoeia 8.0 – changes are underlined.*

The revised monograph was accepted and finally officially published in April 2012 (Ph.Eur., 2012b). One advantage of the final publication was the definition of general terms for oromucosal film preparations, as they were named differently depending on the manufacturer or origin, e.g., fast-dissolving film, oral wafer, edible film (Hoffmann et al., 2011). These terms are now clarified within the European Union.

DEFINITION
Orodispersible films are single- or multilayer sheets of suitable materials, to be placed in the mouth where they disperse rapidly.

PRODUCTION
In the manufacture of orodispersible films, measures are taken to ensure that they possess suitable mechanical strength to resist handling without being damaged.

TESTS
Dissolution. Unless otherwise justified and authorised, a suitable test is carried out to demonstrate the appropriate release of the active substance(s).

Figure 8: *Monograph on orodispersible films in the European Pharmacopoeia 8.0.*

The novelty of the monograph on ODFs and MBFs implies poor regulation of their production and test procedures. Nevertheless, the Ph.Eur. aims to provide suitable

information to ensure the quality of medicinal products and dosage forms. As ODFs should "disperse rapidly", the logical assumption is that there is the need for a disintegration method, e.g., as proposed for ODTs (Ph.Eur., 2012a).

> Oromucosal preparations are solid, semi-solid or liquid preparations, containing one or more active substances intended for **administration to the oral cavity and/or the throat to obtain a local or systemic effect**. Preparations intended for a local effect may be designed for application to a specific site within the oral cavity such as the gums (gingival preparations) or the throat (oropharyngeal preparations). **Preparations intended for a systemic effect are designed to be absorbed primarily at one or more sites on the oral mucosa** (e.g. sublingual preparations). **Mucoadhesive preparations are intended to be retained in the oral cavity by adhesion to the mucosal epithelium and may modify systemic drug absorption at the site of application**. For many oromucosal preparations, it is likely that some proportion of the active substance(s) will be swallowed and may be absorbed via the gastrointestinal tract.
> Oromucosal preparations may contain suitable antimicrobial preservatives and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilising, stabilising, flavouring and sweetening agents. Solid preparations may in addition contain glidants, lubricants and excipients capable of modifying the release of the active substance(s).
> Where applicable, containers for oromucosal preparations comply with the requirements for *Materials used for the manufacture of containers* (*3.1 and subsections*) and *Containers* (*3.2 and subsections*).

Figure 9: *Definition of oromucosal preparations in the European Pharmacopoeia 8.0 with highlighted aspects.*

Additionally, the monograph reveals that films should "possess suitable mechanical strength" (Ph.Eur., 2012b), which is also not described in detail. Questions arising here include, how a high quality and safe dosage form could be provided when no detailed requirements are defined. Most certainly, the Ph.Eur. follows the market situation with respect to existing products. A novel test method must not cut off an existing marketed product and manufactures appreciate the so-called "freedom to operate". However, the implementation of a standardized method should be in accordance with everyone in pharmaceutical development, who have dedicated their work to safe and high-quality medicinal products.

A.6. Film preparations - new challenges and opportunities

With respect to the regulatory aspects and the novelation in the official monograph that are described in the previous chapter, it becomes obvious that oromucosal film preparations are of great interest. This sections aims to give a brief update on recently published findings.

A.6.1. Manufacturing

Films are mostly prepared by solvent casting, meaning the preparation of a polymer solution that is subsequently cast on a plane surface. The solvent will evaporate during the following drying period and a thin film remains that can be further processed, i.e., cutting and packaging (Hoffmann et al., 2011). Other manufacturing methods may be reasonable, such as laminar hot-melt extrusion to avoid the use of solvents, especially when the processed API has stability issues (Repka et al., 2005; Repka et al., 2003). However, hot-melt extrusion has not been a method of choice thus far, but it will, nonetheless, offer new opportunities especially in modified drug release formulations (Low et al., 2013). More details on manufacturing methods are provided in Chapter B and C.

The preparation of films for oromucosal drug delivery can be challenging compared to other dosage forms. Nevertheless, films offer many opportunities with respect to the way the drug is released in the mouth (compare to Chapter A.2) and the dosing flexibility (Figure 6, Chapter A.4.1.). The importance of flexible doses is discussed in a previous chapter (A.4.2.1.) and focuses on requirements for pediatric dosage forms. An interesting and promising approach is the use of printing technologies, where an API solution or suspension is printed onto the film surface (Janßen et al., 2013, Genina et al., 2013). This new opportunity in manufacturing reveals several advantages, as the API is not involved in the film preparation itself. Furthermore, individual doses could be printed onto the films, or different APIs could be printed next to each other that would interact when being processed together, thereby avoid incompatibility (Kolakovic et al., 2013).

A.6.2. Recent advances in the characterization of film preparations

The latest literature research reveals that there are several novel scientific approaches with regard to film preparations. In addition to investigations on orodispersible films as dosage forms for drug nanosuspensions (Shen et al., 2013) and the buccal delivery of peptides that is described in a study by Giovino et al. (2013) using insulin-loaded nanoparticles that are embedded in a chitosan-based film preparation, the characterization of film preparations and the evaluation of film properties is described in current research:

Similar pharmacokinetics of a fast-dissolving film and an oral solution containing ondansetron in rats has been found; these findings encourage the use of films as an alternative oral dosage form (Choudhary et al., 2013).

Most recently, a novel approach in dissolution testing of ODFs has been published. A flow-through system with saliva flow mimicking media flow rates of 1.23 – 493 mL/min was developed (Xiu et al., 2014), which can lead to more realistic dissolution profiles.

The microstructural characterization of films by positron annihilation lifetime spectroscopy to determine free volume fractions and free volume size distributions in solids has been introduced and could be correlated to drug release (Szabó et al., 2014).

Porous versus nonporous films with respect to mucoadhesive and drug delivery aspects were investigated by Kumar et al. (2013) and the study revealed advantages of porous films.

Insight into the effects of in vitro parameters of mucoadhesive buccal films on their in vivo properties are described in a novel study by Vetchy et al. (2014). The use of porcine or sheep mucosa to investigate mucoadhesive properties can be found in recent literature (Govindasamy et al., 2013; Shiledar et al., 2014). However, the use of alternative materials like agar gel layers is investigated to circumvent the need for animal mucosa (Giovino et al., 2013).

Experimental design, in this case a 3^2 factorial design, has been employed to investigate the influenced film characteristics like buccoadhesion, swelling index, and disintegration time, when the amount of film-forming agent and filler was varied (Chakraborty et al., 2013).

Process analytical technology in film manufacturing by means of the in-line measurement of the drug content has been introduced by Hammes et al. in 2014. The study describes the use of an infrared sensor during the coating and drying process of a film to quantify the drug content, which allows a real-time process adjustment when the desired drug content is not achieved or exceeded.

The research on orodispersible and buccal films is increasing. Novel therapeutic areas are addressed and the introduction of quality control tools, such as the use of experimental design and process analytical technology, points out the industrial interest in this innovative dosage form.

A.7. Aims of the thesis

This thesis aims to gain a better understanding about ODFs and MBFs as pharmaceutical products. It should reveal the latest findings and outline the needs in requirements for providing a high quality pharmaceutical product. The novelty of the monograph implies a low limit of requirements that may be, in terms of industry, to ensure the freedom to operate. Nevertheless, from a scientific point of view, there is the need for more specifications and standardized characterization methods.

The aims of this thesis were:

To gain experience in the development of film formulations in order to develop and provide suitable methods to characterize a novel dosage.

To develop test systems for investigating disintegration behavior, mechanical strength and drug dissolution with respect to pharmacopoeial definitions.

A dosage form that is intended to stay in the mouth /to release the drug substance in the mouth is a major challenge in pharmaceutical development with regard to taste.

Therefore, further aims were:

To investigate the use of taste-masking techniques in the formulation design of oromucosal film preparations.

To investigate the use of maltodextrin as a harmless potential complexing and taste-masking agent for pediatric purposes, through the use of electronic tongue studies.

To evaluate the transfer of taste-masking techniques derived for liquids to film preparations, including novel experimental setups.

To compare and further establish commercially available electronic tongue systems by conducting experiments to reveal limits and opportunities.

A.8. Outline of the thesis

The present thesis is based on five parts:

- Introduction (Chapter A)
- Overview: oromucosal film preparations and classifications (Chapter B)
- Formulation development (Chapter C)
- Characterization methods (Chapter D)
- Electronic taste sensing (Chapter E)

Orodispersible and buccal films are innovative dosage forms and despite the most recent implementation of these preparations in the European Pharmacopoeia, research in this field has already been conducted for a number of years. The survey in Chapter B aims to point out the different types of film preparations and to summarize the proposed characterization methods described in the scientific literature. Film preparations are described in detail and different approaches like the determination of disintegration and dissolution behavior, mechanical properties, solid state, mucoadhesion and taste assessment are discussed. The literature reveals a high number of characterization methods; unfortunately, in all these years of research, gold standard methods have yet to be determined. The findings of this literature review intends to reveal the absence of standardized methods and to encourage the demand for novel approaches.

To be able to develop and provide suitable methods to characterize a novel dosage, experience gain in the development of formulations needs to be aspired (Chapter C.1). An orodispersible film containing dimenhydrinate, a popular drug for the treatment of vomiting and nausea especially in children, has been developed and the use of maltodextrin, sweetener and different cyclodextrins were investigated with regard to the suitability for a film formulation and taste-masking capacities. A film-forming polymer derived from pea starch was investigated, which has not been described in detail in the literature so far. Disintegration behavior has been studied using methods derived from the literature. The application of commercially available electronic tongues to assess taste-masking properties of masking agents was investigated and a novel procedure was introduced to enable the assessment of orodispersible films.

The second approach in formulation development was aimed at investigating the preparation of bilayered buccal films (Chapter C.2). The local anesthetic lidocaine hydrochloride was used as a model drug. The idea was to develop a buccal film with a backing layer that can be attached to the oral mucosa. To avoid drug release in the oral cavity and to ensure the release towards the oral mucosa, various methods are investigated to manufacture film bilaminates. Different polymers and solvents are processed and findings and experiences in formulation development are discussed. Additionally, an optimized setup

is presented to monitor the drug release out of the bilayered buccal films from the very beginning by means of a fiber-optic spectroscopy probe.

To date, there are no standardized methods available for assessing mucoadhesive properties. However, mucoadhesive preparations are defined in the Ph.Eur. The literature review in Chapter D.1 provides an overview, including research papers of the last 30 years on test methods, to determine mucoadhesion. The survey reveals a lack of methods applicable for a wide range of polymers and dosage forms, large diversities in set parameters and the lacking correlation to in vivo measurements. The findings of the literature research should point out the strong need for standardized methods.

As a certain mechanical strength of film preparations is required by the competent authorities, a study has been conducted to develop a test system that can be used for films of diverging sizes (Chapter D.2). The literature reveals standardized tensile tests for other materials that may be transferred, but require certain shapes of specimen and no limits are defined to ensure suitable mechanical properties. In order to develop a system that is suitable for either marketed film products or films under development, the evaluation of the method takes place with regard to marketed product properties. To gain an impression of "suitable mechanical strength", as it is requested in the Ph.Eur., reference materials known by daily use (paper, facial tissue, foil) are included for investigation. Finally, results of marketed film products, reference materials and film samples are provided, for which it could not be determined whether they had been described elsewhere in literature to date. The samples are evaluated according to the marketed film products to provide results that are "following the actual market situation".

Rapid dispersion is described as the main property of orodispersible films according to the European Pharmacopoeia. Nevertheless, there is no suitable disintegration test available. It is evident from the literature that there are many innovative approaches available, but the detection of the disintegration end-point is challenging in most cases. Two new approaches are developed and evaluated in order to provide tests with a clear end-point that can either be detected automatically or visually (Chapter D.3). The one test is equipped with a time clock to register the disintegration, while the other aims to provide a sample holder that can be adapted to a conventional tablet disintegration tester. The study aims to evaluate the feasibility of both approaches in the characterization of orodispersible films.

The assessment of taste attributes of medicinal products is gaining interest in pharmaceutical development, not least because of the novel guideline on pediatric medicines, which underlines the importance of palatable and acceptable products. Taste-masking of poor tasting active substances or excipients is accomplished by different approaches and the evaluation of results has been found to be inconsistent. Therefore, a literature research has

been conducted to point out different ways to assess taste-masking with respect to in vivo data, drug release studies and electronic tongue measurements (Chapter E.1).

The electronic tongue provided by Insent® has been qualified according to ICH guideline Q2 before (Woertz, 2010). In a first attempt, the qualification of the second commercially available system, the αAstree, failed. After the supplier provided novel sensor batches, a novel measurement protocol has been investigated and the performance qualification is conducted according to the new findings (Chapter E.2).

The use of a novel maltodextrin product and hydroxypropyl-ß-cyclodextrin as taste-masking and solubilizing agents in the development of film formulations has previously been investigated (Chapter C.1). To compare the use of these excipients in more detail, a study has been conducted using three low-dose APIs that are known for poor taste (dextromethorphan HBr, cetirizine HCl, loperamide HCl). An electronic tongue study has been performed evaluating different amounts of the additive mixed with the APIs (Chapter E.3).

Finally, interesting findings for the new maltodextrin product line have been investigated further, using ibuprofen sodium as model drug (Chapter E.4). The novel maltodextrin has been compared to conventional maltodextrin grades and different types of cyclodextrin (α-, ß-, γ- and hydroxypropyl-ß-cyclodextrin) by means of electronic taste sensing. The aim of the study is to determine the potential use of the maltodextrin as a taste-masking component for an alternative liquid formulation of ibuprofen.

Chapter A

Introduction

Chapter B

State-of-the-art:
Oromucosal film preparations: classification and characterization methods

Chapter C

Formulation development of oromucosal film preparations

- Development of a taste-masked orodispersible film containing dimenhydrinate
- Design and evaluation of bilayered buccal film preparations for local administration of lidocaine hydrochloride

Chapter D

Test systems to characterize oromucosal film preparations

- Assessment of test methods evaluating mucoadhesive polymers and dosage forms: An overview
- Mechanical strength test for orodispersible and buccal films
- Comparative study on novel test systems to determine disintegration of orodispersible films

Chapter E

Electronic taste sensing in formulation development

- Taste-masking assessment of oral solid dosage forms – a critical review
- New protocol for αAstree electronic tongue enabling full performance qualification according to ICH Q2
- A comparative study on solubilizing and taste-masking capacities of hydroxypropyl-ß-cyclodextrin and maltodextrins with high amylose content
- Application of electronic tongues in preformulation studies to evaluate taste-masking capacities of maltodextrins

Figure 10. *Overview: outline of the thesis*

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Xia, Y., Chen, F., Zhang, H., Luo, C., 2014. A new method for evaluating the dissolution of orodispersible films. Pharmaceutical Development and Technology, article in press, DOI: 10.3109/10837450.2014.882936

B. Oromucosal film preparations: classification and characterization methods

This chapter provides an initial overview on the state of the art with regard to oromucosal film preparations. The literature review points out the different types of oromucosal film preparations and to summarize the proposed characterization methods described in the scientific literature. Film preparations are described in detail and different approaches like the determination of disintegration and dissolution behavior, mechanical properties, solid state, mucoadhesion and taste assessment are discussed. The literature reveals a high number of methods, unfortunately, within all these years of research, gold standard methods are hardly to be determined. The findings of this literature review intended to reveal the absence of standardized methods and to encourage the demand for novel approaches.

The following literature review has been published by Expert Opinion on Drug Delivery in 2013 (Impact factor 2013: 4.116). The first author, Maren Preis, is responsible for the concept, literature research and evaluation, and writing of the manuscript. Prof. Dr. Dr. h.c. Peter Kleinebudde is responsible for evaluation and revision of the manuscript. Prof. Dr. Jörg Breitkreutz, listed as senior authors, is responsible for the concept and ideas as well as revision of the manuscript. Christina Woertz was responsible for the concept and writing of the chapter on mucoadhesion, and for revision of the manuscript.

Oromucosal film preparations: classification and characterization methods

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C. Formulation development of oromucosal film preparations

C.1. Development of a taste-masked orodispersible film containing dimenhydrinate

This chapter deals with the exemplary pharmaceutical development of an orodispersible film. Excipients are investigated with regard to their taste-masking capacities to be evaluated by two electronic tongues. A film-forming polymer derived from pea starch is introduced, which has not been described in detail in literature so far. The disintegration behavior has been studied using modified methods derived from literature. Finally, the application of commercially available etongues to assess taste-masking properties of masking agents has been investigated and a novel procedure is introduced to enable the assessment of orodispersible films.

The following research paper has been published by Pharmaceutics in 2012, which is a new open-access, focused journal. The first author, Maren Preis, is responsible for the concept, experimental work, and writing of the manuscript. Dr. Miriam Pein is responsible for the concept and revision of the manuscript. Prof. Dr. Jörg Breitkreutz, listed as senior author, is responsible for the concept and ideas as well as revision of the manuscript.

Development of a taste-masked orodispersible film containing dimenhydrinate

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C.2. Design and evaluation of bilayered buccal film preparations for local administration of lidocaine hydrochloride

Another approach in formulation development aims to investigate the preparation of bilayered mucoadhesive buccal films. The idea was to develop a buccal film with a backing layer that can be attached to the oral mucosa. To avoid drug release in the oral cavity, and to ensure the release towards the oral mucosa, various methods are investigated to manufacture film bilaminates. Different polymers and solvents are processed and findings and experiences in formulation development are discussed. Additionally, an optimized setup is introduced to monitor the drug release out of the bilayered buccal films from the very beginning by means of a fiber-optic spectroscopy probe.

The following research paper has been published by the European Journal of Pharmaceutics and Biopharmaceutics in 2014 (Impact factor 2013: 4.245). The first author, Maren Preis, is responsible for the concept, experimental work, and writing of the manuscript. Christina Woertz and the undergraduate students Katharina Schneider and Jennifer Kukawka participated in experimental work guided by the first author. Prof. Dr. Jörg Breitkreutz, listed as senior author, is responsible for the concept and ideas as well as revision of the manuscript. Prof. Dr. Dr. h.c. Norbert Roewer and Dr. Jens Broscheit have initiated the work by funding and are responsible for revision of the manuscript.

Design and evaluation of bilayered buccal film preparations for local administration of lidocaine hydrochloride

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D. Test systems to characterize oromucosal film preparations

D.1. Assessment of test methods evaluating mucoadhesive polymers and dosage forms: An overview

To date, there are no standardized methods available to assess mucoadhesive properties. The following chapter is a description of mucoadhesion test methods and provides an overview including research papers of the last 30 years.

The chapter supplies information on mucoadhesive polymers and the principles of available methods, which are either based on mechanical force determination or particle interactions. Furthermore, studies providing in vivo results of mucoadhesion performance or residence time of preparation are discussed.

The literature review has been published by the European Journal of Pharmaceutics and Biopharmaceutics in 2013 (Impact factor 2013: 4.245). The first author, Christina Woertz, is responsible for the idea, concept, literature research, structure and writing of the manuscript. Maren Preis is responsible for the fundamental idea, literature research and revision of the manuscript. Prof. Dr. Jörg Breitkreutz, is responsible for revision of the manuscript. Prof. Dr. Dr. h.c. Peter Kleinebudde, listed as senior author, is responsible for the concept and revision of the manuscript.

Assessment of test methods evaluating mucoadhesive polymers and dosage forms: An overview

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D.2. Mechanical strength test for orodispersible and buccal films

The development of a characterization method in order to provide a system that can be used for films of diverging sizes, is described in this chapter.

A test is developed aiming to provide values for "suitable mechanical strength" as required by the pharmacopoeial monograph, since there are no limits given that indicate for the appropriateness of a film preparation. In order to develop a system that is suitable for either marketed film products or film preparations under development, the evaluation is conducted with regard to marketed product properties. The results of marketed film products, reference materials and film samples are provided, which could not be determined being described elsewhere in literature so far.

The research paper has been published by the International Journal of Pharmaceutics in 2014 (Impact factor 2013: 3.785). The first author, Maren Preis, is responsible for the idea, concept, experimental work, and writing of the manuscript. Dr. Klaus Knop is responsible for ideas and revision of the manuscript. Prof. Dr. Jörg Breitkreutz, listed as senior author, is responsible for the concept and ideas as well as revision of the manuscript.

Mechanical strength test for orodispersible and buccal films

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D.3. Comparative study on novel test systems to determine disintegration time of orodispersible films

The experiments presented in this chapter focus on the development and evaluation of two novel approaches to determine the disintegration of orodispersible films.

The tests are developed and evaluated in order to provide systems with a clear end-point that can either be detected automatically or visually. One test is equipped with a time clock to enable automatic end-point detection, when the film disintegrates; the other tester provides a new sample holder that can be adapted to conventional tablet disintegration testers. The feasibility of both approaches in the characterization of orodispersible films is investigated throughout this study.

The research paper has been published by the Journal of Pharmacy and Pharmacology in 2014 (Impact factor 2013: 2.161). The first author, Maren Preis, is responsible for the concept, experimental work, and writing of the manuscript. The undergraduate students Dorothee Gronkowsky and Dominik Grytzan participated in the guided experimental work. Prof. Dr. Jörg Breitkreutz, listed as senior author, is responsible for the concept and ideas as well as revision of the manuscript.

Comparative study on novel test systems to determine disintegration time of orodispersible films

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E. Electronic taste sensing in formulation development

E.1. Taste-masking assessment of solid oral dosage forms – a critical review

Taste-masking of poor tasting active substances or excipients is accomplished by different approaches and the evaluation, and interpretation of the results is described in this chapter.

The literature research points out different ways to assess taste-masking with respect to in vivo data, drug release studies and electronic tongue measurements, and the correlation of these data.

The chapter mainly serves as an introduction to describe the critical aspects of taste assessment and the evaluation of study results with respect to the efficacy of taste-masking approaches.

The following literature review has been published by the International Journal of Pharmaceutics in 2014 (Impact factor 2013: 3.785). The first author, Dr. Miriam Pein, is responsible for the concept, literature research and evaluation, and writing of the manuscript. Maren Preis participates in the development of the concept and writing of chapters on in-vivo taste panels and in-vitro taste assessments by electronic tongues and is responsible for revision of the manuscript. Carolin Eckert and Florian Kiene are responsible for literature research, as well as revision of the manuscript, and participated in writing of the manuscript.

Taste-masking assessment of solid oral dosage forms – a critical review

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E.2. New protocol for αAstree electronic tongue enabling full performance qualification according to ICH Q2

As the first attempt to qualify the αAstree electronic tongue failed in a previous study, this chapter describes the second approach to qualify the system according to ICH guideline Q2. Novel sensor batches are used and the development of an alternative measurement protocol has been conducted. Further, the comparison of two sensor sets, one for pharmaceutical applications and one for food administration is investigated.

The following research paper has been published by the Journal of Pharmaceutical and Biomedical Analysis in 2013 (Impact factor 2013: 2.829). The first author, Dr. Miriam Pein, is mainly responsible for the concept, experimental work and writing of the manuscript. Maren Preis and Carolin Eckert participate in the experimental work and the revision of the manuscript. Prof. Dr. Jörg Breitkreutz, listed as senior author, is responsible for the idea and revision of the manuscript.

New protocol for αAstree electronic tongue enabling full performance qualification according to ICH Q2

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E.3. A comparative study on solubilizing and taste-masking capacities of hydroxypropyl-ß-cyclodextrin and maltodextrins with high amylose content

The presented study in this chapter describes the evaluation of a new promising maltodextrin product with high amylose content. To compare the use of this excipient in more detail, a study has been conducted using three low-dose APIs, which are known for poor taste (dextromethorphan HBr, cetirizine HCl, loperamide HCl). The electronic tongue study has been performed evaluating different amounts of the additive mixed with the API.

The use of two commercial electronic tongues is reasonable to obtain information on formulations without the need of human sensory panels in first place, when comparing them to a neutral or good tasting corresponding drug-free formulation.

The following research paper has been published by Sensors and Actuators B: chemical in 2014 (Impact factor 2013: 3.840). The first author, Maren Preis, is responsible for the concept, experimental work, and writing of the manuscript. Carolin Eckert is responsible for experimental work and revision of the manuscript. Dr. Olaf Häusler is responsible for the idea and revision of the manuscript. Prof. Dr. Jörg Breitkreutz, listed as senior author, is responsible for the concept and ideas as well as revision of the manuscript.

A comparative study on solubilizing and taste-masking capacities of hydroxypropyl-ß-cyclodextrin and maltodextrins with high amylose content

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E.4. Application of electronic tongues in preformulation studies to evaluate taste-masking capacities of maltodextrins

The interesting findings for the new maltodextrin productline are further investigated in this chapter using ibuprofen sodium as model drug.

The study describes the comparison of the novel maltodextrin to conventional maltodextrin grades and different types of cyclodextrin (α-, ß-, γ- and hydroxypropyl-ß-cyclodextrin) by means of electronic taste sensing. The aim of the study is to determine the potential use of the maltodextrin as a taste-masking component for an alternative liquid formulation of ibuprofen.

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Application of electronic tongues in preformulation studies to evaluate taste-masking capacities of maltodextrins

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Conclusions and future perspectives

Chapter B: Oromucosal film preparations – classification and characterization

Film preparations for application in the oral cavity are a novel and interesting approach in drug delivery. Despite the fact that the European Pharmacopoeia introduced different types of film preparations (orodispersible and buccal films), the monograph lacks specifications. It is therefore a tremendeous need to introduce standardized test procedures to characterize this novel dosage form, not least with regard to quality aspects of marketed products.

Chapter C: Film formulation development:

The results of the present thesis revealed the successful design of orodispersible films that disintegrate rapidly. It has become evident from the results that thickness and amount of excipients influence the time needed by the film to disintegrate. The solubility enhancing effects of the novel maltodextrin quality and the investigated cyclodextrins could be determined for various solid film formulations resulting in transparent film with no apparent crystal growth, which was validated by polarized light microscopy and X-ray. Further, the novel protocol of the αAstree electronic tongue enabled the opportunity for including two commercially available systems in the study. The complementary use of the obtained data from two electronic tongues resulted in an even sharper outcome when comparing different taste-masking approaches.

The second approach revealed that it was feasible to apply the backing layers on the drug-loaded layers to achieve bilayered buccal films. The polymers should be chosen carefully with regard to the final properties of the film. The manufacturing of bilayered films can be performed in several ways, whereas the application of small drug-loaded layers on larger backing layers was found most suitable; however, depending on the polymer used, appropriate shielding by the backing layer could only be confirmed for hypromellose layers during the dissolution experiments in this particular study.

With respect to the numerous polymers providing widely differing properties that are available today, film preparations may be designed with the desired properties. This could be either rapidly dissolving films, slowly or moderately dissolving ones, or even films that only swell on the saliva wetted mucosa with the need to be removed after the drug release.

The choice of film type is highly dependent from the active substance that is desired to be administered. Not all active substances are feasible for oromucosal absorption (see Chapter A.2) and some may require too high doses to be appropriately implemented into a film formulation.

Chapter D: Appropriate test systems to characterize oromucosal film preparations:

European Pharmacopoeial defaults that are only describing "suitable mechanical strength" for ODFs and buccal films are indeed a commitment for the pharmaceutical industry. When the films can be produced, then they accordingly provide suitable mechanical strength. However, to understand the crucial aspects that need consideration in formulation development from a scientific point of view, there is the tremendous need to validate these formulations through appropriate test methods. Therefore, the puncture test was developed to enable a method that is easy to adopt by everyone working on film formulations. Finally, results of marketed film products, reference materials and film samples can be provided, the nature of which could not be determined as being described elsewhere in literature to date. The samples were evaluated according to the marketed film products and a minimum limit for mechanical strength could be set that is considered to be following the market situation.

The rapid disintegration of ODFs is another aspect that was addressed in this thesis. As described for the mechanical strength test, a method was needed to clearly determine the disintegration of ODFs. This is of immense importance with respect to safety and quality aspects. It needs to be ensured that the ODF disintegrates to avoid the danger of aspiration or choking. The study displayed the feasibility of both approaches in the characterization of orodispersible films. The sample holder that was adapted to the conventional disintegration tester may provide a suitable system; also for industrial purposes. Multiple films could be investigated at the same time and a clear end-point is provided that might not be correlated to in vivo disintegration times, but would however, ensure the consistence and quality of the product.

Chapter E: Electronic taste assessment in formulation development:

Finally, the αAstree could be proven to successfully provide reliable results, once the new measurement protocol has been conducted. It turns out that the proposed setups by the suppliers lacked scientific reconsideration in some cases and a scientific revision of procedures and the demand for different product batches will lead to an improved performance of provided systems.

The use of electronic tongues is reasonable for obtaining information on formulations without the need for human sensory panels in first place when comparing them to a neutral or good tasting corresponding drug-free formulation. It was evident that the electronic tongue was feasible for detecting differences in the investigated samples and reduced responses of bitterness sensors could, for example, be claimed for the maltodextrin and cyclodextrin used in this study. Additionally, the limited solubility of dextromethorphan and loperamide could be increased either by the novel quality line of maltodextrin or the cyclodextrin.

It was found that the new maltodextrin quality line containing high amounts of amylose and long glucose chains resulted in taste-masking effects allied to those of ß- and hydroxypropyl-ß-cyclodextrins, according to the sensory results. Furthermore, the electronic tongue was able

to detect the difference in effects due to the slight sweetening and the glucose backbone chains of the maltodextrin compared to the cyclodextrin.

Future perspectives:

Different aspects in the formulation development and characterization of oromucosal film preparations were addressed in this thesis. With regard to the present situation in the market, oromucosal films are an emerging field. The number of newly licensed products is increasing and although the public in Europe might still need time to get used to a new and innovative way for drug administration, there is the belief that patients and caregivers will be convinced by the convenience of this innovative dosage form.

There will be further optimization of today's formulations and the latest information reveals an upcoming trend, which is for example the delivery of peptides via the oral mucosa. Many active substances are considerable for oromucosal drug delivery via films, especially low dose drugs for daily intake, such as oral contraceptives or thyroid hormones.

Still, there is the need for appropriate characterization methods. This thesis aimed to propose potential test methods for ensuring and evaluating novel and existing products and to underline the tremendous need for standardized protocols. In terms of mucoadhesion, the future is expected to favorably bring a standardized solution for determining the adhesive properties of films, perhaps by revealing a novel synthetic material providing mucosa mimicking characteristics to enable the evaluation of adhesiveness.

As the developed sample holder for the conventional disintegration tester has been adopted by a company specializing in the design and construction of disintegration and dissolution test systems, future studies will reveal, if the developed tester will catch on in the pharmaceutical development of film preparations.

Electronic taste sensing is an emerging field and besides the two available systems on the market, the scientific community is developing numerous alternative approaches. It will be interesting to see how this development progresses. The more studies are conducted by means of electronic tongues that could be correlated to human taste panels, the more information can be collected and evaluated regarding the quality of predictions obtained from these tools.

Summary

Oromucosal film preparations, namely orodispersible films and buccal films, as defined by the European Pharmacopoeia, are innovative, new oral dosage forms. Placed in the mouth, the films disperse rapidly or are attached to the mucosal site. These films can either be used as an alternative form of peroral administration, without the need for swallowing large tablets and capsules, or deliver the active substance directly via the oral mucosa to the systemic blood stream. As such, they represent a promising and convenient new dosage form with the potential to facilitate drug administration, especially among patient groups facing issues like swallowability, e.g. children and the elderly.

Following extensive study of the literature, the results have been summarized and critically discussed in three separate literature reviews focusing on different aspects of the thesis' purpose:

- classification and the latest findings in film characterization
- methods to determine mucoadhesion
- assessment of taste-masking in solid oral dosage forms

Different aspects of film manufacturing and characterization have been addressed in the experimental part of the present thesis:

- monolayered orodispersible films and bilayered mucoadhesive buccal films
- development of test systems to investigate disintegration and mechanical strength
- preformulation analysis using electronic tongues

Orodispersible films containing dimenhydrinate, a drug that is commonly used to treat vomiting and nausea, especially in children, could be developed. In order to create a product that not only dissolves rapidly when it comes into contact with water or saliva, but that also has an acceptable taste, the films were submitted to several tests evaluating dissolution and investigating taste-related properties with electronic taste sensing systems. These so-called electronic tongues are based on a potentiometric mechanism and feature sensors that are equipped with lipid membranes, enabling comparisons between drug formulations, pleasant-tasting, drug-free formulations and the pure drug substance. The comparative study revealed that the use of cyclodextrins and maltodextrins as taste-masking agents influenced the in vitro taste attributes detected by the electronic tongue. The main advantage of electronic tongues is that they circumvent human sensory assessment. Furthermore, it was possible to use both available electronic tongues for the study and the data could be evaluated comparatively. In the past, one system had failed the performance qualification and did not provide reliable results. While working on this thesis, this system was rehabilitated thanks to new sensor batches and the introduction of a new measurement protocol.

Furthermore, a buccal film with two layers (the outer drug-free layer shields the oral cavity from the drug-loaded layer) has been developed. Numerous polymers were investigated. Fiber-optic spectroscopy was used to assess the drug-free layer's capacity to shield the drug release. Hypromellose was found to be the most promising polymer in this regard. The drug dissolution study showed that the hypromellose layer shielded the drug-loaded layer long enough to allow the drug-loaded layer, which disintegrated very rapidly, to dissolve.

Due to the novelty of the dosage form and its recent inclusion in the European Pharmacopoeia, no test methods have yet been defined to characterize and validate the test systems developed.

Another research aim was to develop test systems capable not only of determining whether the films could withstand the mechanical stresses of handling and processing without damage, but also to investigate their disintegration behavior.

To assess the films' mechanical properties, a sample holder was constructed to facilitate the measurement of films of different sizes and shapes. The sample holder was used in a puncture test, performed with a universal force detection apparatus. In order to provide a measurement setup that could be adopted easily and that enables obtaining data of reference materials, marketed film products and developed film samples, this novel approach has been presented. It has not been found to be conducted elsewhere thus far. Finally, the evaluation of the results could be performed by comparing the developed samples to actual marketed products and their properties.

To assess the disintegration of orodispersible films in contact with fluid, two different test systems were developed to provide accurate end-point detection. The basic principle was the attachment of a small weight at the bottom of the film prior to having contact to the test medium. The weight falling down indicated the disintegration of the film. One system automatically registered the disintegration time by means of a clock connected to an electronic measuring device. The second system was designed to resemble as closely as possible the conventional disintegration tester used for tablets. Both systems were proved suitable for the intended purposes.

The potential of electronic taste sensing was further investigated in several studies conducted to evaluate taste-masking approaches. A new maltodextrin line found to provide taste-masking and solubility-enhancing properties in the dimenhydrinate film study was explored in more detail. Solubility studies with other pharmaceutical ingredients were performed and taste-masking effects were compared to other maltodextrin grades and cyclodextrin types.

In this thesis, oromucosal film preparations were developed and characterized. New test systems were introduced and their appropriateness to characterize film preparations was investigated with the aim to provide specifications in terms of quality requirements. Another goal was demonstrating the features of electronic tongues as an alternative to human taste panels in the investigation of the taste of formulations.

Zusammenfassung

In dieser Arbeit wurden filmförmige Zubereitungen zur oralen Anwendung untersucht und eigene Zubereitungen entwickelt. Neue Testsysteme wurden entwickelt und deren Eignung zur Charakterisierung dieser neuen Darreichungsform wurde überprüft, sodass mithilfe dieser neuen Tests potentiell Qualitätsanforderungen an die Zubereitungen festgelegt werden können. Ein weiterer Schwerpunkt wurde auf die Untersuchung der geschmacklichen Eigenschaften der Zubereitungen gelegt und hierzu die vielversprechende Verwendung von elektronischen Zungen als Alternative zu humanen Geschmackstests untersucht.

Oromukosale filmförmige Zubereitungen, in dieser Arbeit „orodispersible oder bukkale Filme“ genannt, wie in der englischen Fassung des europäischen Arzneibuches definiert, sind innovative Darreichungsformen. In den Mund gelegt, zerfallen sie in kürzester Zeit, oder sie werden auf der Mundschleimhaut appliziert. Diese Filme können auf zwei Arten im Mund angewendet werden: zum einen als alternative perorale Darreichungsform, durch die die Einnahme und das Schlucken von großen Darreichungsformen, wie Tabletten oder Kapseln vermieden werden können, oder zum anderen kann die aktive Substanz direkt über die Aufnahme durch die Mundschleimhaut systemisch bereitgestellt werden. Filmförmige Zubereitungen zur oralen Anwendung repräsentieren eine neue, vielversprechende und anwendungsfreundliche Arzneiform, die die Arzneimittelgabe potentiell vereinfacht. Dies ist besonders interessant für Patientengruppen, wie Kinder oder ältere Menschen, für die das Schlucken von Arzneimitteln eine Herausforderung darstellen kann.

Das Ziel dieser Dissertation war es, auf Basis der aktuellsten Erkenntnisse, filmförmige Zubereitungen und dazugehörige Methoden zur Charakterisierung zu entwickeln. Besonderes Augenmerk wurde dabei auf den Geschmack der Arzneiformen gelegt, da sich diese für eine längere Zeit im Mund befinden kann.

Die Literaturrecherche im Rahmen dieser Arbeit wurde in Form von drei separaten Übersichtsartikeln zusammengefasst und kritisch diskutiert. Mit den folgenden Aspekten wurde sich beschäftigt:

- Klassifizierung von Filmzubereitungen und die neuesten Fortschritte in der Arzneiformcharakterisierung
- Methoden zur Bestimmung der Mukoadhäsion
- Bestimmung von geschmacksmaskierenden Eigenschaften in festen Arzneiformen

Im experimentellen Teil dieser Arbeit wurde sich mit verschiedenen Aspekten der Filmherstellung und –charakterisierung befasst:

- einschichtige orodispersible filme und zweischichtige mukoadhäsive bukkale Filme

- Entwicklung von Testsystemen zur Untersuchung des Zerfalls und der mechanischen Festigkeit
- Analyse von Präformulierungen mithilfe von elektronischen Zungen

Im ersten Abschnitt der praktischen Arbeit wurden orodispersible Filme mit dem Wirkstoff Dimenhydrinat entwickelt. Dieser Wirkstoff wird überwiegend zur Behandlung von Schwindel und Übelkeit, insbesondere bei Kindern, eingesetzt. Bei der Produktentwicklung wurde neben einem akzeptablen Geschmack auch auf das schnelle Zerfallen im Mundraum, sobald das Arzneimittel mit Speichel in Kontakt tritt, Wert gelegt. Der Zerfall wurde mit geeigneten Methoden und die geschmacklichen Eigenschaften mithilfe von elektronischen Geschmackstestsystemen untersucht. Diese so genannten elektronischen Zungen basieren auf potentiometrischen Messmechanismen und bestehen aus Sensoren, die mit Lipidmembranen überzogen sind (simulierte Biomembran). Diese Sensoren reagieren auf verschiedene geschmacksübermittelnde Moleküle mit Potentialänderungen, wodurch zwischen arzneistoffhaltigen Zubereitungen, angenehm schmeckenden arzneistofffreien Zubereitungen und reinem Arzneistoff verglichen werden kann, um Hinweise auf die geschmacklichen Qualität zu erhalten. Die Vergleichsstudie hat ergeben, dass die Verwendung von Cyclodextrinen und Maltodextrinen als geschmacksmaskierende Agentien die in-vitro detektierten geschmacklichen Eigenschaften des Arzneistoffs beeinflussen konnten. Der besondere Vorteil der elektronischen Zungen ist die Tatsache, dass Geschmackstests am Menschen zunächst umgangen werden können, um einen ersten Eindruck über eine neue Formulierung zu erhalten. Außerdem war es möglich, beide kommerziell erhältlichen elektronischen Zungen für diese Studie zu verwenden und so die Daten vergleichend und gemeinsam auszuwerten. In der Vergangenheit konnte eines der beiden Geräte nicht nach internationalen analytischen Standards qualifiziert werden, sodass keine verlässlichen Ergebnisse erzielt werden konnten. Während der Arbeit an dieser Dissertation konnte durch die Verwendung von neuen Sensorchargen und der Einführung eines neuen Messprotokolls das System rehabilitiert werden.

Des Weiteren wurden im Rahmen dieser Arbeit zweischichtige bukkale Filme entwickelt (die äußere arzneistofffreie Schicht schirmt den Mundraum von der arzneistoffhaltigen Schicht ab). Eine Vielzahl von Polymeren wurde auf ihre Eignung als Filmbildner untersucht. Eine faseroptische Sonde zur UV-Spektroskopie wurde verwendet, um die Fähigkeit der arzneistofffreien Schicht die Arzneistofffreisetzung aus der arzneistoffhaltigen Schicht abzuschirmen zu untersuchen. Es stellte sich heraus, dass Hypromellose das vielversprechendste Polymer in dieser Studie war, um die Abschirmung über einen gewissen Zeitraum zu ermöglichen. Die Ergebnisse zeigten, dass die arzneistoffhaltige Schicht genügend Zeit hatte, um zu zerfallen und den Arzneistoff freizugeben, bevor die abdeckende Hypromellose-Schicht sich auflöste bzw. durchlässig wurde.

Aufgrund der Neuheit der filmförmigen Arzneizubereitungen und ihrer erst kürzlich stattgefunden Aufnahme in das europäische Arzneibuch, sind bislang keine Testmethoden

definiert worden, um diese Zubereitungen zu charakterisieren und ihre Qualität zu validieren.

Ein weiterer Teil dieser Arbeit hatte die Entwicklung von Testmethoden zum Ziel, mit denen untersucht werden kann, ob die Filme mechanischer Belastung in der Handhabung und Verarbeitung standhalten können und ob sie in einer angemessenen Zeit zerfallen.

Zur Beurteilung der mechanischen Eigenschaften der Filme, wurde ein Probenhalter konstruiert, um die Messung von unterschiedlich großen und geformten Filmen zu ermöglichen. Die Halterung wurde für einen Punktierungstest verwendet, der mithilfe eines Kraftmessgeräts durchgeführt wurde. Dieser neue Ansatz wurde entwickelt, um eine Messmethode bereitzustellen, die einfach übernommen werden kann und die Möglichkeit bietet, Daten für Referenzmaterialien, Marktprodukte sowie Zubereitungen in der Entwicklung zu generieren, was bei keinem anderen beschriebenen Versuch berücksichtigt wurde, wie Recherchen dazu zeigten. Abschließend konnten die Resultate für die entwickelten Filme im Vergleich zu den vorliegenden Marktprodukten und ihren Eigenschaften bewertet und verglichen werden.

Um den Zerfall der orodispersiblen Filme nach dem Kontakt mit Flüssigkeit messen zu können, wurden zwei Testsysteme entwickelt, die eine genaue Endpunktbestimmung möglich machen. Das zu Grunde liegende Prinzip war die Befestigung eines kleinen Gewichts an der Unterseite des Films, wenn er in die Flüssigkeit getaucht wird. Das Herunterfallen bzw. -sinken des Gewichts zeigte dann den Zerfall des Films an. Durch die Verbindung zu einer zwischengeschalteten Uhr, die mit dem elektronischen Messsystem verbunden war, registrierte das erste System den Endpunkt automatisch. Das zweite System wurde entworfen, um dem konventionellen Zerfallstest für Tabletten möglichst nahe zu kommen. Dazu wurde ein Probenhalter für Filme konstruiert, der in den Testapparat eingesetzt werden kann. Beide Systeme konnten für die Bestimmung des Film-Zerfalls eingesetzt werden. Besonders der an das konventionelle System adaptierte Test überzeugte durch die schnelle Durchführung mit mehreren Zubereitungen gleichzeitig.

Das Potential der elektronischen Zungen wurde im abschließenden Teil der Arbeit weiter untersucht, in dem Ansätze zur Geschmacksmaskierung von Arzneistoffen in verschiedenen Experimenten evaluiert wurden. Eine neue Maltodextrin-Linie, die bereits in der ersten Zubereitungsentwicklung von orodispersiblen Filmen mit Dimenhydrinat geschmacksmaskierende und löslichkeitsverbessernde Eigenschaften zeigte, wurde weitergehend untersucht. Löslichkeitsstudien mit anderen Arzneistoffen zeigten ähnliche Effekte und die geschmacksmaskierende Wirkung wurde mit weiteren Maltodextrin- und Cyclodextrin-Typen verglichen. Es zeigte sich, dass die neue Maltodextrin-Linie mit einem relativ hohem Gehalt an langkettigen Glucose-Polymeren, ihren Vorgängern überlegen war und, insbesondere im Hinblick auf pädiatrische Zubereitungen, eine gesundheitlich unbedenkliche Alternative zu Cyclodextrinen darstellt.

List of publications

Original publications

1. Preis, M., Gronkowsky, D., Grytzan, D., Breitkreutz, J., *Comparative study on novel test systems to determine disintegration time of orodispersible films*. Journal of Pharmacy and Pharmacology 2014, 66(8): 1102-1111

2. Preis, M., Häusler, O., Breitkreutz, J., *Application of electronic tongues in preformulation studies to evaluate taste-masking capacities of maltodextrins.* Die Pharmazeutische Industrie: pharmind 2014, 76(6): 957-962

3. Preis, M., Woertz, C., Schneider, K., Kukawka, J., Broscheit, J., Roewer, N., Breitkreutz, J., *Design and evaluation of bilayered oromucosal film preparations for local administration of lidocaine hydrochloride*. European Journal of Pharmaceutics and Biopharmaceutics 2014, 86(3): 552-561

4. Guhmann M., Preis M., Gerber F., Pöllinger N., Breitkreutz J., Weitschies W., *Design, development and in vitro evaluation of a diclofenac taste masked orally disintegrating tablet formulation*. Drug Development and Industrial Pharmacy 2014, *in press, 10.3109/03639045.2014.884122*

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6. Preis, M., Eckert, C., Haeusler, O., Breitkreutz, J., *A comparative study on solubilizing and taste-masking capacities of hydroxypropyl-ß-cyclodextrin and maltodextrins with high amylose content*. Sensors & Actuators B: Chemical 2014, 193: 442-450.

7. Pein, M., Eckert, C., Preis, M., Breitkreutz, J., *New protocol for αAstree electronic tongue enabling full performance qualification according to ICH Q2*. Journal of Pharmaceutical and Biomedical Analysis 2013, 83: 157-163.

8. Preis, M., Pein, M. and Breitkreutz J., *Development of a taste-masked orodispersible film containing dimenhydrinate*. Pharmaceutics 2012, 4(4): 551-562.

9. Guhmann, M., Preis, M., Gerber, F., Pöllinger, N., Breitkreutz, J., Weitschies, W., *Development of oral taste masked diclofenac formulations using a taste sensing system*. International Journal of Pharmaceutics 2012, 438(1-2): 81-90.

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1. Preis, M., Woertz, C, Kleinebudde, P., Breitkreutz, J., *Oromucosal film preparations: classification and characterization methods*. Expert Opinion on drug delivery 2013, 10(9): 1303-1317.

2. Woertz, C., Preis, M., Breitkreutz, J., Kleinebudde, P., *Assessment of test methods evaluating mucoadhesive polymers and dosage forms: An overview*. European Journal of Pharmaceutics and Biopharmaceutics 2013, 85(3): 843-853.

3. Pein, M., Preis, M., Eckert, C., Kiene, F., *Taste-masking assessment of solid oral dosage forms - a critical review*. International Journal of Pharmaceutics 2014, 465(1-2): 239-254.

Contributions to meetings

Oral presentations

1. Preis, M.*, Breitkreutz, *Classification and assignments of film preparations,* APV Hot Topic Seminar: Orodispersible and buccal films, Dortmund 2013 (invited talk)

2. Preis, M.*, Breitkreutz, J., *How to determine suitable mechanical strength of orodispersible films?* 5th Conference of the European Paediatric Formulation Initiative, Barcelona 2013

3. Preis M.*, Schneider K., Kukawka J., Broscheit J., Roewer N., Breitkreutz J., *Development of bilayer oral films.* 6th PSSRC Meeting, Lisbon 2012

4. Eckert C.*, Preis M., Häusler O., Breitkreutz J., *Comparative study on the taste masking capacity of hydroxypropyl-ß-cyclodextrin and maltodextrin by an electronic tongue.* 8th PBP World Meeting, Istanbul 2012

5. Pein M.*, Eckert C., Preis M., Breitkreutz J., *Taste sensing system αAstree as analytical tool – Performance Qualification using caffeine citrate as model substance.* 8th PBP World Meeting, Istanbul 2012

6. Preis M.*, Breitkreutz J., *Enhancement of drug solubility in oral patch formulations by cyclodextrins and maltodextrin.* 5th PSSRC Meeting, Helsinki 2011

7. Guhmann M.*, Preis M., Gerber F., Pöllinger N., Breitkreutz J., Weitschies W., *Taste-masked micropellets of ibuprofen using an innovative spouted bed continuous pelletizing technology*, 9th PBP World Meeting, Lisbon 2014

*presenting author

Poster presentations

1. Preis M., Breitkreutz J., *Development of novel disintegration test systems for orodispersible films.* 9th PBP World Meeting, Lisbon 2014

2. Preis M., Broscheit J., Roewer N., Breitkreutz J., *Buccal films containing midazolam hydrochloride as an alternative to tablets in premedication,* 9th PBP World Meeting, Lisbon 2014

3. Preis M., Schneider K., Kukawka J., Broscheit J., Roewer N., Breitkreutz J., *Development of bilayer oral films containing lidocaine hydrochloride.* AAPS Annual Meeting and Exposition, Chicago 2012

4. Guhmann M., Preis M., Gerber F., Pöllinger N., Breitkreutz J., Weitschies W., *Development and evaluation of multiparticulate orally disintegrating tablets comprising diclofenac*. Oral Multiparticulate Dosage Forms – What's new?, Prague 2012

5. Preis M., Broscheit J., Roewer N., Breitkreutz J., *Development of a palatable midazolam formulation for paediatric use.* 4th Conference of the European Paediatric Formulation Initiative, Prague 2012

6. Preis M., Schneider K., Kukawka J., Broscheit J., Roewer N., Breitkreutz J., *Electronic taste assessment of bilayer orodispersible films.* 4th Conference of the European Paediatric Formulation Initiative, Prague 2012

7. Preis M., Breitkreutz J., Introduction of a new disintegration test for orodispersible films. 4th Conference of the European Paediatric Formulation Initiative, Prague 2012

8. Preis M., Woertz C., Breitkreutz J., *Mucoadhesive polymer films – influence of thickness on disintegration time and mouthfeeling.* 8th PBP World Meeting, Istanbul 2012

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