Development of a novel composite dosage form for oromucosal administration of locally and systemically active drugs

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Für alle, die einen Teil in meinem Herzen haben

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List of Abbreviations

abbreviation	
approx.	approximately
BA	bioavailability
CDI	chronic diabetes insipidus
C_d	donor concentration
C_{max}	maximum concentration
cm^2	square centimeter
ΔC	concentration difference
D	diffusion coefficient
DDAVP	desmopressin acetate
EMA	European Medicine Agency
FDA	Food and Drug Administration
GI tract	gastrointestinal tract
HPMC	hypromellose (hydroxypropyl methyl-cellulose)
J / J_{ss}	flux
LCW	liquid core waveguide
MBF	mucoadhesive buccal film
min	minute
mL	milliliter
mm	millimeter
ODF	orodispersible film
Ph. Eur.	European Pharmacopoeia
P_{app}	apparent permeation coefficient
s	second
Δx	distance
µg	microgram
µL	microliter

Publications

Published manuscripts:

Y. Tian, M. Orlu, H. J. Woerdenbag, M. Scarpa, O. Kiefer, D. Kottke, E. Sjöholm, H. Öblom, N. Sandler, W. L. J. Hinrichs, H. W. Frijlink, J. Breitkreutz & J. C. Visser, **Oromucosal films: from patient centricity to production by printing techniques**, *Expert Opinion on Drug Delivery 16 (2019) 1652595.*

D. Kottke, A. Lura, D. J. Lunter, J. Breitkreutz, **Manufacturing and characterisation of a novel composite dosage form for buccal drug administration**, *International Journal of Pharmaceutics 589 (2020) 119839.*

D. Kottke, H. Majid, J. Breitkreutz, B. B. Burckhardt, **Development and evaluation of mucoadhesive buccal dosage forms of lidocaine hydrochloride by ex-vivo permeation studies**, *International Journal of Pharmaceutics 581 (2020) 119293.*

D. Kottke, B. B. Burckhardt, J. Breitkreutz, B. Fischer, **Application and validation of a coaxial liquid core waveguide fluorescence detector for the permeation analysis of desmopressin acetate**, *Talanta 226 (2021) 122145.*

D. Kottke, B. B. Burckhardt, T. C. Knaab, J. Breitkreutz, B. Fischer, **Development and evaluation of a composite dosage form containing desmopressin acetate for buccal administration**, *International Journal of Pharmaceutics: X 3 (2021) 100082.*

Contributions to meetings

Oral presentations

D. Kottke, H. Majid, J. Breitkreutz, B. B. Burckhardt, **Ex-vivo permeation studies to facilitate the development of a buccal child-appropriate dosage form by using lidocaine minitablets**, *12th International Conference and Workshop on Biological Barriers (BioBarriers), Saarbrücken 2018.*

(Award for best oral presentation)

D. Kottke, H. Majid, D. Lunter, J. Breitkreutz, B. B. Burckhardt, **Established and innovative buccal dosage forms controlling oromucosal lidocaine permeation**, *3rd European Conference on Pharmaceutics, Bologna 2019.*

D. Kottke, J. Breitkreutz, **Impermeability studies of ethyl cellulose films for unidirectional drug permeation**, *PSSRC Annual Meeting, Duesseldorf 2019.*

(Shared award for best oral presentation)

Poster presentations

D. Kottke, Y. Thabet, J. Breitkreutz, **Individual drug dosing by printing enalapril maleate onto orodispersible films using various devices**, *European Paediatric Formulation Initiative Conference, Lisbon 2016.*

D. Kottke, J. Breitkreutz, **Composites drug dosage forms made from tablet and film formulations**, *European Paediatric Formulation Initiative Conference, Warsaw 2017.*

D. Kottke, L.-M. Gröpper, S. Tillmanns, **Dissolution behaviour of 3D printed lidocaine formulations onto mucoadhesive buccal films conventionally produced for pediatric use**, *European Paediatric Formulation Initiative Conference, London 2018.*

(Award for best poster presentation)

D. Kottke, H. Majid, J. Breitkreutz, B. B. Burckhardt, **Ex-vivo permeation studies to facilitate the development of a buccal child-appropriate dosage form by using lidocaine minitablets**, *12th International Conference and Workshop on Biological Barriers (BioBarriers), Saarbrücken 2018.*

D. Kottke, A. Lura, J. Breitkreutz, **Formulation development of a composite drug dosage form with lidocaine hydrochloride for pediatric use**, *11th PBP World Meeting, Granada 2018.*

H. Majid, D. Kottke, A. Bartel, B. B. Burckhardt, **Approach of a physiologically-based permeation model utilizing LC-MS/MS to investigate the safety potential of buccal drug application**, *DPhG Annual Meeting, Hamburg 2018.*

D. Kottke, T. C. Knaab, S. Kerski, J. Breitkreutz, **Development of desmopressin minitablets for buccal administration**, *3rd European Conference on Pharmaceutics, Bologna 2019.*

H. Majid, D. Kottke, A. Bartel, B. B. Burckhardt, **Development of a suitable LC-MS/MS quantification method as key element in intraoral ex-vivo permeation studies within pharmaceutical research**, *Euroanalysis Conference, Istanbul 2019.*

Section A.

Introduction

A. 1 The oral cavity as alternative route of application

A. 1.1 Anatomy and physiology

Within the past years, the interest in alternative routes of administration for the oral application has steadily increased. In particular, drug administration to the oral mucosa has proven to be a promising route for locally but also systemically active drug substances. Within the oral cavity, different application sites can be distinguished into buccal, sublingual, palatal and gingival sites (Figure 1). Within drug delivery research, the buccal and sublingual administration routes are the most studied routes.

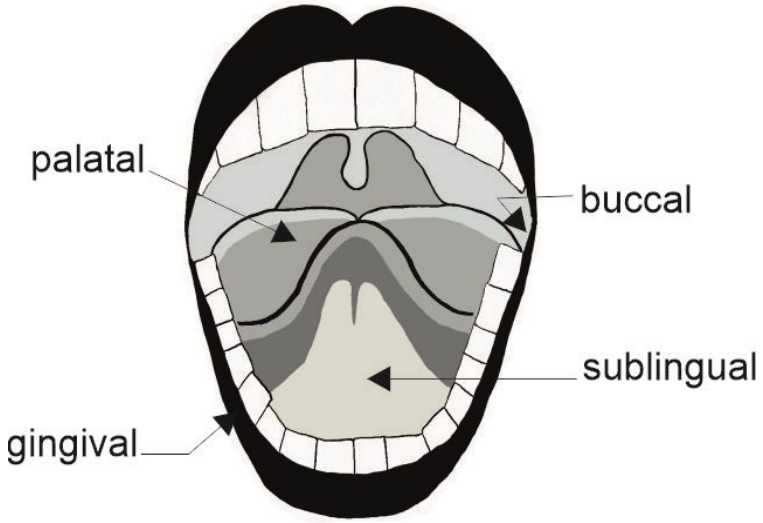

Figure 1. Application sites within the oral cavity.

Anatomically, the oral mucosa can be divided into three superordinate sections: the epithelium, the basal membrane and the connective tissue. The choice of the most suitable application region mainly depends on regional differences in terms of efficacy (local or systemic) and, based on this, on the nature of the respective mucosa, which has an influence on the resulting permeability (Table 1).

Table 1. Epithelial thickness and permeability pattern of different oromucosal tissues within the oral cavity, + means “suitable” ++ means “very suitable” and -- means “least suitable” [1].

Tissue	Epithelial thickness [µm]	Permeability pattern
Buccal	500-600	+
Sublingual	100-200	++
Palatal	250	--
Gingival	200	--

Within the oral cavity, there are different types of mucosa which differ in terms of their composition and texture properties (Table 2). Keratinized mucosa shows a higher barrier function and thus generally reveals lower drug permeability. Permeability is increasing from palatal, buccal to sublingual mucosa [2]. Thus, the sublingual and buccal mucosa are the most promising and most studied areas in terms of drug permeation and formulation efforts.

Table 2. Mucosa types of the oral cavity locations and key properties [3].

Mucosa type	Surface area proportion in the oral cavity [%]	Keratinization	Region
Masticatory mucosa	25	Keratinized	Gingival, hard palate
Specialized mucosa	15	Keratinized and non-keratinized	Dorsum of the tongue
Lining mucosa	60	Non-keratinized	Soft palate, buccal, sublingual

The buccal mucosa is relatively immobile if compared with the highly frequented sublingual mucosa and hence it is a suitable site for the application of long-adherent

transmucosal delivery systems [4]. The anatomy of the buccal mucosa is discussed in more detail below.

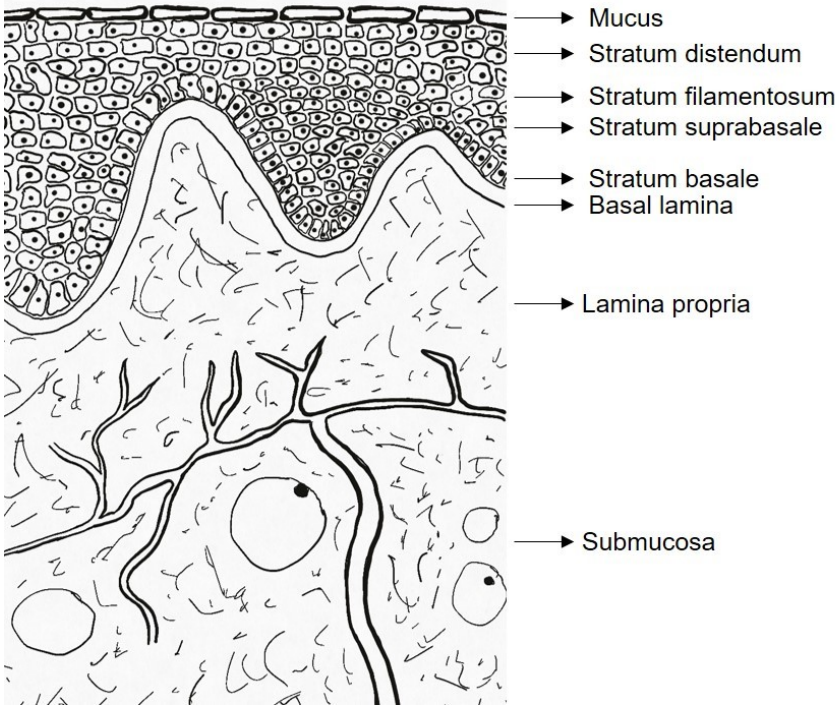

Figure 2. Cross section of the buccal mucosa with its components (adapted from Harris et al. [5]).

The buccal epithelium is composed of the following sections: Mucus, stratum distendum, stratum filamentosum, stratum suprabasale and stratum basale (Figure 2). Additionally, this tissue is the prime barrier for oromucosal drug permeation, whereby the composition of the epithelium varies depending on the location within the oral cavity. Connecting the epithelium and the connective tissue is the main function of the basal lamina. Furthermore, this tissue provides additional mechanical protection. Directly adjacent to the basement membrane lies the lamina propria, which belongs to the superior connective tissue layer (consists of lamina propria and submucosa). This layer is characterized by the fact that it is rich in blood vessels that directly lead to the internal jugular vein. Therefore, the lamina propria plays a major role in drug absorption into the bloodstream via the oromucosal mucosa.

Other important components of the oral mucosa include the adhered mucus and the produced saliva. The mucus is an aqueous layer that is located on top of the epithelial cells and acts as wetting agent. Saliva is the product of the salivary glands and consists primarily of inorganic and organic macromolecular components in an aqueous solution [6]. In healthy state, saliva consists of 99% water with a pH value between 6.5-7.5 [7], has an average flow rate between 100-500 µL/min (corresponds to a daily production of 144-720 mL) and a total volume in the oral cavity of approx. 1 mL [8].

A. 1.2 Key aspects of oromucosal drug delivery

Drug delivery via the oral mucosa of the oral cavity offers several advantages compared to other routes of administration. Ease of administration as well as excellent accessibility may increase patient convenience, which may consequently improve compliance [9]. This does not only provide an advantage in drug administration but also allows rapid removal of the drug product, for example, if there are signals of drug intolerance or overdosing. This contributes substantially to the safety of the medication. Especially with regard to geriatric and pediatric populations, the application of this alternative route offers some advantages because the swallowing of dosage forms can be avoided. Spitting out or dripping of the liquid, especially by children, may result in drug loss and the administered amount of drug can no longer be monitored. The blood capillaries within the well perfused lamina propria directly lead into the jugular vein, bypassing the gastrointestinal tract. Avoiding the intestinal and hepatic first pass metabolization may enable a dose reduction maintaining drug efficacy and reducing adverse drug effects. This has been demonstrated for the product Xilopar, an oral lyophilizate containing selegilin hydrochloride, in which only 12.5 % of the dose used in a conventional tablet were able to produce similar areas underneath the plasma

concentration over times curves compared to the conventional tablet [10]. Further, oromucosal administration can prevent contact to the acidic gastric environment. In particular, peptide drugs are remarkably degraded after oral administration by enzymatic and/or acidic degradation. Despite the numerous beneficial aspects of oromucosal drug delivery, there are also a few disadvantages, which should be overcome by suitable drug dosage forms. Compared to the intestinal surface, the oral cavity possesses a much smaller surface of approx. 214 cm² [11]. Nevertheless, the surface area is sufficient to absorb some drug substances like for example propranolol, glibenclamide and oxytocin from oral dosage forms to achieve systemic efficacy [12].

The continuous production of saliva can result in lower drug concentrations at the site of oral absorption or the drug can be washed off completely. In contrast, in patients with the "dry mouth syndrome", the indication of an insufficient amount of saliva production may result in disadvantaged drug release in the oral cavity. Another general problem can arise from simultaneous talking, eating or drinking by the patient. Food can not only change the key conditions within the oral cavity, such as pH value, fluid volume and the increased movements of the jaws and the tongue. It may also lead to displacement or detachment of adhesive formulations. Although there are some obvious benefits to developing an advanced drug delivery system for oromucosal absorption, there are some major challenges that need to be overcome.

A. 1.3 Drug penetration and permeation

The physicochemical properties of drug substances have a decisive influence on their penetration and permeation. In general, there are two different routes in which the transport of a drug can occur. These are the paracellular and transcellular routes (Figure 3).

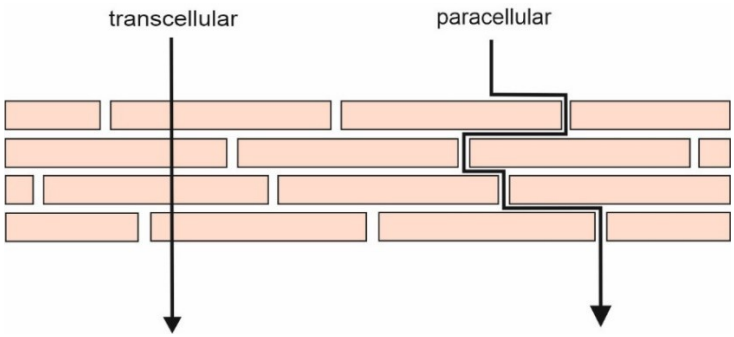

Figure 3. Transcellular and paracellular transport routes through the oral mucosa [13].

Even if some drugs are able to use both transport routes due to their physicochemical properties, one of the two routes usually dominates. In the paracellular route, the drug substance migrates through fluid channels between epithelial cells. Which of the two routes is preferably used, mainly depends on the hydrophilicity/lipophilicity of the drug substance. Even if there are some lipophilic molecular substructures, the hydrophilic nature of the fluidic channel is decisive and is therefore preferred by hydrophilic drugs. Transcellular transport is performed by migrating through the epithelial cell layers. Due to the fact that cell membranes consist of a lipophilic double layer, this is the preferred transport route for lipophilic substances. The driving force for transcellular absorption mechanism is passive diffusion, which follows Fick's 1st law of diffusion (Equation 1).

$$J = -D \frac{\Delta c}{\Delta x} \quad (1)$$

J = flux, D = diffusion coefficient, Δc = concentration and Δx = distance.

The mass transport follows a concentration gradient from the compartment of higher to lower concentration. With regard to drug delivery systems offered within the donor compartment, this means that the oral lumen represents the higher concentration area and the blood capillaries the lower concentration area. How much of a substance can

pass through the oromucosal membrane depends on various factors. Key variables influencing transmucosal absorption are: pKa value, hydrophilicity/lipophilicity, molecular weight, saliva volume, salivary flow, saliva pH, drug residence time and also the application site [14, 15]. The key factors mentioned above must be taken into consideration in penetration and permeation studies. Both, *in-vitro* and *ex-vivo* permeation studies, have proven to be a useful tool for the assessment of permeation. Traditionally, Franz diffusion cells are used for this purpose. There are approaches of optimized permeation cells, such as so-called Kerski diffusion cells, which allow easier handling [16]. In addition, the Franz cells are often modified with regard to the underlying experimental requirements [17]. In literature, animal membranes are used most often as physiological model barriers for the experimental setup in order to mimic the human mucosa. Esophageal [18, 19] and buccal [20] porcine membranes are predominantly used for this purpose. Previous studies have shown that the lipid composition of the porcine esophageal and buccal membranes shows a high degree of concordance and thus both areas are suitable for permeation studies [21]. However, previous papers also describe permeation studies using chicken [17], sheep [22], goat [23] and rabbit [24] mucosa. Despite the wide range of usable animal tissues for permeation studies, research approaches are still trying to more accurately reflect the physiological conditions in humans. For instance, Morales et al. were able to cultivate a three-dimensional human buccal tissue, called EpiOral [25]. Nevertheless, a major drawback of permeation studies is the comparatively high fluctuation of measured data [26]. Scientific research but also industrial development, is increasingly moving towards alternative dosage forms and administration routes and their characterisation. However, the pharmacopoeias do not provide standardized assays for permeation investigations yet.

The evaluation and assessment of the permeation profile is based on the flux in steady state (J_{ss}), which represents the slope of the resulting drug permeation curve. A supplementary evaluation is performed using the apparent permeation coefficient (P_{app}) (Equation 2) [27].

$$P_{app} = \frac{J_{ss}}{c_D} \quad (2)$$

P_{app} = apparent permeation coefficient, J_{ss} = steady state flux, c_D = initial concentration of substance in donor compartment.

If the flux is divided by the initial concentration of a substance, the P_{app} value can be calculated, which characterizes both the permeability of the used membrane and the permeation properties of the drug substance [27]. High membrane resistance results in a lower P_{app} value, which means a low permeability of the substance through the barrier under investigation.

Even though permeation of peptides is challenging, several approaches have already been described in the literature (Table 3).

Table 3. Apparent permeation coefficients of various peptidic drugs considering molecular weight and permeation barrier.

Drug substance	Molecular weight [g/mol]	Permeation barrier	P_{app} [cm/s]	Literature
Oxytocin	1007	Rabbit mucosa	7.02×10^{-8}	[28]
Calcitonin	3432	Porcine buccal mucosa	2.5×10^{-8}	[29]
Antisense oligonucleotide	6405	Porcine buccal mucosa	1.83×10^{-8}	[30]
Desmopressin acetate	1069	Rabbit nasal mucosa	0.78×10^{-6}	[31]

A. 2 Drug dosage forms for administration within the oral cavity – Benefits and challenges

In recent years, there have been many efforts in scientific research to optimize drug dosage forms for oromucosal drug administration [32-36]. As for other routes of administration, the options range from liquid to semi-solid [37, 38] and solid dosage forms [39-41]. The following chapter will address the current state of research regarding semi-solid and solid dosage forms for buccal administration to highlight the benefits but also challenges of each approach.

A. 2.1 Semi-solid dosage forms

One of the established oromucosal dosage forms on the pharmaceutical market are gels and ointments. The main advantage of the application of gels and ointments is their facile spread on the mucosa. Additionally, they have the beneficial property to deform easily, which enables optimal adapting to the uneven superficial structure of the oral mucosa [42, 43]. Due to the variety of gel formers available for the formulation, the properties of the dosage form such as mucoadhesion or viscosity can be modified with negligible effort. In particular, hydrogels still seem to be a promising dosage form for oromucosal administration. These gels, through the use of suitable polymers, are first hydrated in an aqueous environment, which enables them to physically entrap and disperse the drug molecules. After drug administration the active ingredient is released by diffusion or erosion [44]. One major advantage of hydrogels for oromucosal administration is that they exhibit different swelling behavior depending on the external environment [45], which is why they are also called physiologically-responsive hydrogels [46, 47]. Some hydrogels are first present in the sol state and modify their constitution after entry into the body under physiological conditions [37, 38].

Despite the beneficial aspects and many new research approaches, the disadvantages in terms of buccal drug application should not be neglected. A major disadvantage is the short residence time of these semi-solid formulations after oromucosal application, which makes targeted and prolonged drug treatment difficult or even impossible, especially when systemic drug efficacy is required. Another disadvantage is the difficulty of accurate dosing from a multi-dose container. Subjective instructions for use such as "apply a pea-sized form four times a day" [48] make it almost impossible for the patient to redundant administration of the same drug dose, which may lead to serious adverse effects, especially with regard to the patient group of infants and children due to accidental swallowing of drug portions and potential overdosing [49]. Therefore, it becomes clear that, especially with regard to patient's safety, there is a need for the development of improved drug dosage forms for oromucosal application.

Film formulations represent a relatively novel approach to drug delivery via the oral cavity [32]. A general distinction can be made between orodispersible films (ODF) and mucoadhesive buccal films (MBF). ODFs are defined by Ph. Eur. as *"solid oromucosal preparations intended for administration in the mouth, where they disperse rapidly to deliver active substances"*. According to Ph. Eur. MBFs *"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."*. Typically, film formulations are produced via the solvent casting method. Suitable polymer solutions are used for this technology, which are casted on a film casting bench [50, 51]. After evaporation of the solvent, the films can be cut into single pieces of defined sizes [52]. Other manufacturing methods such as hot-melt extrusion [53] or innovative printing methods using flexography [33] or inkjet [34] technologies are also suitable for the production of the films.

There are many advantages using ODFs in comparison to solid dosage forms like tablets. One main advantageous purpose is the use in patients with swallowing difficulties, as the dosage form quickly disintegrates in the oral cavity and the drug dose can be easily swallowed with the saliva. This mainly concerns geriatric but also pediatric patients as well as patients with diseases such as Parkinson's disease, dysphagia, mucositis or chronic vomiting [54]. In addition, ODFs cannot easily be spit out, as they disintegrate in the oral cavity within a few seconds, which is an advantage for use in non-compliant patients such as infants and children [55]. Due to their flexibility, they allow practical handling as well as easy administration and are robust against mechanical forces [56]. The specified film size allows a more accurate dosing if compared to the previously mentioned gels and ointments, which provides a major advantage in terms of safe drug delivery [57]. Nevertheless, the oral administration of ODFs also shows some disadvantages. Since the drug dose is usually administered by the surface area of the film with very low thickness, this represents a major limitation of drug loading. As a result, this dosage form only offers potential for high-potent and thus low-dosed drug substances. Due to the fact that film formulations are commonly produced by solvent casting, the use of solvents and heat for the drying process is usually indispensable. Here, problems can arise with the use of drugs, excipients, sweeteners and flavors, which may show stability problems with regard to solvent and heat exposure [58].

Due to the rapid disintegration of ODFs, some parts of the drug may already be absorbed in the oral cavity, others are absorbed from the GI tract. Controlled drug delivery is difficult and potentially only possible by incorporated multiparticulate approaches [59, 60]. The MBFs are not listed as a separate dosage form within the Ph. Eur. but are listed together with other mucoadhesive forms under the category of

"mucoadhesive preparations." The main difference between ODFs and MBFs is, that MBFs do not have the property of rapid disintegration. Closely related to the principle of mucoadhesive films are the mucoadhesive patches [35]. Mucoadhesive patches may consist of two layers or more, at least one serving as an impermeable shielding layer and the other as a drug reservoir. From this drug-containing mucoadhesive layer, the drug can be released in a controlled manner towards the oral mucosa [61]. The different designs for MBFs compared to ODFs are shown in Figure 4.

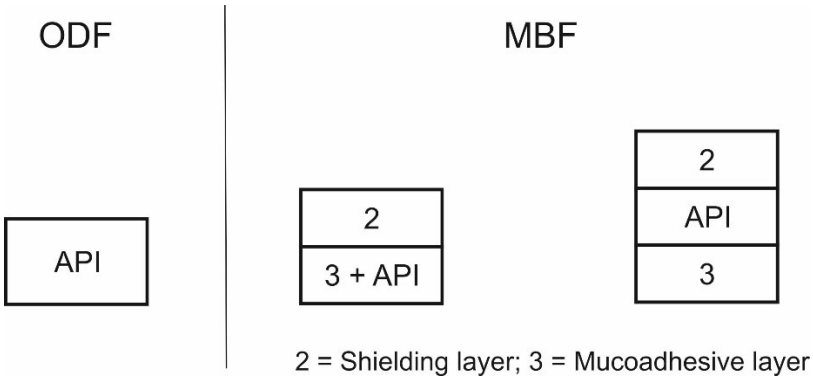

Figure 4. Schematic drawing of the structural design of ODF and MBF.

By the mucoadhesive character, a longer residence time on the mucosa can be achieved, which can be decisive in particular for the absorption of systemically active substance. While gels, ointments but also ODFs can be quickly washed out by the saliva, MBFs adhere to and remain at the oral mucosa. Due to this important advantage, many research approaches are dealing with the development and optimization of further MBFs [12]. In a recent study, the use of a MBF with cholin salicylate against aphthous lesions of the oral cavity has been investigated [62]. It was observed that the MBF led to a significant improvement in the healing process compared to the application of common oromucosal gel.

Another widely used approach is the production of multilayer films. Rana et al. developed a three-layered film formulation consisting of a mucoadhesive layer, a drug layer made from a nanosuspension and a backing layer [36]. This study revealed that the pharmacokinetic parameter c_{max} of the formulation was 7.3 times higher compared to an oral tablet, which allowed the formation of a stable nanosuspension with appropriate size, size distribution and surface charge. Several approaches focused on making systemically active drugs available via the oral mucosa. In literature, an impermeable shielding layer, called backing layer, is often used in the development of MBFs to ensure unidirectional drug release towards the mucosa [63]. Both locally active drugs such as lidocaine incorporated in MBFs but also systemically active drugs such as ondansetron, propranolol, selegiline, calcitonin and vitamin B12 have been described [18, 63-66]. Reda et al. developed an innovative approach to ketoprofen-containing MBFs using nanofibers via electrospinning technique [67]. The potential and resulting interest in the delivery of systemically active drugs via MBFs is evident from the various research approaches, but they also exhibit many of the disadvantages of ODFs described above, since their production is based on the same principle. An additional disadvantage arises in the swelling behavior of the polymers, which can cause discomfort for the patient, if the swelling and water loss of the oromucosal tissue is too severe [68].

A. 2.2 Solid dosage forms

Tablets are a long-established solid dosage form, which also has a potential application in the oral cavity if modified as a mucoadhesive tablet. Approaches for mucoadhesive tablets have already been described in the literature [39-41].

In contrast to conventional tablets, mucoadhesive tablets adhere to the oral mucosa due to the incorporation of mucoadhesive compounds. A major advantage of the mucoadhesive tablet is that both higher and lower drug loadings can be produced compared to film formulations. In addition, there are fewer or even no limitations caused by stability problems (hydrolysis, heat exposure, etc.), which considerably expands the field of application. The aspect of precise dosing via the production of tablets offers an advantage over other oromucosal dosage forms in terms of safety. The simplest method for producing mucoadhesive tablets is direct compression. Mucoadhesive tablets containing ritodrine hydrochloride [69] and omeprazole [70] have already been successfully produced using the polymeric excipient sodium alginate. Spray-drying processes were used to produce co-spray-dried particles of chitosan and diazepam, which were subsequently compressed into a tablet [71]. Other approaches showed the development of spray-dried microspheres from a carvediol/chitosan mixture, which was subsequently compressed into a tablet using double compression [72]. A nicotine tartrate tablet consisting of chitosan and carbomer [73], as well as a combination tablet of felodipine and pioglitazone, using the polymers carbopol and hypromellose (HPMC) for buccal application [74], have also been described in the literature. Despite the various research approaches and previously mentioned advantages, some drawbacks also exist for this dosage form. The lack of flexibility can result in reduced compliance for the patient [75-77]. The presented composition examples illustrate the need for adhesive polymers in the manufacturing of MBFs, which results in the development of a diffusion barrier due to the swelling process by achieving the required mucoadhesion [78-81]. In particular, drug diffusion, tablet erosion and swelling are important mechanisms for the drug release [82].

This enables better control and variation of drug release, but makes it nearly impossible to produce a formulation that releases the drug substance as quickly as possible. The mechanism of mucoadhesion is based on swelling of the formulation, which leads to an extension of the diffusion path for the drug from the formulation. Consequently, the absence of a mucoadhesive excipient is the key factor in generating the fastest possible drug release.

Not only the lack of flexibility may negatively affect patient's compliance but also the size of the mucoadhesive tablet. One approach to overcome this hurdle of size could be the production of minitablets, which are defined as tablets with a maximum size of up to 3 mm [83]. Currently, no approaches for minitablets for buccal use are described in the literature.

All the respective dosage forms described in this chapter have a lot of exciting benefits with regard to drug administration via the oral mucosa when considered separately, but they also have a number of disadvantages and challenges. Therefore, the development of a dosage form that combines the advantages of each formulation principle and at the same time solves or reduces their disadvantages would be desirable for advanced and controlled drug administration to the oral mucosa.

A. 3 Active pharmaceutical ingredients for oromucosal administration used in the thesis

In the present thesis one API for local action and one for systemic action should be considered. Lidocaine hydrochloride was selected to represent local drug efficacy and desmopressin acetate to represent systemic drug efficacy. Both APIs have been considered critically by FDA warning letters on both of them in 2014 (lidocaine hydrochloride) [49] and 2007 [84] as well as 2020 (desmopressin acetate) [85].

A. 3.1 Lidocaine hydrochloride

Lidocaine hydrochloride is a drug substance classified into the group of local anesthetics with an amide type, which is used in local pain therapy. The target of lidocaine is the inner part of the sodium channel, which is located inside the cell membranes and is necessary for the formation of electronic action potentials and thus for the transmission of stimuli. First, lidocaine permeates the cell membrane and after intracellular protonation (Figure 5) it binds at the inner part of the sodium channel. Therefore, the influx of sodium ions is inhibited, which results in a blocked stimulus transmission.

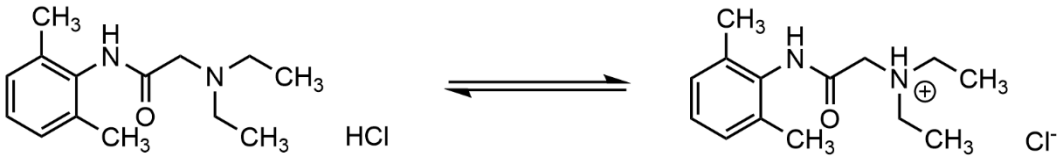

Figure 5. Molecular structure and dissociation of lidocaine hydrochloride.

Due to its *local* anesthetic effect, lidocaine is widely used in various indications especially with regard to infants and children. Widely used medicinal products for treating local pain in teething children, among others, are oral gels containing lidocaine,

such as Dynexan Mundgel®. Unfortunately, most commercially available medicinal products up to now (Dynexan Mundgel®, INFECTOGINGI®, Kamistad®) are based on gel formulations. Besides the common use as an anesthetic, lidocaine is also used as a class 1b antiarrhythmic drug. Therefore, the potential cardiac risks associated with the oral use of lidocaine in infants and children should not be underestimated, as a FDA warning letter demonstrates [49]. This warning letter from 2014 is about local anesthetics like lidocaine and the risks associated with the intake.

"Topical pain relievers and medications that are rubbed on the gums are not necessary or even useful because they wash out of the baby's mouth within minutes. When too much viscous lidocaine is given to infants and young children or they accidentally swallow too much, it can result in seizures, severe brain injury, and problems with the heart. Cases of overdose due to wrong dosing or accidental ingestion have resulted in infants and children being hospitalized or dying." [49].

The FDA 's warning clearly indicates that there is a specific need of improved dosage forms to ensure drug safety. According to the leaflet, exemplified by Dynexan Mundgel® oral gel, a pea-sized amount of the gel should be applied to the affected area [48]. Due to the unavoidable subjective component, it is easy to illustrate that precise dosing is almost impossible and thus the risk of over- or underdosing. Nevertheless, current research in the field of gel formulations continues [86-88]. For the critical reasons outlined above, among others, lidocaine has increasingly become the focus of research with regard to innovative dosage forms.

Within the last few years, many research approaches have focused on improving accurate dosing of lidocaine-containing formulations, particularly with regard to the pediatric use. The mucoadhesive film formulations [35, 89-91] and oral patches have a pronounced role in these advances [92, 93]. The development of bilayer films made it possible to apply the drug at the desired location while achieving unidirectional drug release through the incorporation of insoluble polymers such as ethyl cellulose [12, 19, 94-96]. This has enabled substantial progress to be made in the direction of improved safety in drug administration. Ribeiro et al. developed a so-called hybrid nanofilm in the area of film formulations, whereby they observed a sustained release of lidocaine up to 8 hours [97]. Another research approach dealt with the lyophilization of films containing ketorolac and lidocaine. Within the study it could be shown that the developed films are an effective as well as convenient method for pain relief with increased wound healing for dental diseases [98]. Prolonged drug release was observed by incorporating microspheres into mucoadhesive patches [99]. Furthermore, Clitherow et al. investigated the development of electrospun mucoadhesive patches [100]. In addition to the extensively studied field of film formulations, a bilayer buccal tablet for lidocaine administration has also been developed [101]. The versatility of these new approaches reflects the steadily growing popularity of oromucosal application and the need for optimized controlled drug delivery and improved safety mechanisms. Approaches to drug loading using printing techniques such as inkjet-printing and fused deposition modeling have also been described in the literature [102]. Eleftheriadis et al. developed lidocaine hydrochloride loaded mucoadhesive films by combining the two different printing techniques [102].

Silva Favacho et al. sought to improve noninvasive local anesthesia by combining biocompatible polymers with a mixture of surfactants and then incorporating them into freeze-dried tablets [103]. The presented development proved to be an effective strategy to enhance oromucosal absorption. By using iontophoresis, an increase in permeated drug amount through esophageal porcine membrane could be observed [104]. Moreover, an enhancing effect on permeation was also demonstrated by the application of microneedle systems for oral delivery [105]. Based on the diversity of research approaches described, it is clear that lidocaine hydrochloride plays a key and promising role as a drug substance with regard to future improved oromucosal drug administration.

A. 3.2 Desmopressin acetate

Drug therapy with peptidic drugs reveals multiple challenges compared to other drug molecules. Due to their disadvantageous physicochemical properties such as high molecular weight, hydrophilicity, enzyme and pH sensitivity, resulting in low oral bioavailability, these drug substances are usually administered parenterally to achieve the desired systemic effect. Challenging permeation of efficient doses as well as instability in the GIT are barriers that must be overcome. As a result, to this day, parenteral administration is still the gold standard for the administration of peptidic drugs [105]. Despite its establishment as the gold standard, parenteral administration is unfavorable, which can cause low compliance or even complete refusal of therapy by the patient. In recent years, increased research has been conducted in the field of alternative routes of administration to overcome the current obstacles to systemic availability of orally administered peptide drugs. In the present thesis, desmopressin has been chosen as an example for peptide drugs with systemic efficacy. Desmopressin (DDAVP, 1-desamino-8-D-arginin-vasopressin) is a nonapeptide with a molecular weight of 1069.22 g/mol, that is structurally related to the endogenous peptide vasopressin. Desmopressin differs in two amino acids from vasopressin. The amino acid at position eight, L-arginine, has been replaced by D-arginine and the amino acid cysteine at position one has been removed. Based on the molecular structure (Figure 6), a pronounced hydrophilicity of the drug substance can already be predicted, which is also illustrated by its negative clogP of -3.16 (calculated independently using chemdraw). In comparison to vasopressin, desmopressin has a lower hydrophilicity (clogP vasopressin = -3.8, self-calculated using (chemdraw software package)), which results in better bioavailability.

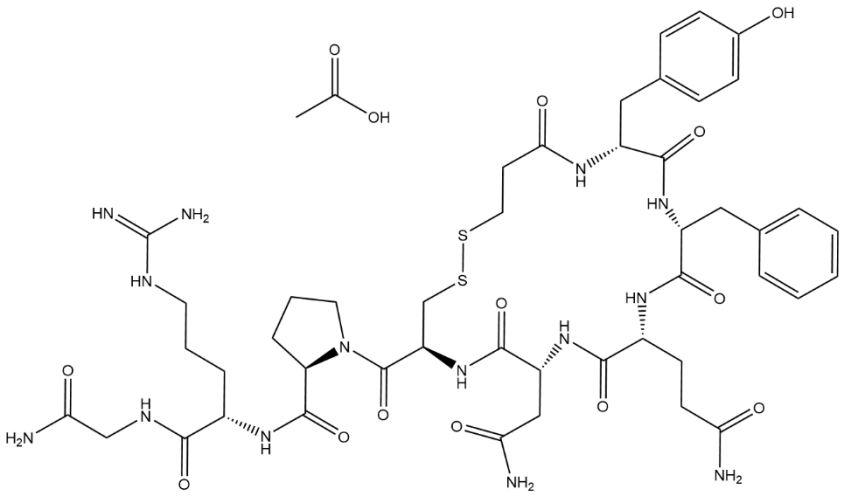

Figure 6. Molecular structure of desmopressin acetate.

The main indications for desmopressin include diabetes insipidus centralis, enuresis nocturna, and nocturia due to idiopathic polyuria in adults [106, 107]. In addition, it is approved for the treatment of hemophilia A and von Willebrand disease type I [108]. Although desmopressin shows higher oral bioavailability than vasopressin, it is still low at 0.08-0.16% [109]. The main reasons for this low oral BA are, on the one hand, the rapid and efficient degradation by the acidic gastric fluid after swallowing. On the other hand, the usually high molecular weight leads to poor permeability of these drugs, which also results in a lower BA.

In addition to parenteral formulations, desmopressin is available in other dosage forms like tablets, nasal sprays, nasal drops and, since 2007, sublingual tablets (oral lyophilizates) [110]. Previous studies have shown that bypassing the gastrointestinal tract and thus the intestinal and hepatic first pass effect, results in increased bioavailability. Nasal (5-10%) [111] as well as sublingual (0.28%) administration results in higher desmopressin bioavailabilities [109]. The administration of tablets was widely reduced in favor for nasal and sublingual administration [112].

Despite the high bioavailability after nasal administration, there is a considerable drawback with regard to the high variation of bioavailability, which can cause serious and uncontrollable side effects (e.g. hyponatremia), especially in the pediatric population [113]. In addition, the high variability of the amount absorbed via the nasal route can lead to an unintentional, uncontrollable overdosing resulting in undesirable adverse effects [114, 115]. Consequently, the approvals for previously authorized nasal sprays, indicated for enuresis nocturna in children, has been withdrawn by FDA [84].

"The US FDA is warning that certain patients, including children treated with the intranasal formulation of desmopressin for primary nocturnal enuresis (PNE), are at risk for developing severe hyponatraemia that can result in seizures and death" [84].

In a study by van Kerrebroeck et al. it was elaborated that 80% of desmopressin-induced hyponatremia cases were due to use of nasal sprays [116]. In contrast, the sublingual administration of desmopressin induced critical hyponatremias in only 1% of all cases. The results of the study illustrate significant differences even within the alternative application routes. Due to the higher bioavailability compared to oral tablets, as well as the lower risk of hyponatremia, the sublingual formulation came more into the scientific focus. Lottmann et al. conducted acceptance studies with the outcome, that the target group of children between 5-11 years preferred sublingual desmopressin intake over oral tablets [117]. Particularly when administered via the oral cavity, the ingestion of food may influence the absorption of the drug, which has also been shown with respect to desmopressin [118]. The study by De Guchtenaere et al. showed that, despite food interaction, the effectiveness of sublingual administration was higher compared to oral tablets [119]. These studies illustrate the promising potential of alternative orally administered drug delivery systems.

Therefore, various investigations have been conducted for further increasing the bioavailability and drug safety of desmopressin. Ilan et al. observed a 12-fold increase in bioavailability compared with pure saline using a mucoadhesive submicron emulsion [120]. A different approach was taken by Merwe et al. by incorporating desmopressin and the absorption enhancer N-trimethyl chitosan chloride into 3 mm minitablets [121]. After oral administration, an initial burst effect with subsequent delayed release was observed. Incorporation of desmopressin into a mucoadhesive multi-layer film for buccal and sublingual application enhanced drug permeation through porcine membranes [122]. While clinically relevant dosages have not been used within this study, the presented formulation was evaluated as a promising approach for increasing oromucosal bioavailability. Nevertheless, exact statements regarding permeability and bioavailability can only be made under the assumption that the drug loading has clinical relevance. Depending on the particular formulation, the therapeutic dose to be administered varies according to the indication, age and desired bioavailability (Table 4).

Table 4. Market desmopressin formulations, indications, patient group, single dose and bioavailability (adapted from Gasthuys et al. [123]).

Formulation	Indication	Patient group	Single Dose [µg]	BA [%]
Injection	CDI*	Adult	1-4	100
	CDI*	Child	0.4	
Nasal spray	CDI*	Adult	10-20	5-10
Nasal drops	CDI*	Adult	10-20	
Oral tablet	Enuresis	Adult / child (> 5 years)	200-400	0.08-0.16
	CDI*	Adult / child (> 5 years)	100-200	
	Nocturia	Adult / child (> 5 years)	100-400	
Oral lyophilizate	Enuresis	Adult / child (> 5 years)	120-240	0.26
	CDI*	Adult / child (> 5 years)	60-120	
	Nocturia	Adult / child (> 5 years)	60-240	

*CDI = chronic diabetes insipidus

This chapter has demonstrated that the field of innovative dosage forms for the administration of desmopressin, particularly with regard to the pediatric population, may offer many opportunities to improve drug safety and compliance, which is urgently needed.

A. 4 Aims of the thesis

Within this thesis, the aim was to develop a composite dosage form consisting of a film preparation and a minitablet as API reservoir in order to combine the advantages of the individual dosage forms and to eliminate their disadvantages. This approach should focus on unidirectional drug release and controlled drug application, thereby improving drug safety. This innovative dosage form is well suited for buccal administration and should increase drug safety, especially considering the pediatric population. Considering that buccal administration is a promising alternative for both locally and systemically active drugs, lidocaine hydrochloride was chosen as a representative for local efficacy and desmopressin acetate was selected as a peptide model drug with required systemic efficacy.

Section B should provide an overview of the mucoadhesive film formulations, their preparation and application.

In section C, the work should systematically investigate which manufacturing processes and materials are advantageous for the production of innovative dosage forms for buccal administration (section C.1). The focus should be on how different manufacturing processes affect handling and how the active ingredient (lidocaine hydrochloride) within the dosage form behaves during drug release and storage. Subsequently, drug permeation should be investigated using animal barriers to compare the composite dosage form containing lidocaine hydrochloride with existing alternative solid and semi-solid buccal dosage forms (section C.2). Drug permeation should serve as an indicator for comparability of efficacy.

In section D of the thesis, it should be investigated whether it is feasible to prepare low-dose composites with therapeutic dosage of desmopressin acetate and to study the subsequent permeation (section D.2).

For this concern, it was necessary to verify whether the detection of desmopressin acetate in the lower nanomolar concentration range, and thus its permeation behavior using therapeutic doses, is possible with both conventional and a new coaxial liquid-core waveguide (LCW) fluorescence detector system for HPLC (section D.1). Furthermore, the novel LCW detector should be validated with regard to the current bioanalytical guidelines of the European Medicines Agency (EMA) [124] and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Q2 [125].

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Section B.

Mucoadhesive film formulations

B. 1 Oromucosal films: from patient centricity to production by printing techniques

Pretext

This section contains a review of oromucosal films focusing on printing techniques. A sub-section deals, in more detail, with mucoadhesive films for local and systemic drug delivery. In addition, common polymers for MBFs as well as single-layer and multi-layer films will be described. With regard to oromucosal application, the advantages, especially with regard to the circumvention of the first pass effect, are also addressed in more detail. Based on this, permeation studies, using MBFs, are discussed in more detail in this section.

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Evaluation of authorship:

author	idea [%]	evaluation [%]	manuscript [%]
Yu Tian	45	35	35
Mine Orlu	5	5	5
Herman J. Woerdenbag	5	5	5
Mariagiovanna Scarpa	0	5	5
Olga Kiefer	0	5	5
Dina Kottke	0	5	5
Erica Sjöholm	0	5	5
Heidi Öblom	0	5	5
Niklas Sandler	5	5	5
Wouter L. J. Hinrichs	5	5	5
Henderik W. Frijnk	0	5	5
Jörg Breitkreutz	5	5	5
J. Carolina Visser	30	10	10

Oromucosal films: from patient centricity to production by printing techniques

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Section C.

Development and evaluation of a composite dosage form for local buccal administration

C. 1 Manufacturing and characterisation of a novel composite dosage form for buccal drug administration

Pretext

This sub-section describes the conception, development as well as evaluation of a novel composite dosage form. In order to investigate these so-called composite dosage forms in more detail, two different manufacturing methods (direct incorporation / gluing) were compared within this study to investigate the resulting properties. The purpose of this section was to determine which of the production methods would be more suitable for a potential further application. The decision was made on the basis of drug release studies, confocal Raman microscopic measurements and other investigations performed in the study.

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Evaluation of authorship:

author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Dina Kottke	70	80	70	85	75
Ard Lura	0	0	20	5	10
Dominique J. Lunter	0	0	10	10	5
Jörg Breitkreutz	30	20	0	0	10

Manufacturing and characterisation of a novel composite dosage form for buccal drug administration

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C. 2 Development and evaluation of mucoadhesive buccal dosage forms of lidocaine hydrochloride by ex-vivo permeation studies

Pretext

In this sub-section the main focus was set to comparative *ex-vivo* permeation studies with lidocaine hydrochloride loaded dosage forms. For this purpose, the previously manufactured composite dosage form was compared with minitablets and mucoadhesive films, taking into account the resulting apparent permeation coefficients. These *ex-vivo* permeation studies were performed under physiologically relatable conditions in combination with LC-MS/MS quantification to enable the evaluation of permeation in clinically relevant durations of less than one hour.

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Evaluation of authorship:

author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Dina Kottke	50	45	40	40	55
Haidara Majid	10	15	35	30	20
Jörg Breitkreutz	25	20	0	5	10
Bjoern B. Burckhardt	15	20	25	25	15

Development and evaluation of mucoadhesive buccal dosage forms of lidocaine hydrochloride by ex-vivo permeation studies

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Section D.

Development of a sensitive detection system to investigate ex-vivo permeation of systemically effective desmopressin acetate

D. 1 Application and validation of a coaxial liquid core waveguide fluorescence detector for the permeation analysis of desmopressin acetate

Pretext

In this sub-section a novel detector system based on a liquid core waveguide coupled with HPLC using fluoresence detection is described. By increasing the sensitivity, the detection of concentrations in the lower nanogram range shall be investigated using the new detector. The aim of this study is to enable the permeation of the systemically active desmopressin acetate during buccal application via composite dosage form in a clinically relevant time interval of one hour. For this purpose, the new detector system was validated according to pharmaceutical guidelines (ICH, EMA).

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author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Dina Kottke	55	65	70	70	55
Bjoern B. Burckhardt	10	10	0	20	10
Jörg Breitkreutz	5	0	0	0	10
Björn Fischer	30	25	30	10	25

Application and validation of a coaxial liquid core waveguide fluorescence detector for the permeation analysis of desmopressin acetate

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D. 2 Development and evaluation of a composite dosage form containing desmopressin acetate for buccal administration

Pretext

The advanced study described in this sub-section was performed to investigate the suitability of the composite dosage form for both local and systemic buccal administration of low-dose peptide drugs like desmopressin acetate. Drug permeation tests were conducted to determine the permeation profiles of the desmopressin acetate-loaded composite dosage forms compared with a regular, single minitablet.

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author	idea [%]	study design [%]	experimental [%]	evaluation [%]	manuscript [%]
Dina Kottke	70	85	80	80	60
Bjoern B. Burckhardt	0	5	0	10	20
Tanja C. Knaab	0	5	10	0	5
Jörg Breitkreutz	10	0	0	0	10
Björn Fischer	20	5	10	10	5

Development and evaluation of a composite dosage form containing desmopressin acetate for buccal administration

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Section E.

Summary and Perspectives

Summary and Perspectives

Within the present thesis, the focus was placed on the development of a combined dosage form of already established dosage forms with the aims of either local, or systemic controlled efficacy of drugs administered to the oral cavity.

Initially, two manufacturing methods were investigated, with both the direct incorporation method and the adhesive method being suitable for the manufacturing of the composite dosage form consisting of a bilayer mucoadhesive film and a solid matrix, in the form of a minitablet. The application of a shielding layer should ensure unidirectional release towards the oral mucosa to counteract uncontrolled swallowing of the drug. Different resulting properties were observed. The directly incorporated minitablets revealed less surface homogeneity compared to the glued ones, resulting in faster drug release but also more drug migration within the dosage form over storage. However, the adhesive method was found to be generally more suitable in terms of robustness, manual handling and lower drug migration within the dosage form. In terms of release behavior, differences could be identified but were within the specifications of Ph. Eur.

A suitable formulation of the composite dosage form was developed for the incorporation of the locally active drug substance, lidocaine hydrochloride. Within this study, the composite was shown to exhibit comparable *ex-vivo* permeations compared to a commercially available gel and higher permeation compared to in-house prepared mucoadhesive films. Even though penetration would be better than systemic uptake for local efficacy of lidocaine hydrochloride in that case, it was shown that the composite was not inferior to the semi-solid formulation.

Using LC-MS/MS as quantification method, the reliable determination of already small amounts of permeated lidocaine was possible, focusing on the clinically relevant application period of less than one hour. It could be shown that a controlled drug application could be achieved by the composite dosage form, whereby the risk of inadvertent and fully swallowed as well as uncontrolled absorbed drug amount may be considerably minimized.

For fast and reliable in-time analysis, successful coupling of a coaxial fluorescence detector system based on a liquid core optical fiber with an HPLC system was established and validated according to bioanalytical guideline (ICH Q2 and EMA bioanalytical method validation). Thus, a tenfold increase in sensitivity in quantification, compared to previous data from the dissertation of Lindert, could be achieved in the detection of desmopressin. This enabled the reliable detection of clinically relevant doses of desmopressin. Subsequently, the applicability for *ex-vivo* permeation studies could be proven, especially considering peptide therapeutics.

Finally, the composite dosage form should be used to enable desmopressin oromucosal permeation. Minitablets were prepared as a solid matrix, which contained a precise dose of 200 µg desmopressin acetate, showing fast disintegration as well as immediate drug release properties. Due to the plate-shaped structure of desmopressin acetate, it was not possible to produce minitablets with uniform content via direct compression. To produce minitablets which fulfill the requirements of the Ph. Eur. 2.9.40, a two-step granulation process and the addition of a loss supplement was necessary. Moreover, reliable determination of desmopressin delivery was achieved at a clinically relevant application dose and time. The permeation of the composite dosage form was threefold reduced compared with the plain minitablet.

Despite the lower permeation of the composite form, no significant differences in the fluctuation range were observed, suggesting a comparable dosing accuracy.

The present work has created a new option to make locally and systemically active drugs available via the oral mucosa with a higher precision and dosing accuracy compared to commercially available formulations such as gels. The main advantage is that no adhesive components need to be incorporated within the drug reservoir, thus the solid matrix of a minitablet, which can inevitably have a slowing effect on release and also on permeation due to swelling, for example. The two-layered structure of the composite MBF also enables unidirectional release towards the oral mucosa. This contributes to an improved drug safety, which is an aspect that should not be neglected, especially in infants and children.

The insights gained provide many more perspectives, which remain to be explored. One question that stays unanswered is the patients' compliance of the new composite dosage form in adults as well as in infants and children. The results of an acceptance study may provide information on optimizing the formulation and processing technologies (e.g. adhesion time, shape, size). Further investigations could focus on the permeation profiles when using even higher matrix exposure and biological membranes, especially compared with other dosage forms containing desmopressin acetate, such as nasal sprays, oral tablets, or MBFs. In addition, the creation and evaluation of a physiologically based pharmacokinetic model (PBPK model) would be an important issue, as this would provide direct information on the resulting bioavailability.

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Eidesstattliche Erklärung

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

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Dina Kottke