Oromucosal drug delivery

Trends in in-vitro biopharmaceutical assessment of new chemical entities and formulations

Brandl, Martin; Bauer-Brandl, Annette

Published in:
European Journal of Pharmaceutical Sciences

DOI:
10.1016/j.ejps.2018.11.031

Publication date:
2019

Document version:
Accepted manuscript

Document license:
CC BY-NC-ND

Citation for published version (APA):

Go to publication entry in University of Southern Denmark's Research Portal

Terms of use
This work is brought to you by the University of Southern Denmark. Unless otherwise specified it has been shared according to the terms for self-archiving. If no other license is stated, these terms apply:

• You may download this work for personal use only.
• You may not further distribute the material or use it for any profit-making activity or commercial gain
• You may freely distribute the URL identifying this open access version

If you believe that this document breaches copyright please contact us providing details and we will investigate your claim. Please direct all enquiries to puresupport@bib.sdu.dk

Download date: 14. Sep. 2023
Oromucosal drug delivery: Trends in in-vitro biopharmaceutical assessment of new chemical entities and formulations

Martin Brandl, Annette Bauer-Brandl

PII: S0928-0987(18)30522-0
DOI: https://doi.org/10.1016/j.ejps.2018.11.031
Reference: PHASCI 4765
To appear in: European Journal of Pharmaceutical Sciences

Received date: 3 August 2018
Revised date: 14 November 2018
Accepted date: 27 November 2018


This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.
Review article intended for VSI of EJPS in honor of Hartmut Derendorf

**Oromucosal drug delivery: trends in in-vitro biopharmaceutical assessment of new chemical entities and formulations**

Martin Brandl, Annette Bauer-Brandl*

Drug Transport & Delivery Group, Department of Physics, Chemistry & Pharmacy, University of Southern Denmark, Odense, Denmark

* Corresponding author.
E-mail address: annette.bauer@sdu.dk (Annette Bauer-Brandl)

**Keywords**

Oral mucosal absorption

Drug absorption

Drug penetration

Prediction

Permeability barrier

In vitro techniques

Permeapad®

Drug formulations

Excipients
Introduction

Delivery of drugs via the buccal or sublingual route has some well-known advantages over (per-)oral drug delivery: The oral mucosa, in particular the sublingual mucosa, is well permeable because the epithelium neither is keratinized nor does it develop tight junctions. There is also no significant expression of active transporters, and drugs are readily absorbed via passive transport mechanisms. The trans-cellular transport is the most significant and high capacity route.

Moreover, buccal and sublingual barriers are well-supplied with blood vessels, whereby the drug molecules are directly transferred into systemic circulation. This can lead to a rapid onset of the desired action. Furthermore, the route circumvents harsh gastric and intestinal environments regarding chemical degradation of the compounds as well as metabolic stress, such as the first-pass effect in the liver, typically observed upon (per-) oral administration. This may lead to clinical advantages such as enhanced bioavailability, less inter-individual variation, and improved safety. For systemic effect, sublingual route provides faster absorption when compared to buccal route.

In particular, oromucosal administration appears as a promising option for chemically unstable and sensitive substances

However, use of buccal and sublingual delivery is restricted by the small epithelial surface area, stratified epithelia, and the practical challenge how to ensure that the drug delivery system is retained in the mouth. Therefore, for any oromucosal drug preparations it needs to be considered which proportion of the released active compounds (in particular from disintegrating formulations) may be swallowed and in how far it may then be absorbed via the gastrointestinal tract. Furthermore, eating, drinking, or smoking, can affect drug absorption, and open sores can make it impossible to use the oromucosal route.

Oromucosal preparations are of good patient compliance due to their ease of administration without the need of swallowing. Furthermore, in most cases the preparations are of a pleasant taste and flavour. Therefore a number of pharmaceutical products, including OTCs for self-medication, have reached the market.

The classical sublingual and buccal formulation has been the lozenge. However, during the past decade, increasing interest has been put into orally disintegrating tablets (ODTs). The term “orodispersible” is the most common for such formulations, which also are found denoted rapid-disintegrating, mouth-dissolving, quick-dissolve, and even “melting”. However, for all of them the fraction of material that may be swallowed is considerable for all of them.

Until today, numerous drug substances have been studied regarding sublingual and buccal delivery; however, there are only a few products available in the market yet, mostly such ODTs and some fast dissolving preparations. Therefore, there is an increasing interest to develop alternative technologies and formulation types to improve the fraction that is not swallowed, to improve biopharmaceutical properties, and for life-cycle management.
**Current Status**

Several recent literature reviews discuss various aspects of oral mucosal (buccal/sublingual) drug delivery, such as physiology, pathways and in vivo /ex vivo models (Sattar et al, 2014), comparison of porcine mucosal sites as barrier model (Franz-Montan et al, 2016). In terms of formulations, in addition to classical lozenges and ODTs, recent trends in orodispersible films (Hoffmann et al, 2011), their use within personalized medicine (Goulooze et al, 2017; Visser et al, 2015) and for special patient populations (Slavkova & Breitkreuz, 2015) have been discussed. Others review formulation approaches and excipients, such as the technology of oral fast dissolving films (Morales & McConville 2011; Borges et al, 2015), and novel biomaterials for patches (Santos et al, 2018); for an overview over dosage forms for oral mucosal delivery see (Patel et al, 2011). Especially the aspect of muco-adhesion has been discussed extensively, e.g. thiolated polymers for mucoadhesion (Duggan et al, 2017) and their quality assessment (Woertz et al, 2013; Preis et al, 2013). Furthermore, in order to overcome the problem of poor solubility of active ingredients, advanced formulations comprising solubility –enhancing ingredients are studied (Morales et al., 2017; Tetyczka et al., 2017). Examples thereof are the use of surfactants in order to solubilize the molecules, and complexation agents such as cyclodextrins.

**Predictive bioavailability assessment**

Bioavailability predicting tools need to consider the physiology of the conditions in the oral cavity. Oral epithelium is covered by a mucus layer of glycoproteins and by saliva. The pH value of saliva typically is approximately 6. Thus drug absorption, as it is predominantly passive in mechanism, is favoured for weak acids (pKa >3) and bases (pKa <9). It should be noted that many drug substances fall into this category. Furthermore, formulations and excipients with an effect on the local pH value at the absorption site may help to increase the passive transport as well.

Molecules of low molecular mass and small volume in the solvated state, with a large number of rotatable bonds (i.e. flexible molecules) and high distribution coefficient (logD) values at pH 6 are the preferred entities in terms of a high buccal permeability. Such relationships have been quantified by in silico modelling using porcine buccal tissue as a reference transport barrier (Kokate et al, 2009).

In-silico tools appear very helpful to support the biopharmaceutical assessment of active substances from solutions and simple formulations possibly in the presence of selected excipients, e.g. pH modifiers. However, still there is a lack in predictability of drug transport of the substances from advanced formulations by in silico models.

**Ex-vivo and cell-based permeation-tools**

In order to gain an overview over recent trends in oromucosal transport studies, we screened recent research publications with respect to the transport type of set-up (Table 2). Obviously besides in-vivo animal studies in rabbits or rats, ex-vivo studies employing buccal or sublingual tissues from various species (pig, chicken, sheep, hamster pouch etc.) still represent the vast
majority of approaches chosen. In the extensive number of case studies described in the literature the porcine buccal mucosa appears to be most frequently used. Such studies are common because the tissues are relatively easily available and can be stored in the frozen state; however they are unpleasant to carry out and the biological interindividual variability may be unfavourable for ranking type of screening studies. Typical experimental set-ups are Franz cells and Ussing chambers (side-by-side diffusion cells) and variants thereof. An overview over these classical methods can be found in (Kolli & Pather, 2015).

Evaluation of drugs and formulations has also been done in vitro using cell-based models (in many cases TR146 cell type from human cancer), however, the number of such studies is much lower. The studies may be quite reproducible in intra-laboratory comparison; however, the cost of such cell-based work is high. Artificial models using non-cellular barriers such as dialysis membranes, or phospholipid-based biomimetic barriers (PAMPA, Permeapad®) are even less frequently used, although they are much cheaper to carry out and should be expected to be most reproducible also betweeen different laboratories.

The vast majority of transport studies aims at performance ranking of drug substances and buccal / sublingual formulations (tablets, ODTs, strips, buccal films, mucoadhesive formulations etc.). For this purpose, artificial models appear attractive to reduce cost, time and the number of animal studies.

To this end we want to restrict ourselves and focus on artificial in-vitro tools for biopharmaceutical assessment and ranking of oral mucosal drugs and formulations, an aspect, which is gaining increasing attention in the light of advanced delivery system development. At the same time it is not covered extensively in recent review articles and book chapters.

**Non-cell based biopharmaceutical assessment tools**

Artificial barriers may represent attractive alternatives to evaluate permeation as compared to any cell- or tissue-based models as they are less laborious in preparation and are expected to yield more reproducible results since variability typically coming along with biological models is circumvented (Berben et al, 2018). In essence, non-cellular permeation models appear less expensive, readily available and therefore most suitable for screening settings in high throughput formats in order to rank drug substances (drug discovery) and their formulations (early drug development) with respect to their biopharmaceutical performance.

It should be kept in mind, however, that non-cellular barriers are best suited to mimic the transcellular passive transport pathway. This appears as an disadvantage with respect to the gastric pathway for compounds primarily taken up via tight junctions, or in cases where transporter-associated uptake or excretion plays a role cellular models may thus be better suited. It is thus an advantage to use non-cellular barriers for oromucosal uptake, where both active transport and tight junctions do not play much of a role. However, biotransformation and specific interactions
with buccal epithelium is reserved for ex vivo and in vivo studies and cannot be mapped by artificial barriers. It may, however, be possible to study the interaction with mucus in artificial models by applying (artificial) mucus on the respective barrier.

**Artificial barriers for oromucosal permeation studies**
Table 1 shows an overview over artificial membranes that have been used in oromucosal transport studies

First of all, it needs to be mentioned that in the case of mucoadhesive drug dosage forms it is very difficult to exactly distinguish the processes of drug release from the dosage forms and the permeation step.

**Filter membranes**
Traditionally, the drug release from buccal patches and other oromucosal dosage forms has been discussed in the literature in the form of mass transport kinetics. For the experiments cellulose acetate membranes have been used to fix the patches in the release vessels. Membranes used for other purposes such as hydrophilic and lipophilic filters of pore sizes of 0.2 µm or 0.45 µm have been used in several studies in the literature:

In one of these studies the release of nicotine from buccal matrix tablets is evaluated where a cellulose acetate membrane (hydrophilic filter of pore size 0.45 µm) in Franz diffusion cells was used (Pongjanyakul & Suksri, 2009). In a follow-up study (Pongjanyakul & Kanjanabat, 2012) prolonged release matrix tablets with nicotine were studied in terms of pH dependent release through the same cellulose acetate membrane (0.45 µm pore size). The effect of pH was as follows: better transport under acidic conditions (better soluble protonated salt form of nicotine) as compared to the free base at higher pH. This observation is in clear contradiction to the generally acknowledged mechanism of pH dependent partitioning and the permeation mechanism through biological barriers, which is preferred for non-polar compounds. The pH-dependent permeation rate across oesophageal porcine mucosa followed the expectation. This study clearly shows the fundamental difference between simple diffusion of compounds through filter membranes which is not selective for their dissociation states and biomimetic permeation that follows pH partitioning hypothesis.

In yet another study, hydrophilic cellulose acetate filter (0.45 µm pore size) was used for drug release from hydrogels (salbutamol) focussing on mechanical properties such as presence of micelles and viscosities according to the degree of gelation (Zeng et al, 2014).

Similarly, artificial cellulose nitrate membrane (which typically is used as a lipophilic filter membrane) was employed in flux studies attributed to release for different formulations of chitosan gels of celecoxib of different pH values and viscosities (Cid et al, 2012). For the same formulations pig cheek mucosa permeability was measured for a comparison. However, release
kinetics in terms of diffusion and flux revealed not the same rank order as permeation studies through the tissue.

Apart from cellulose acetate and cellulose nitrate membranes discussed above, there are commercially available membranes of alternative materials made of polyethersulfone PES (hydrophilic filter material typically of 0.1 µm pore size and above for high water flow), polypropylene PP (typically used as hydrophobic pre-filters available at 0.1 µm pore size and above), and cellulose (typically used in the form of syringe filters with pore sizes 0.2 µm and above). Delvadia and co-workers (Delvadia et al, 2012) used such filter membranes for in vitro drug release/flux experiments and compared with an oral transmucosal in vivo permeation study. The dosage form studied in this case was snus – i.e. tobacco in pouches to be put between upper lip and gum. Their work focused on experimental set-ups of permeation cells, using -amongst others - a flow through cell type. In yet another layout the donor cell was located between two receiver cells in order to mimic the location of snus. The flux/permeation kinetics was compared to nicotine absorption in humans. Flow-through cells gave linear relationships between release and in vivo absorption whereas for the bidirectional apparatus a non-linear relationship was found. Both relationships rendered useful for predictive models. Among the tested membranes, cellulose demonstrated the best in vitro- in vivo relationship (IVIVR). However, with respect to the term “biorelevance”, it should be noted that a single formulation was tested in this study under the very same conditions and no information about the effect of pH on permeation through the membranes can be deducted.

**Dialysis membranes**
A number of other studies use dialysis membranes for diffusion studies in similar models. Dialysis membranes typically have much smaller pores as compared to the above discussed filter membranes and are characterized by their molecular weight cut-off (MWCO).

For bioadhesive buccal gels dialysis membranes have been used as a support in release studies (Dhiman et al, 2008) and similarly for studying the drug release from liposomes to be used for buccal administration (Lankalapalli et al, 2016).

A dialysis membrane (of which no information regarding MWCO is available) was also used to study the relationship between release of atenolol from patches and ex vivo permeation through porcine buccal mucosa. However, although formulations of (probably) different pH were used (as there is no mentioning of neutralizing the acrylic acid gels) there are only small differences in release kinetics. The release curves appear very much alike, which is also reflected by the curve fitting results. The highest ex vivo permeation was not the same as found by the dialysis membrane experiments (Adhikari et al, 2010).

**Polysiloxane membranes**
Polysiloxane membranes have already been used in modified release of drugs for a long time because of their permeability for small molecules by diffusion mechanisms (Gaginella et al, 1974).
The permeation rates of weak acids and bases through polydimethylsiloxane membrane (PDMS) are pH dependent. This may be due to the hydrophobic nature of the matrix and/or due to an effect of the basic groups on the surface: they create attraction or respectively repulsion forces towards the ionized forms of the drug molecules thus hindering the bulk transport. The relationship between flux and concentration of neutral form of the drug is not linear (Waters & Bhuiyan, 2016).

Polyethylenoxide (PEO) tablets for the buccal use of diclofenac were studied with a silicone membrane (thickness is reported to be 300 µm) in a Franz cell set-up. Regarding the hypothesis of a matrix permeation mechanism and the effect of pH, Papp values reveal much higher permeability at pH3. However, it needs to be noted that the flux was approximately unchanged between pH 3 and pH 6.8. The interpretation of this result is due to the fact that in both cases suspensions of diclofenac have been used, and the solubility of the non-dissociated form of the drug restricts permeation at both pH values (Miro et al, 2009). Furthermore, it has been reported that the drug transport over the artificial barrier was considerably lower than over porcine mucosa.

**Parallel artificial membrane permeation assay PAMPA**

Variants of PAMPA (parallel artificial membrane permeability assay) models are frequently used for permeation studies and they can be used in high throughput set-ups on microtiterplates.

In order to study pH dependent permeation, Wang and co-workers used a multiscreen filter plate assembly (Millipore) the filter material of which was not specified; the filter plates were impregnated with a hexadecane / hexane blend and used after evaporation(Wang et al, 2008). Modelling of pH dependent permeability for sildenafil in the pH range between 3 and 11 was done. The authors studied solubility of this amphoteric compound at different pH values and the maximal flux at the pHmax values. Reasonable correlation has been achieved between predicted and measured permeation through this PAMPA variant. However, as the solubility of the drug substance depends on the dissociation state and is involved in the experiment, the transport mechanism through this PAMPA variant seems not to be pH dependent.

Alternatively, artificial membranes of the PAMPA type may comprise phospholipids deposited from organic solution on / in membrane filters; these are expected to better reflect biomimetic transport processes than phospholipid free systems. Khdair and co-workers (Khdair et al, 2013) used a variant of PAMPA comprising cellulose acetate nitrate filters and cellulose acetate filters, respectively, which were impregnated with L - phosphatidylethanolamine from octanol solution. The motivation was to create a more viscous lipid membrane as compared to phosphatidylcholine.

Permeation of the model substance carvedilol was studied and the effect of additives (sodium taurocholate, sodium taurodesoxycholate, camphor, and menthol) on solubility as well as on permeation was studied. Linear relationships (with Person coefficients reported to be close to 1) between the permeation of carvedilol through the artificial membrane and through rabbit and
porcine mucosa, respectively, were found. However, the mechanism of permeation enhancement remains unclear in this study.

**Permeapad®**
A recent study (Bibi et al, 2016) discussed buccal formulations in terms of permeability through another phospholipid based barrier artificial barrier (Permeapad®) and discusses the difference thereof as compared to a dialysis membrane. Furthermore, the direct comparison of permeation of the same formulations through a cell-based model, a tissue type as well as in vivo study using mini-pigs from literature (Holm et al, 2013) is shown. The weak base metoprolol as a model drug was used in the form of gels of different pH values in the range 7.4 to 9.5 close to the pKa value of metoprolol as a model system. The permeabilities of these gels were discussed for all 3 models and the in vivo study. The study showed that the dialysis-type membrane (sheer hydrophilic support sheet of the cellulose hydrate type) did not reflect any pH effect on permeation due to its principle of molecular diffusion (or dialysis). However, for the full Permeapad® membrane which includes the phospholipid layers mounted between support sheets, the permeability increased with increasing pH as expected according to pH partitioning hypothesis. All of the permeation systems apart from dialysis (i.e. Permeapad®, in vitro, ex vivo, and in vivo) reflected the pH effect of dissociation state in a similar way. However, none of the models revealed a strict linear relationship according to pH partitioning hypothesis. Permeability values for Permeapad® showed excellent correlation (Pearson correlation values > 0.97 in all cases) not only to in vitro TR146 cell culture, ex vivo porcine buccal mucosa in modified Ussing chambers, but also to the in vivo data from minipigs. In the case described, the formulation optimization for best bioavailability gel could have been done by using the non-cell based permeation model based on phospholipids (Permeapad®), and save a number of animal tests.

**Future Trends**
The attractiveness of the oromucosal drug delivery route for sensitive materials regarding chemical degradation has been widely acknowledged. In addition, there is a current trend towards increased therapeutic efforts based on biologics, including peptides and proteins. For the sake of patient compliance and in order to make such therapy more economic, these substances have a great potential for the oromucosal route. On the other hand, when it comes to small molecule therapeutics, the vast majority of the newly introduced compounds as well as those under development are poorly soluble. In their case there is a current trend towards the use of advanced formulations to overcome this problem. Examples thereof are nano-sized constructs, including lipid base nanoparticles, and amorphous materials. However, the more advanced the formulations are, the more screening work for their optimization is needed.

Consequently, it is expected that the number of in-vitro screening studies will steeply increase in the near future. The currently available in-vitro-tools will be judged according to practicalities in pre-clinical high-throughput screening set-ups and according to their predictive power for bioavailability for new substances and advanced enabling formulations. Therefore, the test...
systems must be robust in the presence of excipients and enzymes and be able to catch pH – dependent effects. In this light, the artificial barriers that are already available also await widespread use because they are cost-effective and time efficient to use. It is also expected that new artificial test systems to improve predictiveness and throughput while reducing cost will be developed. Artificial test systems in general have an advantage in terms of better repeatability of transport properties as compared to ex-vivo studies because any biological variability is excluded. Thus, if cost and time-consumption for the screening of oromucosal preparations can be reduced by using predictive artificial test systems, the development of new and advanced oromucosal formulations will become an even more attractive pathway towards efficient, well-tolerated and economical medicines.

Summary:
Although the development of buccal application forms of drugs is of increasing interest, up to now only few studies have been performed on permeation through cell-free models. However, there is increasing justification for the use of artificial membranes to replace the classical cell- and tissue-based systems. The artificial membranes should distinguish transport kinetics according to molecular mass and molecule flexibility. Furthermore, they should also be biomimetic in the sense that they distinguish different dissociation states according to pH partitioning hypothesis. In accordance with expectations, membrane filters and dialysis membranes are not suitable for this. It appears that dissociation states may be distinguished by silicone membranes, and to a greater extent by phospholipid based models (PAMPA variants and Permeapad®). Regarding other molecule properties such as flexibility, data are available with excellent IVIVR for Permeapad®.

In general the physicochemical properties of the drug do not influence its permeation across synthetic membranes to the same extent as across biological membranes. However, if the explicit relationship is known, excellent predictions are still possible and ranking of substances or respectively formulations appears feasible in order to reduce the number of in vivo studies necessary in drug discovery and drug development.

Acknowledgement
This article is based upon work carried out under COST Action 16205 UNGAP, supported by COST (European Cooperation in Science and Technology) as well as Nordic POP (patient oriented products), a Nordic University Hub funded by NordForsk (Project number: 85352).

References:
Abozaid, D., Ramadan, A., Barakat, H., Khalafallah, N.
DOI: 10.1016/j.ejps.2018.05.016
Adeleke, O.A., Tsai, P.-C., Karry, K.M., Monama, N.O., Michniak-Kohn, B.B.  
Isoniazid-loaded orodispersible strips: Methodical design, optimization and in vitro-in silico characterization  
DOI: 10.1016/j.ijpharm.2018.06.004  
Adhikari, S.N.R., Nayak, B.S., Nayak, A.K., Mohanty, B.  
Formulation and evaluation of buccal patches for delivery of atenolol  
Asthana, G.S., Sharma, S., Asthana, A.  
Formulation and evaluation of alginate-based mucoadhesive buccal patch for delivery of antimigraine drug  
DOI: 10.22159/ajpocr.2018.v11i4.23345  
Baltzley, S., Malkawi, A.A., Alsmadi, M., Al-Ghananeem, A.M.  
Sublingual spray drug delivery of ketorolac-loaded chitosan nanoparticles  
DOI: 10.1080/03639045.2018.1460378  
Drug permeability profiling using cell-free permeation tools: Overview and applications  
DOI: 10.1016/j.ejps.2018.04.016  
Bibi, H.A., Holm, R., Bauer-Brandl, A.  
Use of Permeapad® for prediction of buccal absorption: A comparison to in vitro, ex vivo and in vivo method  
Oral films: Current status and future perspectives: I-Galenical development and quality attributes  
DOI: 10.1016/j.jconrel.2015.03.006  
Castro, P.M., Baptista, P., Madureira, A.R., Sarmento, B., Pintado, M.E.  
Combination of PLGA nanoparticles with mucoadhesive guar-gum films for buccal delivery of antihypertensive peptide  
DOI: 10.1016/j.ijpharm.2018.05.051  
Incorporation of beads into oral films for buccal and oral delivery of bioactive molecules  
DOI: 10.1016/j.carbpol.2018.04.032  
Chen, J., Pan, H., Yang, Y., Xiong, S., Duan, H., Yang, X., Pan, W.  
Self-assembled liposome from multi-layered fibrous mucoadhesive membrane for buccal delivery
of drugs having high first-pass metabolism
DOI: 10.1016/j.ijpharm.2018.05.062

Cid, Y.P., Pedrazzi, V., De Sousa, V.P., Pierre, M.B.R.
In vitro characterization of chitosan gels for buccal delivery of celecoxib: Influence of a penetration enhancer

De Toni, L., Ponce, M.R., Franceschinis, E., Dall’Acqua, S., Padrini, R., Realdon, N., Garolla, A., Foresta, C.
Sublingual administration of sildenafil oro-dispersible film: New profiles of drug tolerability and pharmacokinetics for PDE5 inhibitors
DOI: 10.3389/fphar.2018.00059


Dhiman, M., Yedurkar, P., Sawant, K.K.
Formulation, characterization, and in vitro evaluation of bioadhesive gels containing 5-fluorouracil

Duggan, S., Cummins, W., O’ Donovan, O., Hughes, H., Owens, E.
Thiolated polymers as mucoadhesive drug delivery systems
DOI: 10.1016/j.ejps.2017.01.008

Eleftheriadis, G.K., Monou, P.K., Bouropoulos, N., Fatouros, D.G.
In vitro evaluation of 2D-printed edible films for the buccal delivery of diclofenac sodium
DOI: 10.3390/ma11050864

Freag, M.S., Saleh, W.M., Abdallah, O.Y.
Laminated chitosan-based composite sponges for transmucosal delivery of novel protamine-decorated tripterine phytosomes: Ex-vivo mucopenetration and in-vivo pharmacokinetic assessments
DOI: 10.1016/j.carbpol.2018.01.095

Gaginella, T.S., Welling, P.G., Bass, P.
Nicotine base permeation through silicone elastomers: Comparison of dimethylpolysiloxane and trifluoropropylmethylpolysiloxane systems

Towards personalized treatment of pain using a quantitative systems pharmacology approach


Martins, I.C.F., Raposo, N.R.B., Mockdeci, H.R., Polonini, H.C., de Oliveira Ferreira, A., Fabri, G.M.C., Das Graças Afonso Miranda Chaves, M.
Delivering resveratrol on the buccal mucosa using mucoadhesive tablets: A potential treatment strategy for inflammatory oral lesions
DOI: 10.2174/1567201814666170726102558

Marxen, E., Jacobsen, J., Hyrup, B., Janfelt, C.
Permeability Barriers for Nicotine and Mannitol in Porcine Buccal Mucosa Studied by High-Resolution MALDI Mass Spectrometry Imaging
DOI: 10.1021/acs.molpharmaceut.7b00891

Effect of Permeation Enhancers on the Buccal Permeability of Nicotine: Ex vivo Transport Studies Complemented by MALDI MS Imaging
(2018a) Pharmaceutical Research, 35 (3), art. no. 70, .
DOI: 10.1007/s11095-017-2332-y

Miro, A., Rondinone, A., Nappi, A., Ungaro, F., Quaglia, F., La Rotonda, M.I.
Modulation of release rate and barrier transport of Diclofenac incorporated in hydrophilic matrices: Role of cyclodextrins and implications in oral drug delivery

Monajjemzadeh, F., Bagheri, M., Montazam, S.H., Jelvehgari, M.
Preparation and in vitro/ex vivo evaluation of buccoadhesive discs of an anti-Parkinson drug: Relationship between mucoadhesivity, drug release and permeability
DOI: 10.15171/PS.2018.10

Morales, J.O., McConville, J.T.
Manufacture and characterization of mucoadhesive buccal films
DOI: 10.1016/j.ejpb.2010.11.023

Challenges and Future Prospects for the Delivery of Biologics: Oral Mucosal, Pulmonary, and Transdermal Routes

Mura, P., Orlandini, S., Cirri, M., Maestrelli, F., Mennini, N., Casella, G., Furlanetto, S.
A preliminary study for the development and optimization by experimental design of an in vitro method for prediction of drug buccal absorption
DOI: 10.1016/j.ijpharm.2018.06.032

Padula, C., Telò, I., Di Ianni, A., Pescina, S., Nicoli, S., Santi, P.
Microemulsion containing triamcinolone acetonide for buccal administration
DOI: 10.1016/j.ejps.2018.01.031

Patel, V.F., Liu, F., Brown, M.B.
Advances in oral transmucosal drug delivery
DOI: 10.1016/j.jconrel.2011.01.027

Pongjanyakul, T., Kanjanabat, S.
Influence of pH modifiers and HPMC viscosity grades on nicotine-magnesium aluminum silicate complex-loaded buccal matrix tablets

Pongjanyakul, T., Sukrisri, H.
Alginate-magnesium aluminum silicate films for buccal delivery of nicotine

Preis, M., Woertz, C., Kleinebudde, P., Breitkreutz, J.
Oromucosal film preparations: Classification and characterization methods
DOI: 10.1517/17425247.2013.804058

Rachid, O., Rawas-Qalaji, M., Simons, K.J.
Epinephrine in anaphylaxis: Preclinical study of pharmacokinetics after sublingual administration of taste-masked tablets for potential pediatric use
(2018) Pharmaceutics, 10 (1), art. no. 24, .
DOI: 10.3390/pharmaceutics10010024

Rahbarian, M., Mortazavian, E., Dorkoosh, F.A., Rafiee Tehrani, M.
Preparation, evaluation and optimization of nanoparticles composed of thiolated triethyl chitosan: A potential approach for buccal delivery of insulin

Sahar, S.A.
Sodium cromoglycate mucoadhesive buccal patches: Design, fabrication, in vitro and in vivo characterization
DOI: 10.22159/ijap.2018v10i2.24333

Santos, L.F., Correia, I.J., Silva, A.S., Mano, J.F.
Biomaterials for drug delivery patches
DOI: 10.1016/j.ejps.2018.03.020

Sattar, M., Sayed, O.M., Lane, M.E.
Oral transmucosal drug delivery - Current status and future prospects
DOI: 10.1016/j.ijpharm.2014.05.043
Comparative study of Ex Vivo transmucosal permeation of pioglitazone nanoparticles for the 
treatment of Alzheimer's disease 
(2018) Polymers, 10 (3), art. no. 316, .
DOI: 10.3390/polym10030316

Slavkova, M., Breitkreutz, J. 
Orodispersible drug formulations for children and elderly 
DOI: 10.1016/j.ejps.2015.02.015

Song, Q., Shen, C., Shen, B., Lian, W., Liu, X., Dai, B., Yuan, H. 
Development of a fast dissolving sublingual film containing meloxicam nanocrystals for enhanced 
dissolution and earlier absorption 
DOI: 10.1016/j.jddst.2017.10.020

Development of nanostructured lipid carriers for intraoral delivery of domperidone 

Visser, J.C., Woerdenbag, H.J., Crediet, S., Gerrits, E., Lesschen, M.A., Hinrichs, W.L.J., Breitkreutz, 
J., Frijlink, H.W. 
Orodispersible films in individualized pharmacotherapy: The development of a formulation for 
pharmacy preparations 
DOI: 10.1016/j.ijpharm.2014.11.013

Wang, Y., Chow, M.S.S., Zuo, Z. 
Mechanistic analysis of pH-dependent solubility and trans-membrane permeability of amphoteric 
compounds: Application to sildenafil 

Waters, L.J., Bhuiyan, A.K.M.M.H. 
Ionisation effects on the permeation of pharmaceutical compounds through silicone membrane 

Woertz, C., Preis, M., Breitkreutz, J., Kleinebudde, P. 
Assessment of test methods evaluating mucoadhesive polymers and dosage forms: An overview 
DOI: 10.1016/j.ejpb.2013.06.023

Zaman, M., Hanif, M., Shaheryar, Z.A. 
Development of Tizanidine HCl-Meloxicam loaded mucoadhesive buccal films: In-vitro and in-vivo 
evaluation 
DOI: 10.1371/journal.pone.0194410
Zeng, N., Dumortier, G., Maury, M., Mignet, N., Boudy, V.
Influence of additives on a thermosensitive hydrogel for buccal delivery of salbutamol: Relation between micellization, gelation, mechanic and release properties
Table 1. Permeation, absorption bioavailability studies – recent trends

<table>
<thead>
<tr>
<th>Drug</th>
<th>Formulation type</th>
<th>Type of study</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ketorolac</td>
<td>nanoparticles, spray</td>
<td>in vivo: rabbit, sublingual</td>
<td>Baltzley et al., 2018</td>
</tr>
<tr>
<td>aciclovir</td>
<td>nanocapsule</td>
<td>ex vivo: chicken pouch</td>
<td>Abozaid et al., 2018</td>
</tr>
<tr>
<td>naproxen</td>
<td>none; solution in simulated saliva</td>
<td>ex vivo: porcine buccal mucosa in vitro, non-cellular: various membrane filter supports impregnated with phospholipid</td>
<td>Mura et al., 2018</td>
</tr>
<tr>
<td>carvedilol</td>
<td>liposome</td>
<td>ex vivo: porcine buccal mucosa in vitro, non-cellular: dialysis membrane</td>
<td>Chen et al., 2018</td>
</tr>
<tr>
<td>antihypertensive peptide</td>
<td>nanoparticle, guar-film</td>
<td>In vitro, cellular: TR146</td>
<td>Castro et al., 2018a</td>
</tr>
<tr>
<td>caffeine</td>
<td>nanoparticle, guar-film</td>
<td>In vitro, cellular: TR146</td>
<td>Castro et al., 2018b</td>
</tr>
<tr>
<td>isoniazid</td>
<td>orodispersible film</td>
<td>ex vivo: porcine buccal mucosa</td>
<td>Adeleke et al., 2018</td>
</tr>
<tr>
<td>diclofenac Na</td>
<td>Printed film</td>
<td>In vitro, non-cellular: dialysis membrane</td>
<td>Eleftheriadis et al., 2018</td>
</tr>
<tr>
<td>tripterine</td>
<td>phytosome</td>
<td>ex vivo: chicken pouch</td>
<td>Freag et al., 2018</td>
</tr>
<tr>
<td>fenofibrate</td>
<td>amorphous solid dispersion; sublingual tablet</td>
<td>in vivo: rabbit, sublingual</td>
<td>Ibrahim et al., 2018</td>
</tr>
<tr>
<td>iloperidone</td>
<td>film</td>
<td>In vivo: rat</td>
<td>Londhe &amp; Shirsat, 2018</td>
</tr>
<tr>
<td>sumatriptane succinate</td>
<td>patch</td>
<td>In vivo: rabbit; Ex vivo: porcine sublingual tissue</td>
<td>Asthana et al., 2018</td>
</tr>
<tr>
<td>insulin</td>
<td>nanoparticle</td>
<td>Ex vivo: rabbit buccal mucosa</td>
<td>Rahbarian et al., 2018</td>
</tr>
<tr>
<td>triamcinolone</td>
<td>microemulsion</td>
<td>Ex vivo: pig esophageal mucosaa</td>
<td>Padula et al., 2018</td>
</tr>
<tr>
<td>pioglitazone</td>
<td>nanoparticle</td>
<td>Ex vivo: sublingual mucosa</td>
<td>Silva-Abreu et al., 2018</td>
</tr>
<tr>
<td>ropinirole</td>
<td>film</td>
<td>In vivo: rabbit</td>
<td>Lai et al., 2018</td>
</tr>
<tr>
<td>nicotine</td>
<td>Solution, absorption enhancers</td>
<td>ex vivo: porcine buccal mucosa</td>
<td>Marxen et al., 2018</td>
</tr>
<tr>
<td>tizanidine HCl, meloxicam</td>
<td>film</td>
<td>In vivo: rabbit</td>
<td>Zaman et al., 2018</td>
</tr>
<tr>
<td>epinephrine</td>
<td>Sublingual tablet</td>
<td>In vivo: rabbit</td>
<td>Rachid et al., 2018</td>
</tr>
<tr>
<td>cromoglycate</td>
<td>patch</td>
<td>In vivo: rabbit; Ex vivo: porcine sublingual tissue</td>
<td>Sabry, 2018</td>
</tr>
<tr>
<td>selegiline HCl</td>
<td>patch</td>
<td>Ex vivo: sheep mucosa</td>
<td>Monajjemzadeh et al., 2018</td>
</tr>
<tr>
<td>sildenafil</td>
<td>film</td>
<td>In vivo: human volunteer</td>
<td>De Toni et al., 2018</td>
</tr>
<tr>
<td>mirtazapine</td>
<td>tablet</td>
<td>Ex vivo: sheep mucosa</td>
<td>Koradia &amp; Chaudhari, 2018</td>
</tr>
<tr>
<td>meloxicam</td>
<td>Nanocrystal, film</td>
<td>In vivo: rat</td>
<td>Song et al., 2018</td>
</tr>
<tr>
<td>resveratrol</td>
<td>tablet</td>
<td>Ex vivo: porcine sublingual tissue</td>
<td>Martins et al., 2018</td>
</tr>
</tbody>
</table>
Table 2 Overview over artificial barriers used in oromucosal transport studies

<table>
<thead>
<tr>
<th>Membrane Material</th>
<th>Pore Size</th>
<th>Characteristics</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellulose acetate</td>
<td>0.45 µm</td>
<td></td>
<td>Pongjanyakul &amp; Suksri, 2009, Pongjanyakul &amp; Kanjanabat, 2014, Zeng et al, 2014</td>
</tr>
<tr>
<td>Cellulose nitrate</td>
<td>?</td>
<td></td>
<td>Cid et al, 2012</td>
</tr>
<tr>
<td>Polyethersulfone</td>
<td>0.1 µm</td>
<td></td>
<td>Delvadia et al, 2012</td>
</tr>
<tr>
<td>Polypropylene</td>
<td>0.1 µm</td>
<td></td>
<td>Delvadia et al, 2012</td>
</tr>
<tr>
<td>Cellulose</td>
<td>0.2 µm</td>
<td></td>
<td>Delvadia et al, 2012</td>
</tr>
<tr>
<td>Dialysis membrane (regenerated cellulose)</td>
<td></td>
<td>cut-off MW 12-14 kDa (Ref Lankalapalli); for the other refs: unknown</td>
<td>Dhiman et al, 2008, Lankalapalli et al, 2016, Adhikari et al, 2010</td>
</tr>
<tr>
<td>Silicone; polydimethylsiloxane</td>
<td>300 µm thickness</td>
<td></td>
<td>Waters &amp; Bhuiyan, 2016, Miro et al, 2009</td>
</tr>
<tr>
<td>Non-specified filter-support (PAMPA)</td>
<td></td>
<td>impregnated with hexadecane/hexane</td>
<td>Khdair et al, 2013</td>
</tr>
<tr>
<td>Cellulose acetate nitrate filter; cellulose acetate filter (PAMPA)</td>
<td></td>
<td>impregnated with phosphatidylethanolamine in octanol solution</td>
<td>Khdair et al, 2013</td>
</tr>
<tr>
<td>Permeapad®</td>
<td></td>
<td>Phospholipids deposited between hydrophilic support sheets</td>
<td>Bibi et al, 2016</td>
</tr>
<tr>
<td>Various membrane filter-supports (cellulose, polyamide)</td>
<td>0.025 to 0.2 µm</td>
<td>Impregnated with phospholipid and cholesterol in octanol solution</td>
<td>Mura et al., 2018</td>
</tr>
</tbody>
</table>