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ORAL THIN FILMS – REALMS OF POSSIBILITY?

As interest in oral thin film grows, there is an increasing effort to study new and improved methods of drug delivery in the buccal cavity. Muco-adhesive studies have increased, leading to the introduction of a prescription product approved for chronic pain treatment. This article, from Rick Chan, PhD, Executive Scientific Officer, LTS Lohmann Therapy Systems, will discuss the fundamentals of transmucosal absorption and how formulation effort and the drug properties influence drug absorption in the buccal cavity.

The oral route of drug administration is the most common and offers the significant benefits of being non-invasive, and pain avoidance. Increasingly, there is an interest in transmucosal delivery via the buccal cavity. The sublingual route of administration has been used for decades to deliver glyceryl trinitrate for the treatment of angina. A key advantage of a drug delivered transmucosally in the buccal cavity is the avoidance of first-pass metabolism and consequent increase in bioavailability. Correspondingly, this increase in bioavailability could lead to a lower dose requirement and hence reduce drug exposure and associated side effects.

In addition, oral thin films are typically fast dissolving, negating the need for water when administered. This eliminates the fear of choking associated with swallowing a tablet or for people suffering from dysphagia, difficulty swallowing. They therefore offer significant benefits to patient populations such as the elderly or those suffering from parkinsonism.

SITE OF ABSORPTION & TRANSPORT MECHANISM

The major sites of transmucosal absorption are under the tongue and though the buccal cheek and, to a lesser extent, drug absorption takes place in the palate, and the lingual part of the tongue. The lining of the mucosa in these areas is covered by a stratified, non-keratinised squamous

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epithelium (see Figure 1 and Table 1).¹ Although the surface areas of the oral mucosa are relatively small when compared with the gastrointestinal tract or skin, the high vasculature lends itself to potential drug absorption.

A potential hindrance to drug permeation across the buccal mucosa is the presence of membrane-coating granules (MCGs) which are vesicles observed in the cells composing the epidermis and have been described as the precursors of the keratin layer. It has been reported that some MCGs in the buccal mucosa contain a roughly organised lipid lamellae domain.² The intercellular space of this stratified, non-keratinised buccal



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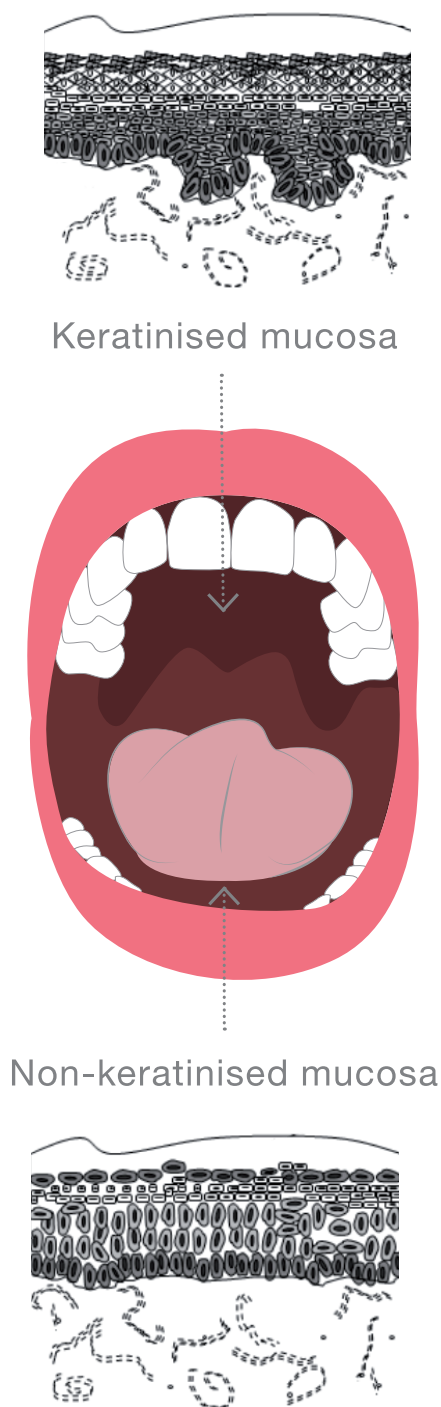


Figure 1: Mucosal regions of the mouth.¹

Regional variation of mucosal tissue within the oral cavity

Mucosa type	Characteristics
Masticatory	Keratinized epithelium Hard palate, gingival 25% of total surface area of oral cavity
Lining	Nonkeratinized epithelium Cheek, sublingual, alveolar 60% of total surface area
Specialized	Both keratinized and nonkeratinized Tongue 15% of total surface area

Table 1: Regional variation of mucosal tissue within the oral cavity.¹

membrane is filled with a combination of amorphous materials where short stacks of lipid lamella can be observed. This structural difference observed in buccal membrane when compared with skin and other keratinised epithelia could be responsible for the difference in permeability of these membranes.^{3,4}

The buccal epithelium structure thus contains two different domains, a lipophilic domain corresponding to the membrane of the stratified epithelium; and the more hydrophilic domain corresponding to the extruded content from the MCGs into the inter-cellular space. This then offers two major routes of drug absorption, namely paracellular (between cells) and the transcellular (through cells) pathways (Figure 2).⁵

The lipophilic nature of the cell membranes favours the passage of molecules with high log P values across the cell whereas the polar nature of the intercellular space favours the penetration of more hydrophilic molecules. Depending on the physicochemical characteristics of the drug molecule, either the more hydrophobic, or the more hydrophilic, or a combination of both routes could allow for absorption.⁷

FACTORS AFFECTING DRUG ABSORPTION

Physicochemical Properties of the API

The primary mechanism of drug permeation is via passive diffusion. As a consequence, the partition coefficient, degree of ionisation and the molecular mass exert a major influence on drug delivery across the oral mucosal membrane.⁷

The extent of absorption is generally proportional to the lipophilicity or oil-in-water partitioning of the active pharmaceutical ingredient (API). However, the solubility of the drug also plays a key role.⁸ The unionised form of the drug is more lipid soluble, and thus would permeate and diffuse across the

biological membrane. The pKa of the drug molecule, and the degree of its ionisation in the pH environment need to be considered for its bioavailability. The effect of pH on drug absorption via the oral mucosa has been studied extensively.⁷

For absorption to occur, the API must be dissolved. If the drug is too lipophilic, it cannot dissolve sufficiently in the aqueous medium and hence may not be available for significant absorption. Thus a delicate balance exists between the lipophilicity of the drug and the solubility. It is therefore important to understand the solubility, pKa of the drug molecule and the pH environment the dosage form is subject to, to maximise drug absorption profile.

Formulation Factors

1. Permeation Enhancers

We discussed earlier that the buccal cavity has limited area for drug absorption, which relies on passive diffusion. This limitation leads to either too small an amount of drug is absorbed or too slow in many cases to exert any therapeutic effects. In order to increase the diffusion of the drug molecule across the membrane, chemical permeation enhancers are commonly used in the formulation to aid absorption.

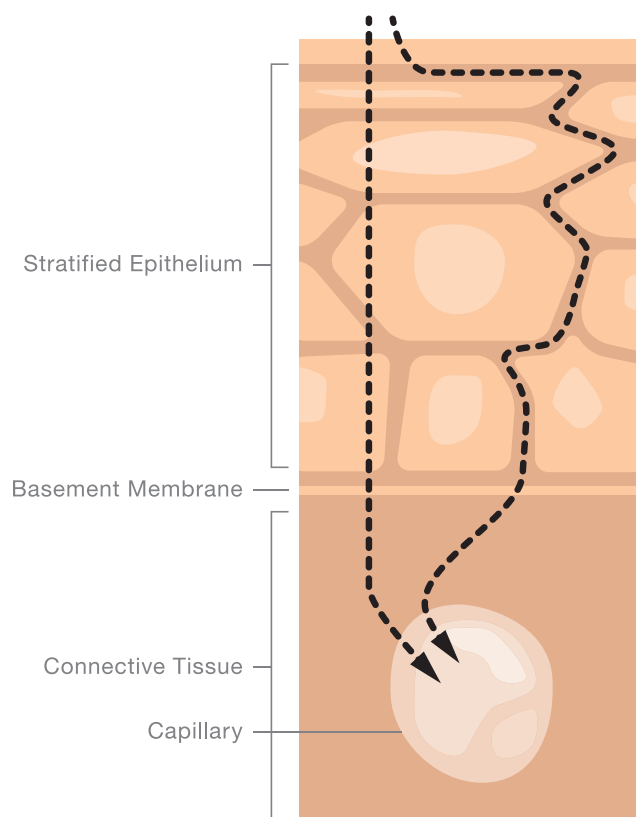


Figure 2: Routes of transepithelial penetration: the transcellular and intracellular pathways.⁶

Permeation enhancers used in transmucosal studies have included surfactants, fatty acids, fatty alcohols, polyols and bile salts.

It has been proposed that permeation enhancers improved mucosal transport in the following ways:^{9,10}

- Changing the mucus rheology in reducing the viscosity and/or elasticity of the mucus layer
- Increasing the membrane fluidity and, in so doing, facilitating transport
- Modifying drug solubility parameters.

Nakane *et al*¹¹ studied the PK profiles of LHRH released from oral films in dogs. The films were formulated with 5% bile salts, either sodium taurodeoxycholate (STDC), sodium deoxycholate (SDC) and sodium cholate (SC). They observed that the films containing the bile salts released significant amount of LHRH compared with a control film without the bile salt. Higher exposure was obtained for the bile salt with corresponding higher lipophilicity, in the order of sodium deoxycholate, then sodium cholate and lastly sodium taurodeoxycholate. There was also a corresponding increase in mucosal irritation (Figure 3).

2. Polymers & Muco-Adhesive Polymers

Oral films are prepared with polymers that form a structure to contain the drug. Many different polymers have been used including cellulose derivatives and gel-forming gums. Cellulosic derivatives include hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CPC) to name a few, and their choice is dictated by the desired solubility characteristics of the finished film with typically a fast dissolving time being preferred. Although higher-viscosity grades of cellulose have also been used as a means to increase the disintegration time of the film, thus allowing a longer residence time for drug absorption.

Gel-forming gums such as xanthan gum, carrageen, and pullulan have been used, mostly in combination with the cellulosic derivatives which impart a greater strength to the film and make them less brittle for handling purposes.

There is an increasing interest in other polymers which possess muco-adhesive properties. Films possessing muco-adhesive properties can adhere to the buccal

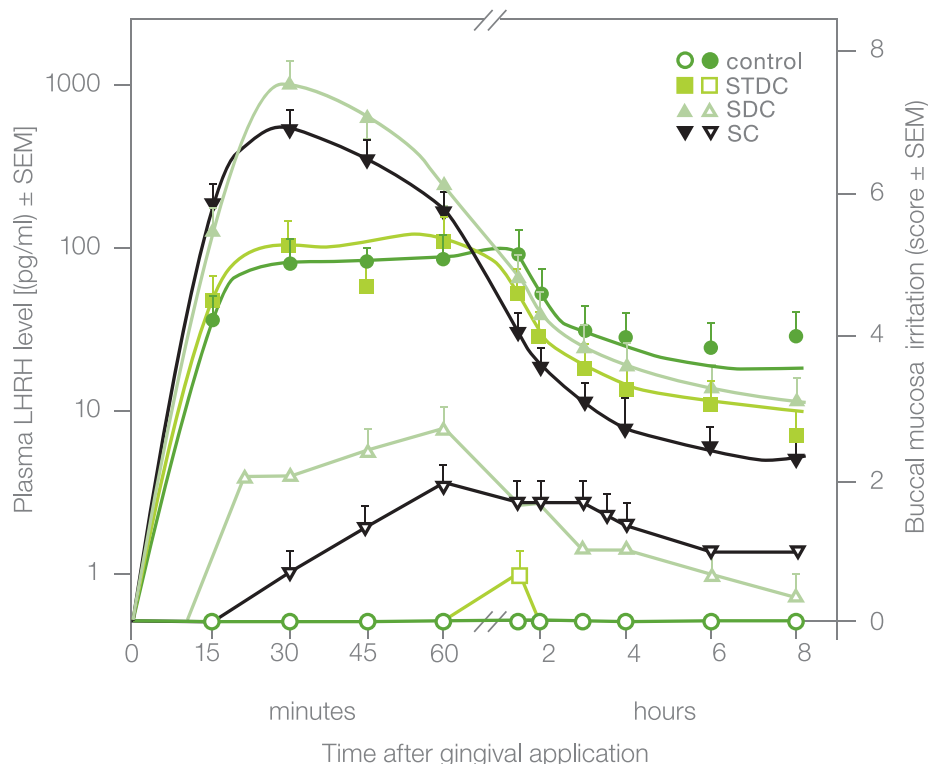


Figure 3: PK profiles of LHRH and buccal mucosal irritation in preclinical study following application of oral thin films containing LHRH 2 mg and 5% bile salt. Closed symbols represent plasma LHRH and open symbols represent buccal mucosal irritation scores.¹¹

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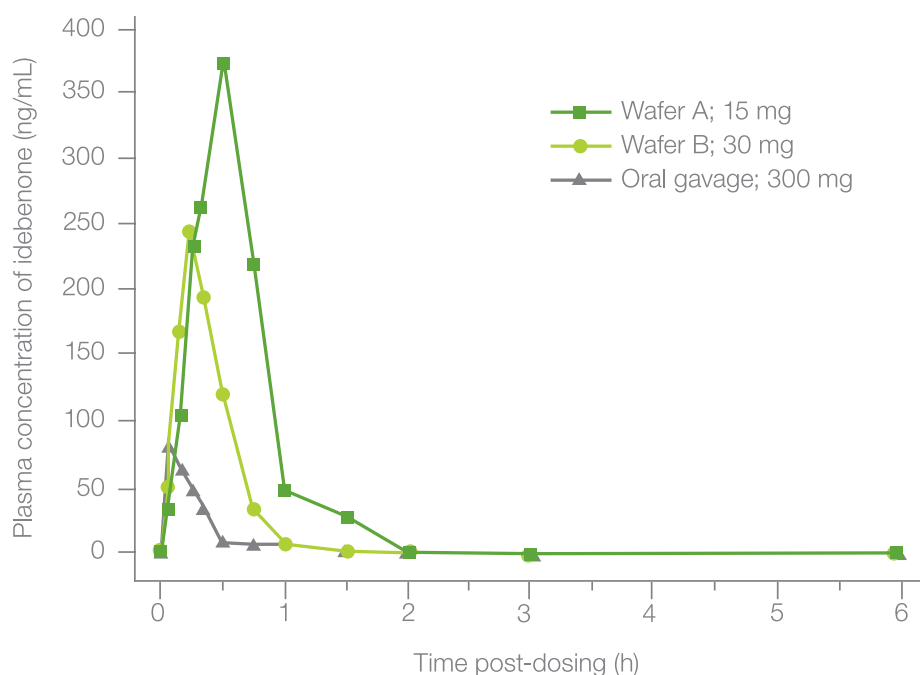


Figure 4: Mean plasma concentrations of free idebenone over time in preclinical study.¹⁴

mucosa for a prolonged period giving intimate contact. They maintain a high local drug concentration for an extended time for absorption. Some muco-adhesive films are designed to have a backing layer, akin to that of a transdermal patch, and in so doing, prevent enzymic degradation of the drug and drainage of the drug from the film due to salivary flow. Some such polymers used in studies have included polyacrylic acid, chitosan and carbomer.^{12, 13}

APPLICATIONS OF ORAL FILM

Fast Dissolving Film with Enhanced Drug Absorption

Oral thin films can dissolve rapidly in the oral cavity and, in some instances, may be absorbed much faster than orally ingested tablets. Especially for drugs which are metabolised extensively by the first-pass effect, an oral thin film formulation provides an opportunity for a faster-acting and better absorption profile. Idebenone is a drug originally developed for Alzheimer's disease. Recently it has been explored for the treatment of a range of neuromuscular diseases. It is well absorbed in the gut but undergoes extensive first-pass metabolism in the liver, leading to a very low bioavailability of less than 5%. The high first-pass effect means that high (multi-gram) doses are required to achieve therapeutic effect, with considerable side effects.

Krumme and Jensen¹⁴ formulated the compounds into oral thin films, one as a suspension (30 mg) and another into a solid solution in which 15 mg of idebenone was dissolved in amorphous form. These films were then administered in a dog study, together with a micro-emulsion (idebenone 300 mg) as a gastric gavage (Figure 4).

The results showed a significant increase in both C_{max} and AUC for the two oral thin film formulations, whereby the 30 mg film achieves three-times the bioavailability, and the 15 mg film achieves five-times bioavailability, compared with that obtained for the microemulsion formulation. When doses were normalised, the suspension formulation showed an improved 26-times bioavailability compared with that of the microemulsion, while the 15 mg solid solution formulation showed an astounding 121-fold improvement! This improvement showed that when the drug is present in amorphous form or in solution, as exemplified by the solid solution formulation, absorption of the

drug becomes more complete.

Fast Dissolving versus Muco-adhesive Products: Buprenorphine/Naloxone

While various oral films have been introduced both as prescription only and over-the-counter medicines, buprenorphine + naloxone (BPN/NLX) combination products can be discussed as example to illustrate the different possibilities the oral film offers. For discussion purposes, we focus on the pharmacokinetics of buprenorphine in these products as there were no discernible

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differences in naloxone PK.

In 2010, Indivior (Slough, UK) received US FDA approval for Suboxone™ (BPN/NLX) oral thin film, which has since become the major product for treatment of opiate addiction, replacing Suboxone sublingual tablet. It has now reached sales exceeding US\$1.3 billion (£1 billion) in 2014. In the evaluation document performed by the Australian Therapeutic Goods Administration (TGA),¹⁵ it was concluded that the oral film gave slightly higher exposure parameters when compared with the sublingual tablets in their PK studies. For example, in study 20-250-SA, the C_{max} for Suboxone 2.0/0.5 mg BPN/NLX film is approximately 22% higher compared with the corresponding dose strength of a tablet. Of the different strengths of the Suboxone film, the disintegration times in vivo were measured at from 1-6 min.

Recently, BioDelivery Sciences International (Raleigh, NC, US) introduced Bunavail™ utilising the company's BEMA (bio-erodable muco-adhesive) technology. Patients were instructed to moisten the

film and which they then adhered onto the buccal cheek until it completely dissolved.¹⁶ The bioavailability of buprenorphine at various dose strengths was studied and found to be almost double that of the Suboxone tablets.¹⁶

In Bunavail, the composition is more complex. In the FDA submission review,¹⁷ some of the key points pertaining to buprenorphine absorption from Bunavail are as follow: 4.2/0.7 mg BPN/NLX was found to exhibit equivalent exposure to Suboxone sublingual tablet; and that the co-administration of low or high pH liquid lowered the C_{max} and AUC for both actives. Low pH fluid intake caused a greater effect on buprenorphine absorption, with C_{max} , AUC_{last} and AUC_{inf} values being reduced by 59%, 52% and 49% respectively. Higher pH liquid intake reduced the corresponding values by 26%, 24% and 24% respectively. No disclosures were made pertaining to the pH values of the liquids.

While it is difficult to compare the results and outcome from different clinical studies, the two different oral film products seemingly offer very different pharmacokinetics of the absorption of the active ingredients. As there was no disclosure of the detailed formulations of Suboxone sublingual tablets, films or Bunavail film, perusal of pertinent patent/patent applications in the public domain might offer some insight into the difference.

There appeared to be differences in three areas:

- pH of the micro-environment
- Site of administration and
- Residence time.

Myers *et al*¹⁸ disclosed some quantitative data on sublingual film formulations of BPN/NLX and one of the key features claimed was the local pH obtained when the film is dissolved should be 2.0-4.0. For the muco-adhesive film, Finn and Vashist¹⁹ incorporated buprenorphine in a muco-adhesive film and a backing layer, both buffered, to pH 4.0-6.0 and 4.0-4.8, respectively.

Buprenorphine hydrochloride has a pKa value of 8.31.20 In a more acidic environment where the pH is at 2.0-4.0, its solubility increases and thus more molecular moieties become available for absorption. However, in accordance with its dissociation constant, the number of unionised species is considerably less than that at a higher pH. At an environmental pH of 4.0-6.0,

while the solubility of buprenorphine is lower, the number of unionised species is significantly increased when compared with a lower-pH environment. Thus, potentially, more unionised species of buprenorphine are available for absorption. This is supported by the fact that when Bunavail was administered with lower pH liquid, its C_{max} and exposure were reduced. One expects that at higher pH, the C_{max} and AUC values for Bunavail should further increase. This was not the case as it was likely that the solubility of buprenorphine was significantly reduced and hence less drug became available for absorption. This is also an illustration of how delicate the balance is between solubility and pH of the oral film for optimal drug absorption.

Suboxone is a sublingual film and disintegrates under the tongue in around five minutes.¹⁵ Bunavail is adhered onto the buccal cheek and allowed to dissolve completely after application.¹⁶ There were no scientific data disclosed pertaining to the dissolution time, but it has been suggested by users of Bunavail that it takes 15-30 minutes to dissolve.²¹

Absorption through mucosal membranes is a passive diffusion process and is concentration and time dependent. As the concentration of the API increases, the rate of flux across the membrane increases. If the flux is constant, more drug will be delivered across the membrane with a prolonged exposure as could be the case in Bunavail.

Thus, it is plausible that the much higher exposure of buprenorphine observed for Bunavail is a combination effect of both the higher pH environment, which brings along more unionised species for absorption, and longer duration for drug molecule to diffuse across the membrane. This helps explain why the lower dose of buprenorphine is required in Bunavail compared with Suboxone. This example illustrates the different approaches for drug delivery across the mucous membrane and is an embodiment of the understanding of the science in absorption.

Delivery of Macromolecules

To date, most of the applications of oral thin films have been in the delivery of small molecules. With the increasing number of large molecules being discovered and under development, there has been considerable interest in research to establish if transmucosal delivery is a viable route for administration.

Jin *et al*¹² studied the mucosal

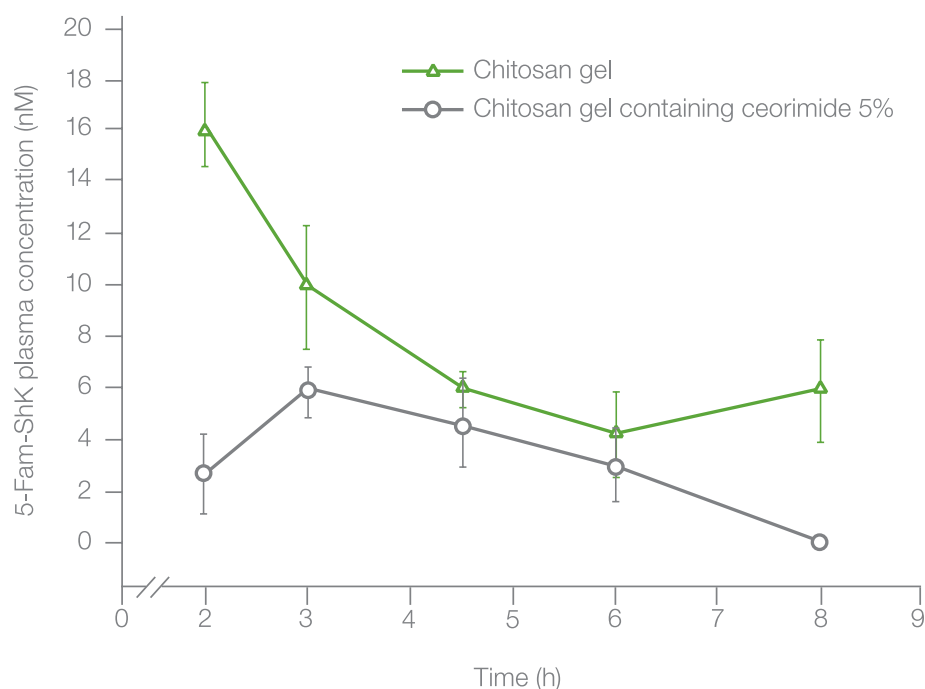


Figure 5: Plasma concentrations of 5-Fam-ShK in mice, following buccal administration of 5-Fam-ShK (10 mg/kg) in 4 mg of a 3% w/v chitosan gel with and without 5% w/w cetrimide. (Data presented as mean \pm SEM (n=3-5)).¹²

Treatment	Glucose consumed (g)		
	Total	Total minus placebo	Per IU insulin administered
SC Insulin Aspart (n=6) Cohort 1 5 IU	135 \pm 17	107 \pm 21	21 \pm 4 (0-600min)
TB Regular Insulin (n=6) Cohort 1 5 IU	87 \pm 19	59 \pm 23	12 \pm 4 (0-600min)
Placebo (n=6)	28 \pm 4 (endogenous) (0-600min)		

Table 2: Summary results from study of transbuccal film delivery of insulin.²²

delivery of a potent peptide, Stichodactyla helianthus neurotoxin (ShK). They performed permeation studies using an *in vitro* Ussing chamber model and found no detectable level of fluorescent 5-Fam-ShK in the receptor cell after application onto untreated porcine buccal mucosa. When formulated with surfactant taurodeoxycholate hydrate or cetrimide, ShK in a chitosan muco-adhesive gel produced 0.005-0.13% and 1.1% respectively of the applied dose over a five-hour period in the receptor cell. Confocal microscopic examination of the mucosal fluorescence associated with 5-Fam-ShK showed enhanced buccal mucosal retention of the peptide. This demonstrated that the potent peptide could be transported across the buccal membrane when appropriately formulated.

There were also encouraging results from the 5-Fam-ShK chitosan-based (3%) gel formulated with or without cetrimide.

When administered to mice it resulted in average plasma concentration of 2.6-16.2 nM at between 2-6 hours (Figure 5). These concentrations were substantially higher than the pM concentration required for therapeutic activity for the treatment of auto-immune disease. This suggests that the buccal route could be a suitable administration route for this potent peptide which otherwise needs to be administered parenterally.

Despite the promising results, the authors acknowledged the “higher” level of cetrimide used and that further work would be required to ascertain the appropriate level for incorporation to elicit its permeability-enhancing properties without unduly causing adverse irritancy.

Phillips *et al*²² formulated an oral film containing insulin-gold ligand nanoparticles. They studied the bioavailability of insulin absorbed buccally from this film compared

with subcutaneous insulin injection. They measured glucose infusion rates to estimate the pharmacodynamic effect and from there derived the bioavailability data. In their analysis, they suggested the ligand-insulin nanoparticle achieved 50% the pharmacodynamic effect compared with subcutaneous insulin. These encouraging results showed promise for the buccal delivery of larger molecules as a non-invasive approach.

CONCLUSIONS

This article has provided an overview of the fundamentals of transmucosal absorption, its mechanism and the science behind absorption. A thorough understanding of the physicochemical properties of the API, together with prudent choice of formulation excipients and system design, could lead to viable products with the desired clinical outcomes. Thin films offer significant advantages over peroral administration for drugs with high first-pass metabolism, especially in reducing drug exposure and side effects. Research into transmucosal delivery of large molecules and peptides also provides further optimism of the future of this novel dosage form.

REFERENCES

1. Repka MA, Chen L, Chan RS, "Buccal Delivery Systems", in Wilson and Crowley (eds) "Controlled Release in Oral Drug Delivery". Springer, 2011.
2. Wertz PW, Swartzendruber DC, Squier CA, "Regional variation in the structure and permeability of oral mucosa and skin". *Adv Drug Deliv Rev*, 1993, Vol 12, pp 1-12.
3. Law S, Wertz PW, Swartzendruber DC, Squier CA, "Regional variation in content, composition and organization of porcine epithelial barrier lipids revealed by thin-layer chromatography and transmission electron microscopy". *Archiv Oral Biol*, 1995, Vol 40, pp 1085-1091.
4. Squier CA, "Membrane coating granules in nonkeratinizing oral epithelium". *J Ultrastruct Res*, 1977, Vol 60, pp 212-220.
5. Veuillez F, Kalia YN, Jacques Y, Desbusses J, Buri P, "Factors and strategies for improving buccal absorption of peptides". *Eur J Pharm Biopharm*, 2001, Vol 51, pp 93-109.
6. Wertz PW, Squier CA, "Cellular and molecular basis of barrier function in oral epithelium". *Crit Rev Ther Drug Carrier Syst*, 1991, Vol 8, pp 237-269.
7. McElnay JC, Hughes CM, "Drug Delivery – buccal route", in "Encyclopedia of Pharmaceutical Technology", Marcel Dekker, New York, 2002, pp 800-810.
8. Zhang H, Zhang J, Streisand JB, "Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications". *Clin Pharmacokinet*, 2002, Vol 41(9), pp 661-680.
9. Ganem-Quintanar A, Kalia YN, Falson-Reig F, Buri P, "Mechanism of permeation enhancement". *Int J Pharm*, 1997, Vol 156(2), pp 127-142.
10. Nicolazzo JA, Reed BL, Finin BC, "Buccal penetration enhancers – How do they really work?" *J Controlled Release*, 2005, Vol 105, pp 1-15.
11. Nakane S, Kakumoto M, Yukimatsu K, Chien YW, "Oramucosal Delivery of LHRH: Pharmacokinetic Studies of Controlled and Enhanced Transmucosal Permeation". *Pharmaceut Dev & Technol*, 1996, Vol 1(3), pp 251-259.
12. Jin L, Boyd BJ, White P, Pennington M, Norton RS, Nicolazzo JA, "Buccal mucosal delivery of a potent peptide leads to a therapeutically-relevant plasma concentrations for the treatment of autoimmune diseases". *J Controlled Release*, 2015, Vol 199, pp 37-44.
13. Warren SJ, Kellaway JW, Timmins P, "Muco-adhesive hydrogels for buccal delivery of peptides". *Proc Int Sym Controlled Release Bioactive Material*, 1989, Vol 16, pp 402-403.
14. Krumme M, Jensen K, "Transmucosal administration system for a pharmaceutical drug". US patent 20130189343A1, 2013.
15. "Australian Public Assessment Report for Buprenorphine/Naloxone – Suboxone Sublingual film". Therapeutic Goods Administration, Australia, March 2011,
16. Full Prescribing Information – Bunavail (http://www.bunavail.com/assets/pdf/BUNAVAIL_Full_Prescribing_Information.pdf)
17. "FDA Summary review of NDA 205637/S-000, Biodelivery Sciences International, Inc", Reference ID: 3520628, June 6, 2014.
18. Myers GL, Hilbert SD, Boone B, Bogue A, Sanghvi P and Hariharan M, "Sublingual and buccal film compositions". US patent 8475832, 2013.
19. Finn A, Visisht N, "Transmucosal Drug delivery devices for use in chronic pain relief". WO2013096811A2, June 2013.
20. Buprenorphine hydrochloride in (<http://www.drugbank.ca>).
21. "Is Bunavail like Suboxone?" (<http://prescription-drug.addictionblog.org/is-bunavail-like-suboxone>).
22. Phillips J, Mous J, Rademacher T, Buhler F, Pfuetzner A, Schobel M, Dadey E, Cook C, "Potential of Novel Nanoparticle Insulin Given in a Transbuccal Film Strip". Poster – American Diabetic Association Meeting, San Francisco, CA, US, 2014.



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