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Oral Cavity Permeability Assessment Using Sublingual and Buccal *In Vitro* Tissue Models

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PURPOSE

The oral cavity is a viable route for administration of drugs that exhibit significant first-pass elimination. Following intraoral administration, permeation of drug occurs predominantly by passive diffusion via the buccal and sublingual mucosa resulting in local and/or systemic pharmacological effects. The aim of this study was to quantitatively assess mucosal permeation properties of selected active pharmaceutical ingredients (APIs) from oral cavity drug products approved by the U.S. Food and Drug Administration using *in vitro* models of the sublingual and buccal tissue barriers.

Table 1: List of Drug Products Used for Assessing Time-dependent Transmucosal Flux of APIs Using In Vitro Tissue Model

Proprietary Name	Active Pharmaceutical Ingredients	Molecular Weight (API)	Log P (API)	Approved Generic
Sitavig	Acyclovir	225.3	-1.2	No
Kynmobi	Apomorphine HCl	303.8	2.0	No
Saphris	Asenapine maleate	401.8	3.7	No
Zubsolv	Buprenorphine HCl	504.1	4.5	No
Fentora	Fentanyl Citrate	336.5	4.1	No
Zubsolv	Naloxone HCl	363.8	1.6	No
Dsuvia	Sufentanil citrate	578.7	3.4	No
Edluar	Zolpidem tartrate	764.9	3.2	Yes

METHODS

For all APIs of the drug products listed in **Table 1**, time-dependent transmucosal flux was measured up to 120 minutes using filter-grown human HO-1-U-1 cells as an *in vitro* tissue model of the sublingual mucosa and the organotypic EpiOral™ tissue model (MatTek Corp., Ashland, MA) for assessing *in vitro* buccal permeability. At the end of the experiment, samples from tissue barrier and donor compartment were removed for mass-balance calculations. Drug concentrations were quantified by high-performance liquid chromatography using either UV or mass spectroscopy detection. Apparent permeability coefficient (Papp) values were calculated from the linear portion of the flux curve according to:

$$Papp = \frac{dQ}{dt} \times \frac{1}{A \times Co}$$

where dQ/dt = the linear mass appearance rate in receiver compartment, Co = initial drug concentration in donor compartment, and A = surface area available for diffusion.

RESULTS

A representative example of time-dependent API flux across the sublingual and buccal *in vitro* tissue models is shown for fentanyl in **Figure 1**.

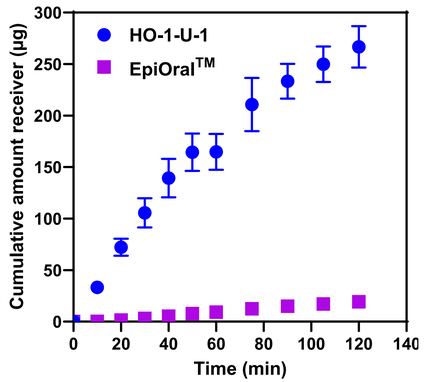

Figure 1: Oral cavity permeability of fentanyl *in vitro*. Cumulative drug amount in the receiver compartment was quantified by HPLC. Data are shown as mean ± SD (n=6).

Papp values were calculated from the linear portion of the curve of drug appearance in the receiver compartment versus time. **Figure 2** summarizes those numerical values obtained for each API in the sublingual HO-1-U-1 cell model and buccal EpiOral™ tissue model, respectively.

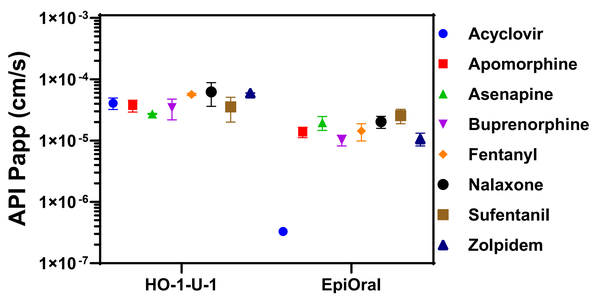

Figure 2: Comparison of apparent permeability coefficient (Papp) calculated for the various APIs using the sublingual HO-1-U-1 cell and buccal EpiOral™ tissue model, respectively. Data are shown as mean ± SD (n=6).

To define the kinetic permeation properties across the buccal EpiOral™ tissue model in different measuring compartments, drug distribution of fentanyl was quantified at various time points in donor, receiver, and tissue barrier compartments (**Figure 3**). Tissue-associated dose fraction of each API measured at the end of the transport experiment in the buccal EpiOral™ tissue barrier is shown in **Figure 4**:

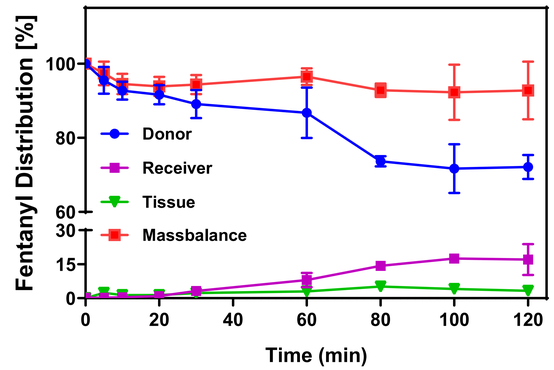

Figure 3: Fentanyl *in vitro* permeation kinetics across the buccal EpiOral™ tissue model. Time-dependent drug amounts in donor, receiver, and tissue compartments were quantified by HPLC. Mass balance was normalized to API amount added to donor compartment at t=0 min. Data are shown as mean ± SD (n=6).

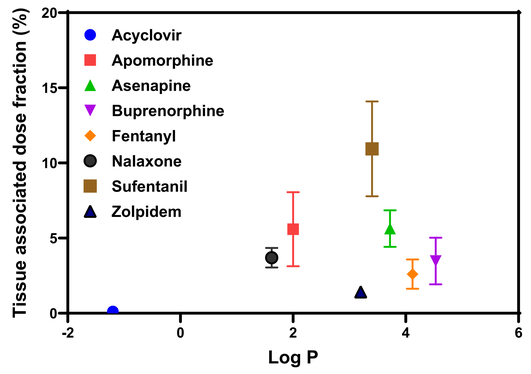

Figure 4: Tissue-associated dose fraction recovered for each API at the end of the *in vitro* transport experiment across the buccal EpiOral™ tissue model. Data are shown as mean ± SD (n=6).

CONCLUSION

- Permeation assessment of selected APIs that vary in lipophilicity from logP from -1.2 to 4.5 and in molecular weight from 225.3 Da to 764.9 Da reveals greater discrimination power by the buccal than the sublingual *in vitro* tissue model.
- Tissue-associated drug fraction recovered at the end of the transport experiment across the thicker, organotypic EpiOral™ buccal tissue model is greater for lipophilic, high-permeability than for hydrophilic, low-permeability solutes. This implies that solutes predicted to permeate this tissue barrier predominantly via the paracellular pathway exhibit limited binding with cellular components of this *in vitro* model of the buccal mucosa.
- Physicochemical properties of APIs appear to have a greater impact on the rate and extent of the drug fraction absorbed via the buccal route when compared to the sublingual route.

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