Formulation Effects of Marketed Oral Cavity Products on In Vitro Buccal Permeability

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PURPOSE

The dose fraction absorbed from the oral cavity depends on dissolution and oral mucosal permeation properties of the active pharmaceutical ingredient (API) released from the drug product. The purpose of this study was to measure and compare the transmucosal flux of APIs when dissolved as powder in artificial saliva or released from the oral cavity drug product approved by the U.S. Food and Drug Administration after short-term dissolution in artificial saliva across the EpiOral™ tissue model.

OBJECTIVE

To provide insights into the impact of formulation excipients on API buccal permeability that may need consideration during development of new and generic drug products intended for oral cavity administration.

METHODS

- Transmucosal flux of buprenorphine, fentanyl, rizatriptan, sufentanil, and zolpidem when dissolved as powder in artificial saliva or released from the oral cavity drug product approved by the U.S. Food and Drug Administration after short-term dissolution in artificial saliva was measured using the EpiOral™ tissue model (MatTek, Corp., Ashland, MA).
- Drug concentrations in donor, receiver, and tissue compartments were quantified using reverse-phase HPLC with UV or mass spectroscopy detection.
- Transepithelial permeation of propranolol (prototypic transcellular marker) and Lucifer Yellow (prototypic paracellular marker) was measured in the presence of drug solutions prepared either from powder or the product in artificial saliva.

RESULTS

Effect of formulation excipients on *in vitro* buccal permeability of selected APIs:

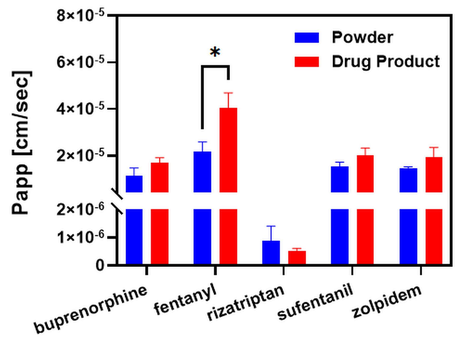

Figure 1 Permeation properties of oral cavity drugs quantified across the EpiOral™ tissue model. Data are shown as mean±SD (n≥3). * Significantly different from powder (p<0.05)

Effect of formulation excipients on API retention in the EpiOral™ tissue model:

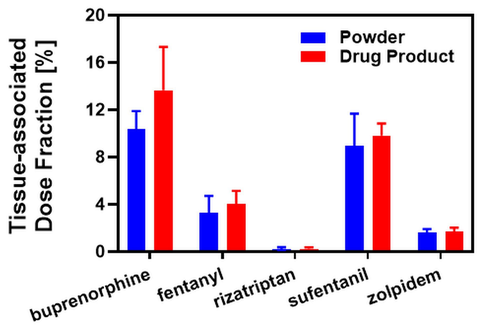

Figure 2: Tissue-associated dose fraction of oral cavity drugs recovered after a 120 min exposure to the EpiOral™ tissue model. Data are shown as mean±SD (n=3).

Effect of FENTORA® excipients on transepithelial flux of fentanyl across the EpiOral™ tissue model:

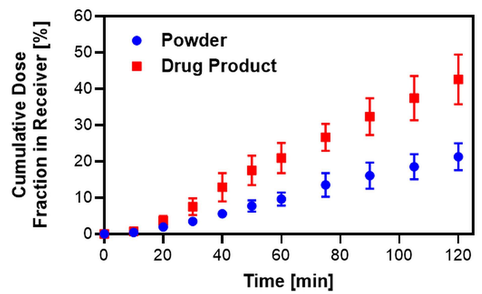

Figure 3: Oral cavity permeation of fentanyl citrate *in vitro*. Cumulative amount of API appearing in the receiver compartment was quantified by HPLC. Data are shown as mean±SD (n=3).

Dose-dependent formulation effect of FENTORA® excipients on fentanyl *in vitro* buccal permeability:

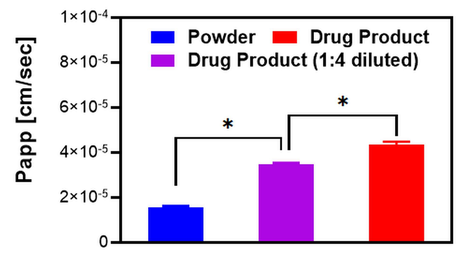

Figure 4: Excipient effects of FENTORA® on fentanyl permeation across the EpiOral™ tissue model. Data are shown as mean±SD (n=3). * Significantly different from powder solution (p<0.05)

RESULTS

Table 1: Effect of FENTORA® Excipients on Buccal Transcellular and Paracellular Permeability of the EpiOral™ Tissue Model

Papp Propranolol (transcellular marker)		Papp Lucifer Yellow (paracellular marker)	
No Excipients (Control)	+ FENTORA® Excipients	No Excipients (Control)	+ FENTORA® Excipients
1.21±0.09 x 10^{-5} cm/s	1.62±0.56 x 10^{-5} cm/s	3.14±1.68 x 10^{-8} cm/s	4.66±0.72 x 10^{-7} cm/s *

Data are shown as mean ± SD (n=3)

*Significantly different from control without FENTORA® excipients ($p<0.05$)

CONCLUSIONS

- The results suggest that excipients used in the marketed oral cavity product FENTORA® may increase fentanyl's paracellular permeation.
- Future studies focusing on the translation of these *in vitro* results to the *in vivo* situation in humans will help formulators to explore the impact of different excipients on product dissolution properties as well as on critical biopharmaceutical properties that affect pharmacokinetic performance *in vivo*.
- Ultimately, this could impact the development of new and generic drug products designed for oral cavity administration.

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