Oral Cavity Permeation of Buprenorphine Across In Vitro Models of the Buccal and Gingival Mucosa

T1130-03-17

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PURPOSE

Buprenorphine hydrochloride is used to treat opioid use disorder and pain. Recent reports suggested that long-term use of buprenorphine oral cavity products may pose unintended dental problems although the underlying mechanisms are not well understood (FDA, 2022). The results from this study are expected to provide insights into the impact of formulation excipients on permeation and local tissue deposition of this active pharmaceutical ingredient (API) within different mucosal regions of the oral cavity that may need consideration during development of generic drug products intended for oral cavity administration.

OBJECTIVE

To quantitatively compare *in vitro* buccal and gingival permeability as well as local tissue retention measured for buprenorphine when dissolved as a powder in artificial saliva or released after short-term dissolution in artificial saliva from an FDA-approved oral cavity drug product.

METHODS

- Transmucosal flux of the API 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 buccal EpiOral™ and gingival EpiGingival™ tissue models (MatTek Corp., Ashland, MA):

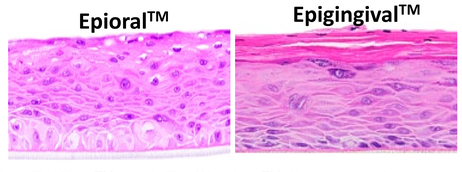

Figure 1: The EpiOral™ and EpiGingival™ tissue models are comprised of normal, human-derived oral epithelial cells and exhibit *in vivo*-like morphological and growth characteristics.

METHODS

- Drug concentrations in donor, receiver, and tissue compartments were quantified using reverse-phase HPLC coupled to mass spectroscopy detection.

RESULTS

Effect of formulation excipients on *in vitro* buccal and gingival permeability of buprenorphine:

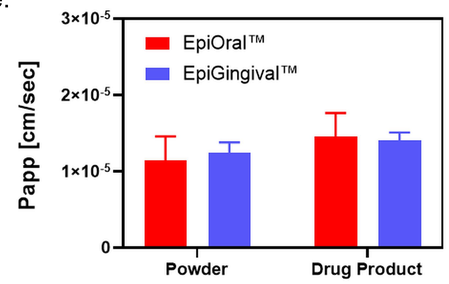

Figure 2: Comparison of permeation properties of buprenorphine across the buccal EpiOral™ and the EpiGingival™ tissue models when dissolved from powder or finished drug product in artificial saliva, pH 6.7, respectively. Data are shown as mean±SD (n=6).

Effect of formulation excipients on buprenorphine retention in the buccal EpiOral™ and gingival EpiGingival™ tissue models:

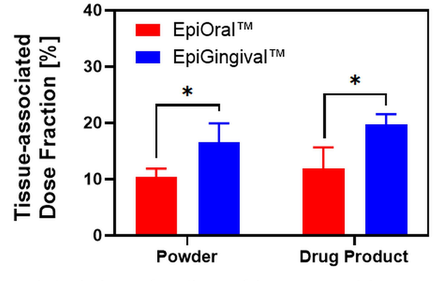

Figure 3: Tissue-associated dose fraction of buprenorphine recovered at the end of the *in vitro* transport experiment across the buccal EpiOral™ tissue model and the gingival EpiGingival™ tissue model, respectively. Data are shown as mean±SD (n=6).

CONCLUSIONS

- Mucosal permeability for buprenorphine seems comparable between the buccal and gingival mucosa using the human-derived EpiOral™ and EpiGingival™ *in vitro* models (Figure 2).
- Formulation excipients of the marketed oral cavity product do not appear to influence the tissue-associated dose fraction of buprenorphine recovered in each *in vitro* tissue model (Figure 2).
- The dose fraction recovered from the tissue barrier after exposure to the drug solution prepared from powder and finished drug product was significantly greater in the gingival mucosa (Figure 3).
- The results suggest that buprenorphine may exhibit greater affinity for cellular components of the gingival mucosa.
- Further research is needed to delineate whether the increased buprenorphine concentration in gingival tissue may help explain idiopathic dental issues observed with long-term use of buprenorphine-containing oral cavity drug products (FDA, 2022).

ACKNOWLEDGEMENT(S)

The project was funded by a contract from the U.S. Food and Drug Administration (Contract # 75F40120C00150). The views expressed here do not reflect official policies of the U.S. FDA or the Department of Health and Human Services, nor does any mention of trade names imply endorsement by the U.S. Government.

REFERENCE

FDA, 2022 “Buprenorphine: Drug Safety Communication – FDA warns about dental problems with buprenorphine medicines dissolved in the mouth to treat opioid use disorders and pain” (https://www.fda.gov/safety/medical-product-safety-information/buprenorphine-drug-safety-communication-fda-warns-about-dental-problems-buprenorphine-medicines).