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MECHANISTIC MODEL OF IN VITRO INTRAORAL ABSORPTION OF BUPRENORPHINE FOR THE BUCCAL AND GINGIVAL MUCOSA

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PURPOSE

- Long-term use of buprenorphine oral cavity drug products (DP) poses risks of dental issues [1] and the underlying reason is not well understood
- This study investigates the buccal and gingival permeability of buprenorphine active pharmaceutical ingredient (API) and buprenorphine generic drug product (DP) using in vitro permeability assays, with a focus on assessing tissue specific retention in different mucosal regions [2,3], and evaluating the impact of formulation excipients on buprenorphine permeation
- Mechanistic *in silico* model in MembranePlus™ software (beta version, Simulations Plus Inc., Lancaster, CA) was employed to deconvolute in vitro permeation data from EpiOral™ and EpiGingival™ tissue models, yielding in vitro diffusivity (D_m) and fraction unbound (f_{ut}) (cf **Poster # T0930-04-22**).
- Future work will determine whether differences in the oral mucosal regions can provide mechanistic insights into the toxicity of long-term buprenorphine use [1]

OBJECTIVES

- Predict D_m and f_{ut} for buprenorphine API and generic buprenorphine DP (sublingual tablet, Eq. 2 mg base) through buccal and gingival tissue to compare buprenorphine interaction with the two tissue types
- Compare the predicted D_m and f_{ut} to assess how formulation affects buprenorphine permeability through oral mucosa tissues

METHOD

- *In vitro* permeability assays used: organotypic EpiOral™ tissue model (ORL-200, MatTek Corp., Ashland, MA) and EpiGingival™ tissue model (GIN-100, MatTek Corp., Ashland, MA) (*cf.* **Poster # T1130-03-17**)
- The *in silico* model describing the drug diffusion through the tissue layers of EpiOral™ and EpiGingival™ incorporates various factors, such as tissue thickness, protein binding of the drug in the media, the accumulation of the drug in the tissue and the receiver compartment, non-specific drug loss, and sampling-mediated media depletion.
- Buprenorphine API and generic buprenorphine DP specific D_m and f_{ut} were compared in Buccal and Gingival tissues
- Model experimental parameters were obtained from the *in vitro* EpiOral™ and EpiGingival™ experiments.

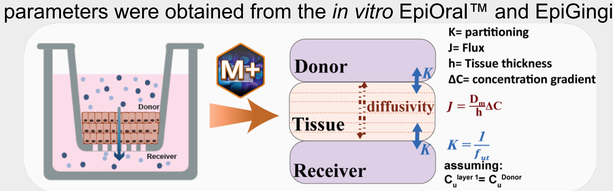


Figure 1: *Visual representation of the EpiOral™ and EpiGingival™ in silico model.*

RESULTS

Predicted Buprenorphine D_m and f_{ut} in Buccal and Gingival Tissues

- First, Buprenorphine (API) D_m and f_{ut} were estimated based on the measured concentration in the donor, tissue, and receiver compartments of the EpiOral™ and EpiGingival™ experiments (Figure 2).
- Then, the estimated Buprenorphine **(API)** D_m and f_{ut} described the corresponding generic Buprenorphine DP experimental data for both tissue types suggesting no impact of formulation on Buprenorphine permeability for generic Buprenorphine DP (Table 1 and Table 2).

Table 1: *Optimized D_m and f_{ut} (from API data) and tissue thickness of the **EpiOral™** in vitro permeability assay for Buprenorphine API and generic buprenorphine DP*

EpiOral™ organotypic tissue model			
Compound	**D_m (cm²/s)**	**f_{ut} (%)**	**Tissue Thickness (µm)**
Buprenorphine API	1.75×10^{-7}	2.4	90
Buprenorphine DP			

Table 2: *Optimized D_m and f_{ut} (from API data) and tissue thickness of the **EpiGingival™** in vitro permeability assay for Buprenorphine and generic buprenorphine DP*

EpiGingival™ organotypic tissue model			
Compound	**D_m(cm²/s)**	**f_{ut} (%)**	**Tissue Thickness (µm)**
Buprenorphine API	3.59×10^{-7}	1.46	100
Buprenorphine DP			

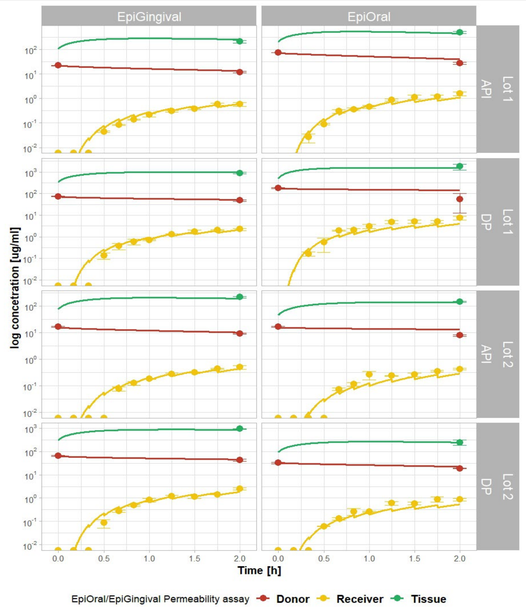
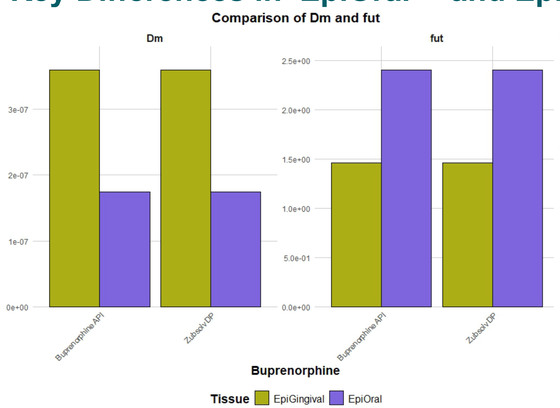


Figure 2: *Buprenorphine API-DP pair concentration time courses in the donor (Red), buccal tissue (Green), and receiver (Yellow) compartments for EpiOral™ and EpiGingival™ tissue following their administration in the donor compartment. Lines represent model simulations and dots are observed mean data (n=3).*

Key Differences in EpiOral™ and EpiGingival™ Models



- **Tissue thickness:** EpiGingival™ tissue was slightly thicker compared to EpiOral™ tissue (100 µm) as measured by MatTek
- **D_m and f_{ut}:** D_m was ~2.22 times higher and f_{ut} ~1.68 times lower for the **EpiGingival™ assay** compared to the **EpiOral™ assay**.

Figure 3: *Bar graph of compared D_m and f_{ut} for EpiGingival™(Green) and EpiOral™(purple) tissue.*

CONCLUSION

An *in silico* mechanistic model was used to analyze the comparative differences in the absorption of buprenorphine in the EpiOral™ and EpiGingival™ tissue.

Significant differences were predicted in accordance with the observed data for buprenorphine permeability between EpiOral™ and EpiGingival™ tissues.

These differenced may be due to unique tissue properties, such as differences in keratinization, tissue surface area and tissue thickness [2,3].

Generic buprenorphine formulation did not alter permeability parameters, indicating no impact of excipient on the permeation.

Mechanistic PBPK model which predicts local tissue specific concentration may improve our understand of the clinical toxicity of long-term buprenorphine use.

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