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MECHANISTIC IN VITRO ORAL ABSORPTION MODEL TO PREDICT MUCOSAL PERMEABILITY OF ORAL CAVITY DRUG PRODUCTS

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PURPOSE

- Buccal delivery allows patient compliance, ease of drug administration and potential bypass of first-pass metabolism
- Evaluation of buccal mucosal permeability may provide insights on the fraction absorbed in the oral cavity impacting the pharmacokinetic (PK) of drug products (DPs) delivered intraorally (IO)
- A mechanistic *in silico* model was developed and validated in MembranePlus™ software (beta version, Simulations Plus Inc., Lancaster, CA) to deconvolute EpiOral™ *in vitro* permeability into drug diffusivity (D_m) and unbound fraction (f_{ut}) within the oral mucosa.
- This study compares predicted D_m and f_{ut} for five DPs and their APIs, revealing formulation-driven differences in oral mucosal permeability.
- This work enables *in vitro* to *in vivo* translation for IO absorption using physiologically based pharmacokinetic modelling (PBPK) framework.

OBJECTIVES

- Compare the predicted D_m and f_{ut} to analyze the effect of excipients on drug permeation
- Identify tissue thickness as primary source of inter-batch variability in EpiOral™ tissue model for the evaluated drugs

METHOD

- *In vitro* permeability assays were conducted using the organotypic EpiOral™ tissue model (ORL-200, MatTek Corp., Ashland, MA) (cf. Poster # **M1430-01-06**)
- The mechanistic *in silico model* (Figure 1) describes the drug diffusion through the tissue layers of EpiOral™ tissue model. It also includes other mechanisms: protein binding in the media, drug accumulation in tissue and receiver compartments, non-specific drug loss, and media depletion due to sampling
- D_m and f_{ut} in the EpiOral™ tissue were compared for the drug (powder form) and the drug product to access excipient effect:
  - Buprenorphine HCl API / Generic Buprenorphine HCl DP
  - Fentanyl Citrate API / Fentora®
  - Sufentanil Citrate API / Dsuvia®
  - Rizatriptan Benzoate API / Generic Rizatriptan Benzoate DP
  - Zolpidem Tartrate API / Edluar®

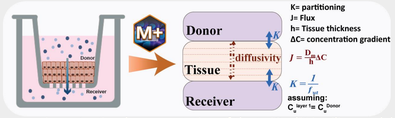

Figure 1: *Visual representation of the EpiOral™ in silico model.*

RESULTS

Excipient effect on drug D_m and f_{ut}

For each drug, D_m and f_{ut} were optimized for the API, and the model effectively predicted observed data for the corresponding DP (Figure 2). Four drugs showed no excipient effect, as API predicted D_m and f_{ut} described API permeation from DP. **Only Fentanyl DP (Fentora®) indicated an excipient impact on permeability.**

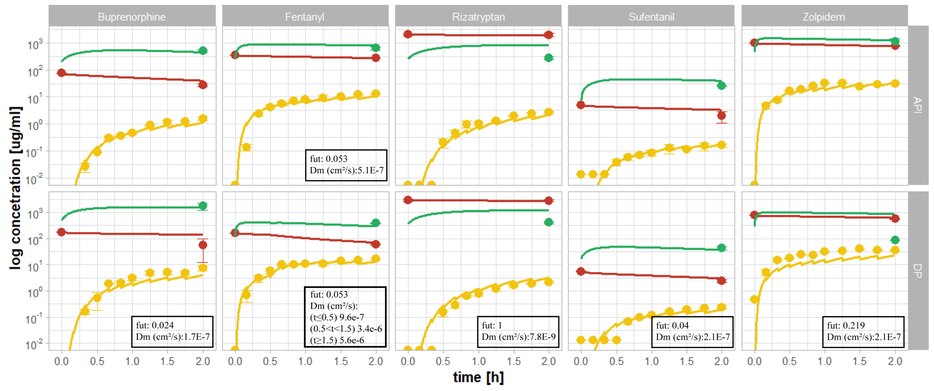

Figure 2: *Five drug concentration time courses in the donor (Red), buccal tissue (Green), and receiver (Yellow) compartments following their administration in the donor compartment. Lines represent model simulations and dots are observed mean data (n=2).*

Impact of Excipient in Fentora®

Time-dependent D_m was introduced to model for evaluating the influence of excipient for Fentora® as the excipient may change the paracellular permeability for the buccal tissue (Figure 3).

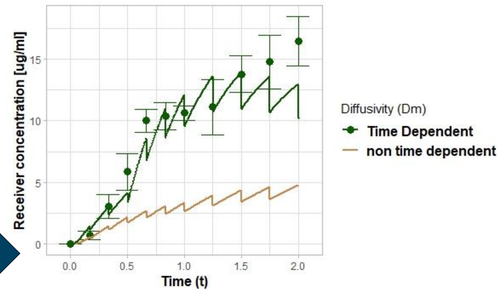

Figure 3: *The impact of excipient for Fentora® DP receiver measurements: time dependent D_m (green) where D_m 9.63e-7 at t<=0.5h; 3.42e-6 at 0.5<t<1.5 h and 5.65e-6 at t>=1.5 h and the non time dependent D_m used for the fentanyl API (brown)*

INTRA-BATCH VARIABILITY:

Parameter Sensitivity Analysis (PSA) identified initial concentration and tissue thickness (physiological range: 90-140 um) as sources of intra-batch variability in receiver side concentration (Figure 4 for Rizatriptan Benzoate).

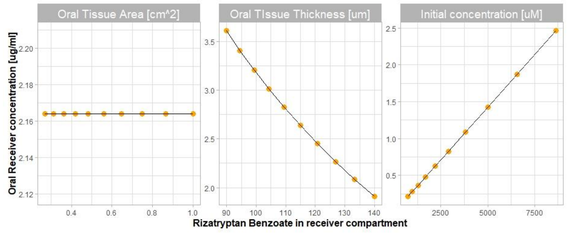

Figure 4: *PSA for Rizatryptan Benzoate concentration at 2 hours in the receiver compartment. Parameter tested: tissue Area (0.27-1 cm²) , tissue thickness (90-140 um) and initial concentration (740-8650 uM).*

Intra-batch variability in the receiver concentrations of Rizatriptan Benzoate is influenced by differences in initial concentration and tissue thickness across the batches (Batch 2: 100 µm, Batch 3: 120 µm) as shown in Figure 5.

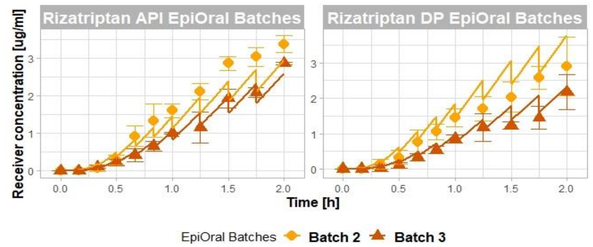

Figure 5: *Rizatryptan benzoate API and DP EpiOral™ measurements for two batches where Batch 2: initial concentration of 7224 uM (API) and 9196 uM (DP); tissue thickness of 100 um and Batch 3: initial concentration of 8069 uM (API) and 7319 uM (DP) and tissue thickness of 120 um was used.*

CONCLUSION

An *in silico* mechanistic model was used to estimate the D_m and f_{ut} for five intraoral drugs based on organotypic EpiOral™ *in vitro* permeability studies.

The model described the impact of excipients on the API diffusion to inform the rational design of intraoral DPs using organotypic in vitro assays.

Future work will integrate these results to inform PBPK models for *in vivo* intraoral absorption for the drug administered to humans.

In future, this will support the development of new and generic intraoral DPs using model-integrated evidence as a framework.

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