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PHYSIOLOGICALLY BASED PHARMACOKINETIC (PBPK) ORAL ABSORPTION MODEL TO PREDICT MUCOSAL PERMEABILITY OF ORAL CAVITY DRUG PRODUCTS

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PURPOSE

- Buccal delivery allows bypassing first-pass metabolism
- Evaluating buccal mucosal permeability is necessary to assess the pharmacokinetics (PK) of active pharmaceutical ingredients (APIs) intraorally delivered using mechanistic *in silico* approaches
- *In vitro* permeability assays were conducted using the organotypic EpiOral™ tissue model (ORL-200, MatTek Corp., Ashland, MA) (*cf*. Poster #T1030-04-26)
- A mechanistic *in silico* model of the EpiOral™ tissue was developed and validated in MembranePlus™ software (beta version, Simulations Plus Inc., Lancaster, CA)
- Diffusivity (D_m) and fraction unbound (f_{ut}) in the oral mucosa of the EpiOral™ tissue were determined for 8 APIs.

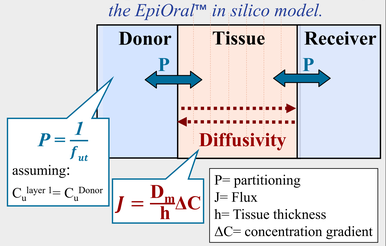
OBJECTIVES

- Develop and validate a mechanistic *in silico* model of the EpiOral™ *in vitro* permeability assay
- Determine API-specific D_m and f_{ut} in EpiOral™ system

METHODS

- The mechanistic oral absorption model for *in vitro* EpiOral™ assay (Figure 1) describes drug dissolution and precipitation in the donor compartment, partitioning and diffusion through the tissue layers, uptake into the receiver compartment, protein binding, non-specific loss, and impact of sampling-mediated media depletion.
- API-specific oral mucosa D_m and f_{ut} were estimated for:
  - Acyclovir
  - Apomorphine
  - Asenapine
  - Buprenorphine
  - Fentanyl
  - Naloxone
  - Sufentanil
  - Zolpidem

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



- Model parameters were obtained from the *in vitro* experiments using EpiOral™ system.

RESULTS

D_m and f_{ut} extrapolation

For each API, the observed concentrations in the donor, tissue, and receiver compartment from the EpiOral™ permeability assay (Figure 2) were analyzed using the developed *in silico* model to determine D_m, f_{ut}, and potential non-specific loss of API (Table 1).

Table 1: D_m, f_{ut}, and estimated non-specific loss of all compounds measured using EpiOral in vitro permeability assay

API	f_{ut}	D_m (cm²/s)	Mean loss [%]
Buprenorphine	2.46E-02	1.75E-07	5.00E+01
Sufentanil	4.00E-02	2.16E-07	9.60E+00
Fentanyl	9.59E-02	5.16E-07	6.92E+00
Zolpidem	2.19E-01	2.13E-07	5.00E-01
Naloxone	9.44E-02	3.64E-07	6.70E+00
Asenapine	6.28E-02	1.258E-7	1.41E+01
Apomorphine	7.68E-02	2.098E-7	1.36E+01
Acyclovir	1.00E+00	6.711E-9	0.00E+00

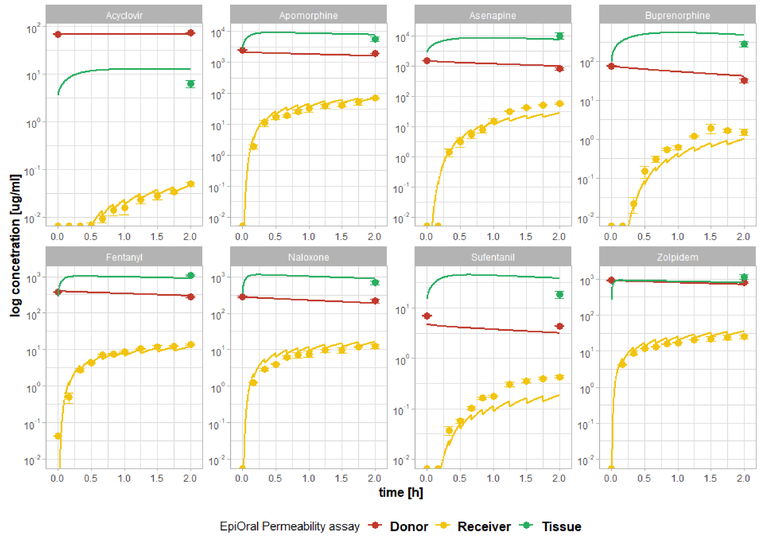


Figure 2: APIs' concentration versus time curves in the donor (Red), buccal tissue (Green), and receiver compartments (Yellow) following their administration in the donor compartment. Lines represent model simulations and dots are observed mean data.

Parameter Sensitivity Analysis (PSA)

PSA suggested the initial API concentration in the donor compartment and the tissue thickness (physiological range: 90-140 um) as the main sources of inter-batch variability in the *in vitro* permeability (Figure 3).

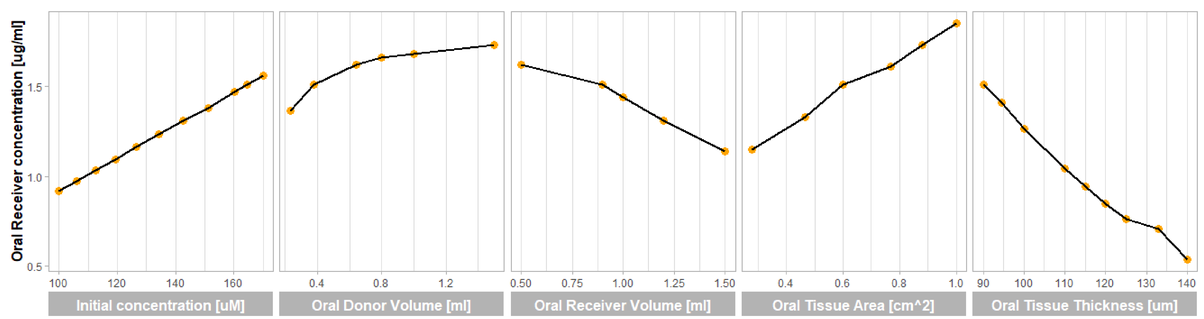


Figure 3: PSA for Buprenorphine receiver compartment concentration at 2 hours. Parameter tested: initial concentration (110-170 uM), donor compartment volume (0.3-1.5 ml), oral receiver volume (0.5-1.2 ml), tissue area (0.6-1 cm2) and tissue thickness (90-140 um).

Figure 4 illustrates the impact of variable initial concentration and tissue thickness on Buprenorphine's receiver concentrations (Batch 1: initial concentration:169 uM, tissue thickness: 90 um and Batch 3: initial concentration: 110 uM, tissue thickness: 80 um).

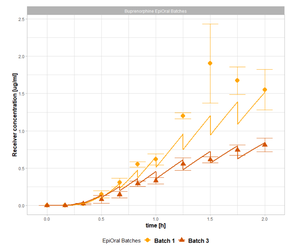


Figure 4: Buprenorphine EpiOral™ measurements for two batches where Batch 1(yellow): initial concentration of 169 uM; tissue thickness of 90 um and Batch 3 (orange): initial concentration of 110 uM and tissue thickness of 80 um was used..

CONCLUSION

- A mechanistic oral absorption model for EpiOral™ assay was developed and validated
- The model was used to determine API-specific D_m and f_{ut} in buccal tissue from *in vitro* permeability studies performed using the EpiOral™ kit
- The model allowed evaluating likely sources of variability in the apparent API permeabilities measured *in vitro*
- Future work will use the determined D_m and f_{ut} values to parameterize PBPK models to predict *in vivo* buccal absorption of these APIs.
- Ultimately, this model-based framework may be able to support the model-informed drug development paradigm of new and generic oral cavity drug products.

DISCLAIMER

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 US FDA or the Department of Health and Human Services, nor does any mention of trade names imply endorsement by the US Government.

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