Novel Physiologically-Based Oral Cavity Model and Its Application for Projection of Clinical Pharmacokinetics of Intermezzo® Sublingual Tablets

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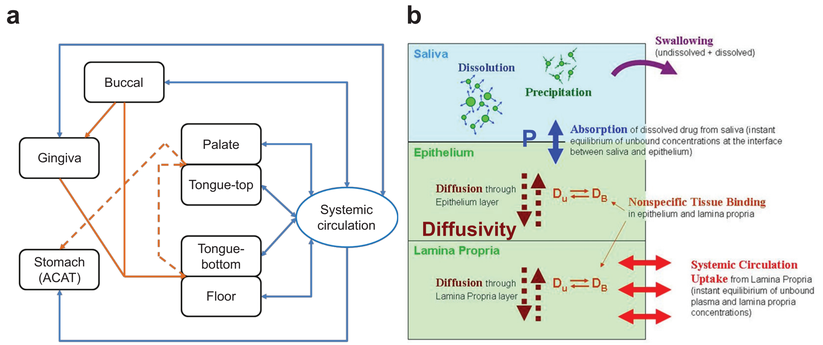
Introduction

Intraoral (IO) delivery refers to an alternative administration route that intends to deliver the drug substance through oral mucosa. The intraoral route provides several advantages over conventional oral dosage forms, such as prompt onset of action, avoiding extensive first-pass metabolism, and improved dosing convenience and patient adherence. There is an increasing interest to apply pharmacokinetic modeling and simulation to evaluate the bioperformance of IO dosage forms in clinics. Physiologically based pharmacokinetic modeling (PBPK) has been proven to provide valuable insights into oral formulation design and development. The purpose of this work was to develop and evaluate a novel physiologically based oral cavity model for projection and mechanistic analysis of clinical pharmacokinetics of intraoral formulations.

Methods

GastroPlus (version 8.0, Simulations Plus, Inc, CA, USA) with the Oral Cavity Compartment Absorption and Transit model (version beta 11) was used to simulate the plasma concentration vs time profiles and the fraction of intraoral drug absorption for a zolpidem tartrate sublingual tablet. Input for simulations included drug physicochemical properties (eg, solubility, permeability, LogP, pKa, API particle size) and systemic pharmacokinetic parameters (eg, clearance, volume of distribution, plasma and tissue binding), and intraoral absorption descriptors (eg, drug diffusivity, epithelium/saliva partition coefficient). The model performance was evaluated by comparing the simulated versus observed mean PK profile judged by visual inspection, correlation coefficient (R^2) between predicted and observed profiles, and the deviation of the key PK parameters (C_{max}, t_{max}, AUC; evaluated by prediction percent deviation). The structure of the physiologically based oral cavity model was described in Figure 1.

Figure 1. Schematic diagram of the (a) oral cavity PBPK model layout† and (b) the drug mass transfer processes included in each oral cavity tissue compartment



† Boxes represent individual oral cavity compartments, the blue arrows symbolize the drug exchange between the perfused layers of individual compartments and systemic circulation, the orange arrows mark the salivary flow, and the orange dash arrows represent the transfer of API upon swallowing.

Results

Physiological parameters for oral cavity

Table 1. Summary of human, dog, and monkey default physiological parameters for each oral cavity compartment in the model

Oral Tissues	Blood flow [mL/min/100 g tissue]	Surface Area [cm²]			Epithelium Thickness [μm]			Lamina Propria Thickness [μm]	pH
		Dog	Monkey	Human	Dog	Monkey	Human		
Buccal	22.78	50.2	16.6	50.2	767	418.8	418.8	500	**6.3**
Gingiva	19.54	46.6	15.4	46.6	193	193	263.8	250	**6.8**
Floor	12.23	5.54	5.96	13.3	168	168	117.6	200	**6.5**
Palate	15.04	20.1	6.6	20.1	257.8	257.8	257.8	200	**7.4**
Tongue-top	100.61	20.67	7.92	25.7	701	701	701	500	7.4
Tongue-bottom	15.84	13.3	4.4	13.3	235	235	235	250	6.5

Diffusivity and partition coefficient

Equations to estimate epithelium/saliva partition coefficient and diffusivity based on LogD(7.4) value of a compound using the experimental results of in vitro mucosa permeability assays for nine compounds.

(a) Epithelium/saliva partition coefficient (P)=2.12 x $e^{0.523 \times LogD(7.4)}$

$$f_{ut} = \frac{C^{epi}_{1,u}}{C^{epi}_{1,t}} = \frac{C^{sal}}{C^{epi}_{1,t}} = \frac{1}{P}$$

f_{ut}: unbound fraction in epithelium tissues

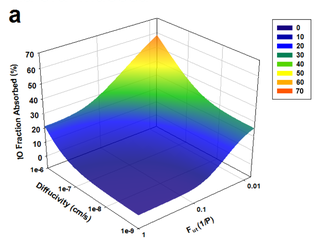
C^{sal}: drug concentration in saliva

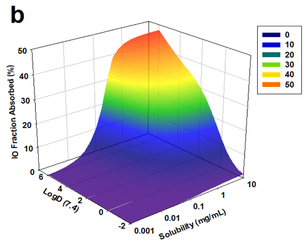
$C^{epi}_{1,u}$; $C^{epi}_{1,t}$: unbound and total concentration in epithelium tissues (sublayer 1)

(b) Compounds with LogD(7.4) <3: Diffusivity=$10^{-0.0803 \times LogD(7.4) \times LogD(7.4) + 0.5006 \times LogD(7.4) - 6.7316}$

Compounds with LogD(7.4) >3: Diffusivity=$10^{-5.9514}$

Figure 2. Simulated surface-response plot for the theoretical interplay of impact of key (a) oral cavity model parameters or (b) physicochemical properties on fraction absorbed via oral mucosa





Assuming a solution formulation is given for intraoral drug administration:

If epithelium/saliva partition coefficient (or unbound fraction in oral mucosa decreases) and tissue diffusivity increase, the fraction of intraoral absorption (F_{a_IO}) will increase.

Assuming a solid dosage form with particle radius of 10 μm is given for intraoral drug administration:

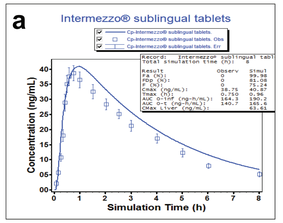
If API has a higher LogD(7.4), the compound will have a higher diffusivity and thus higher F_{a_IO}.
If API has a high solubility, or formulation enhances the solubility of API, high F_{a_IO} is expected.

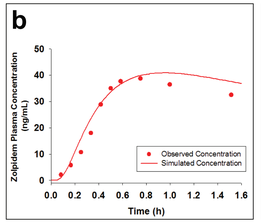
Case example: Intermezzo sublingual tablets

Table 2. Model input parameters for zolpidem tartrate sublingual tablet

Parameters	Values	Resources
Molecular weight	Free base: 307.4; Tartrate salt: 764.9	
Solubility (mg/mL)	23 (salt) in water, 0.18 at pH=7 (base)	Calculated using ACD
LogD (at pH=7.4)	2.42	*Drug Metabolism Reviews.* 1992;24(2):239-266.
pKa	6.2	*Drug Metabolism Reviews.* 1992;24(2):239-266.
Human permeability (×10^{-4} cm^2/s)	10	Estimated from oral PK data
First pass extraction (%)	30	Based on oral bioavailability
Clearance (L/h/kg)	0.157	Calculated based on iv data
Volume distribution (L/kg)	0.525	Calculated based on iv data
Epithelium/saliva partition coefficient	7.46	Equation **(a)**
Diffusivity (×10^{-6} cm^2/s)	1.02	Equation **(b)**
Hold time (min)	2	From clinical study design
pH in oral cavity	5.0	Measured in simulated saliva

Figure 3. Simulated and observed plasma concentration vs time curves (a) from 0-8 h or (b) from 0-1.5 h after the dosing, as well as (c) the predicted fraction of absorption in oral cavity and GI tract for zolpidem after a single dose of 3.5 mg Intermezzo sublingual tablet





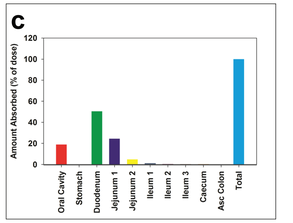


Table 3. Simulated and observed pharmacokinetic parameters after a single dose of 3.5 mg Intermezzo sublingual tablet

Parameters	C_{max} (ng/mL)	T_{max} (h)	$AUC_{0\text{-last}}$ (ng*h/mL)	$AUC_{0\text{-20min}}$ (ng*h/mL)	Fraction Absorbed in Oral Cavity (F_{a_IO}, %)
Observed	38.7	0.75	170	2.27	~13.3†
Predicted	40.9	0.96	190	2.92	18.9
Deviations (%)	5.7	28.0	11.8	28.6	

† $F_{\_IO+PO} = F_{a\_IO} + F_{\_po} \times (F_{a\_IO+PO} - F_{a\_IO})$; rearrange the equation, $F_{a\_IO} = (F_{\_IO+PO} - F_{\_PO}) / (1 - F_{\_PO})$

Assuming 100% absorption in both oral and intraoral administration

- F_{a_IO+PO}: Total fraction absorption via oral cavity and GI tract after a single dose of intraoral (100% based on the assumption)
- $F_{\_IO+PO}$: Absolute bioavailability after a single dose of intraoral administration (74% for zolpidem)
- $F_{\_PO}$: Absolute bioavailability after a single dose of oral administration (70% for zolpidem)

Conclusion

Overall, the novel Gastroplus physiologically based IO absorption model is well designed with reasonable assumptions and satisfactory software performance. Theoretically, intraoral absorption fraction is associated with tissue diffusivity and epithelium/saliva partitioning as well as the lipophilicity and aqueous solubility. The IO PBPK model well captured the observed clinical pharmacokinetics for zolpidem tartrate sublingual tablet. The predicted C_{max}, T_{max}, and AUC were within were all within ±30%. We expect this new modeling capability will be helpful to guide development of future intraoral formulations.