Research Article

Development of a Novel Oral Cavity Compartmental Absorption and Transit Model for Sublingual Administration: Illustration with Zolpidem

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Abstract. Intraoral (IO) delivery is an alternative administration route to deliver a drug substance *via* the mouth that provides several advantages over conventional oral dosage forms. The purpose of this work was to develop and evaluate a novel, physiologically based oral cavity model for projection and mechanistic analysis of the clinical pharmacokinetics of intraoral formulations. The GastroPlus™ Oral Cavity Compartmental Absorption and Transit (OCCAT™) model was used to simulate the plasma concentration *versus* time profiles and the fraction and rate of intraoral drug transit/absorption for Intermezzo® sublingual tablets (zolpidem tartrate). The model was evaluated by the goodness-of-fit between simulated and observed concentrations and the deviation of key PK parameters (e.g., $C_{\max}$, $T_{\max}$, and AUC). In addition, a sensitivity analysis was conducted to demonstrate the interplay and impact of key modeling parameters on the fraction absorbed *via* oral mucosa ($F_{a_{IO}}$). The OCCAT™ model captured the observed pharmacokinetics for Intermezzo® sublingual tablets ($R^2 > 0.9$). The predicted deviations (%) for $C_{\max}$, $AUC_{0-\infty}$, $AUC_{0-20 \text{ min}}$, and $T_{\max}$ were 5.7, 28.0, 11.8, and 28.6%, respectively, indicating good prediction accuracy. The model also estimated ~18% of total drug was absorbed *via* the IO route. Furthermore, the sensitivity analysis indicated that the $F_{a_{IO}}$ was not only associated with drug diffusivity and unbound fraction in epithelium tissue (f_{ut}) but also depended on the physicochemical properties of compounds for IO delivery (e.g., solubility and $\log D_{pH=7.4}$). The novel physiologically based IO absorption OCCAT™ model showed satisfactory performance and will be helpful to guide development of future intraoral formulations.

KEY WORDS: diffusivity; intraoral delivery; oral cavity compartmental absorption and transit (OCCAT™) model; unbound fraction in epithelium tissue; zolpidem.

INTRODUCTION

Intraoral (IO) delivery is an alternative administration approach that aims to deliver a drug substance *via* the oral cavity. Compared with conventional oral products that are absorbed in the gastrointestinal tract, IO formulations disintegrate and dissolve in the mouth and may deliver significant absorption through the mucosal linings of the oral cavity. Commonly developed IO formulations include sublingual tablets, orally disintegrating tablets and films, buccal patches/films/tablets, oral sprays, lozenges, and lollipops. IO formulations provide some unique advantages over conventional oral dosage forms, potentially enabling drug delivery

and improving pharmacokinetic (PK) and pharmacodynamic (PD) profiles [1, 2]. For example, drug compounds could benefit from IO administration by avoiding first-pass metabolism and other unfavorable interactions in the gastrointestinal tract (e.g., degradation, food/pH effects). In addition, as the oral mucosa is highly vascularized, transmucosal absorption could provide fast access directly to the systemic circulation, thus enabling a faster onset of action. In addition to these PK and PD benefits, IO delivery also may improve patient adherence and preference with a more convenient and discreet administration option, as typically no water intake is required during dosing [3].

Modeling and simulation have emerged as useful tools for predicting drug absorption to support formulation and product development [4]. Recently, with the advent of improved physiological knowledge and more powerful software, physiologically based pharmacokinetic (PBPK) modeling has been widely applied. A PBPK model provides a mechanistic analysis to understand the effects of a variety of physicochemical, physiological, and formulation parameters on clinical pharmacokinetics [5]; however, the application of PBPK modeling to IO absorption and delivery has rarely been reported. Historically, simplified compartmental

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modeling was used to analyze absorption kinetics from the oral cavity to the systemic circulation [6, 7]. More recently, the GastroPlus™ (Simulation Plus, Lancaster, CA) Advanced Compartmental Absorption and Transit (ACAT™) model and acsIX (Aegis Technologies, Huntsville, AL) models were used to simulate the clinical pharmacokinetics of propranolol and fentanyl sublingual tablets, respectively [8, 9]. However, all previously reported IO PK models used a simple first-order absorption rate process without sufficiently linking oral cavity physiology and drug physicochemical properties. Absorption within the oral cavity is driven not only by permeability and dissolved concentration but also by a complicated bidirectional partition between saliva and tissue, as well as separate kinetic processes between the disappearance of drug from the oral cavity and absorption into the blood [6, 10]. In addition, various physiological and dosing variables, including the volume of saliva, swallowing frequency, and water intake during IO administration, may significantly alter the pharmacokinetics [11, 12].

There is increasing interest in the early feasibility assessment of IO delivery of drug molecules based on their physicochemical properties [13]. Clearly, a simplified first-order absorption model of the oral cavity is not adequate to integrate the complexity of IO physiology, physicochemical properties, formulation effects, and dosing scenarios. Moreover, the first-order absorption model is not suitable for prospective prediction of IO products/formulations at an early drug discovery and development stage; thus, selection of lead molecules and formulations for IO delivery can be time consuming and costly, requiring significant resources using *in vivo* preclinical models. Therefore, a fully physiologically based IO absorption model that takes intraoral disintegration, dissolution, and transmucosal absorption into account is required and can play an important role in supporting formulation development and bioperformance evaluation for IO drug products.

The purpose of this work was to develop a comprehensive, physiologically based oral cavity model for the prediction and mechanistic analysis of clinical pharmacokinetics for IO formulations. In this manuscript, we describe this novel OCCAT model with detailed model settings, underlying assumptions, and equations. Additionally, the validity of the model is verified by two approaches: a parameter sensitivity analysis to check the overall model performance and evaluation of the simulation accuracy using a model intraoral drug product, zolpidem (Intermezzo®).

MATERIALS AND METHODS

Computer Hardware and Software

GastroPlus (version 8.0; Simulations Plus, Inc., CA, USA) with the Oral Cavity Compartmental Absorption and Transit (OCCAT™) model (version beta 11) was run on a Lenovo computer with an Intel® Core™ i5 processor. Input for simulations included drug physicochemical properties (e.g., solubility, permeability, LogP, pK_a, API particle size) and systemic pharmacokinetic parameters (e.g., clearance, volume of distribution, plasma and tissue binding). Plasma concentration *versus* time profiles and the fraction and rate of IO drug transit/absorption were estimated as part of the model verification.

Schema of the GastroPlus Intraoral Absorption Model

The OCCAT model employs six physiological compartments: buccal, gingival, palate, top of the tongue, bottom of the tongue, and mouth floor. A schematic diagram of how different IO compartments are connected, as well as the link between the OCCAT and ACAT models and systemic circulation, is shown in Fig. 1a. The model accounts for drug dissolution/precipitation in saliva, drug absorption, diffusion through the oral mucosa and into the systemic circulation from the perfused layers of individual tissues, nonspecific tissue binding, and swallowing of unabsorbed drug (dissolved and undissolved), as shown in Fig. 1b. Processes such as dissolution and precipitation are simulated in a way similar to the ACAT model as described previously [14]. The model is linked to the original GastroPlus ACAT model to account for gastrointestinal (GI) absorption of the swallowed portion of the administered dose.

Model Theory

Physiological Properties of the IO Cavity. Parameter values collected from literature for the human IO physiology are summarized in Table I along with commentary on each parameter and data source.

Drug Dissolution and Precipitation. Drug dissolution and precipitation are modeled using the same equations applicable to dissolution and precipitation in the gut lumen, as previously described for the ACAT model [14].

Saliva Flow and Swallowing. In the OCCAT model, saliva production occurs continuously from the buccal tissues and sublingual salivary glands at saliva production rates of 0.04 and 0.32 mL/min, respectively. The default basal saliva volume is 0.9 mL for humans [15]. Saliva produced in the buccal tissue flows along the cheek and around the gingiva to the floor of the mouth, where it mixes with the saliva produced by sublingual salivary glands (Fig. 1a). Saliva will continue to accumulate in the floor of the mouth or flow to the top of the tongue until a swallow event is triggered in the model. Swallowing is assumed to occur when the saliva volume doubles over the basal volumes (≥ 1.8 mL), unless the simulation dictates otherwise (e.g., to allow simulating studies where subjects are instructed not to swallow). During swallowing, the excess saliva volume (volume above the basal saliva volume) will move from the oral cavity to the stomach along with the corresponding amount of drug present in the saliva (undissolved and dissolved). No saliva accumulation is assumed in the buccal and gingival regions, but the model accounts for the dilution of the drug in these regions as the saliva flows through after production in the buccal salivary glands as well as the loss of drug upon swallowing. Upon swallowing, the model assumes complete mixing of saliva in sublingual (floor and bottom of the tongue) and supralingual (top of the tongue and palate) regions and instant equilibrium of drug concentration in saliva in these regions.

Drug Absorption. IO absorption in the model is defined as an instant partitioning between saliva and the top layers of the epithelium. The unbound drug concentration in the epithelium sublayer 1 ($C_{1,u}^{epi}$) is, at any given time, equal to the dissolved

Fig. 1. Schematic diagram of the **a** oral cavity PBPK model layout* and **b** the drug mass transfer processes included in oral cavity tissue compartments. *Boxes represent individual oral cavity compartments, the blue arrows symbolize the drug exchange between the perfused layers of individual compartments and systemic circulation, and the orange arrows mark the salivary flow in the oral cavity. Orange dashed arrows represent the transfer of API upon swallowing

drug concentration in the saliva (C^{sal}), assuming the dissolved drug is always unbound in the saliva. The unbound drug fraction in the epithelium (f_{ut}), or alternatively, the reciprocal of epithelium/saliva partition coefficient (P), can be calculated by the ratio of total drug concentration in the epithelium sublayer 1 ($C_{1,t}^{\text{epi}}$) at the saliva/epithelium interface against unbound drug concentration in epithelium sublayer 1 ($C_{1,u}^{\text{epi}}$) or C^{sal} (Eq. 1):

$$f_{\text{ut}} = \frac{C_{1,u}^{\text{epi}}}{C_{1,t}^{\text{epi}}} = \frac{C^{\text{sal}}}{C_{1,t}^{\text{epi}}} = \frac{1}{P} \quad (1)$$

The mass balance for drug in epithelium at the saliva interface is expressed in Eq. 2:

$$\left(\frac{V^{\text{sal}}}{P} + V_1^{\text{epi}} \right) \times \frac{dC_{1,t}^{\text{epi}}}{dt} = -\frac{\text{Diff}}{h_1^{\text{epi}}} \times \text{SA} \times (C_{1,u}^{\text{epi}} - C_{2,u}^{\text{epi}}) \quad (2)$$

where V^{sal} and V_1^{epi} represent volumes of saliva and the epithelium sublayer 1, respectively, in a given compartment;

Diff (unit cm^2/s) is the drug diffusivity through the oral mucosa; h_1^{epi} is the thickness of the epithelium sublayer 1; and SA is the surface area (unit cm^2) of a given compartment as described before.

Tissue Diffusion and Systemic Circulation Uptake. After the drug enters the epithelium sublayer 1, it will diffuse through the rest of the epithelium tissue layers into the lamina propria. The rate of diffusion is dependent on the drug's diffusivity through the given type of epithelium (soft or keratinized), the surface area of a specific oral cavity tissue compartment, and the thickness of the epithelium layer. To account for the concentration gradient due to slow diffusion through this tissue layer, the epithelium of each compartment is split into six sublayers. Physiologically, the oral mucosa tissue is generally composed of multiple cell layers; however, for computational speed, the current model assumed six hypothetical sublayers to calculate drug diffusion across the epithelium and lamina propria. Moreover, the thickness fraction (expressed as a percentage) for each sublayer was

Table I. Summary of default physiological parameters for each oral cavity compartment in humans

Tissue compartments	Blood flow ^a (mL/min/100 g tissue)	Surface area ^b (cm ²)	Epithelium thickness ^c (μm)	Lamina propria thickness ^d (μm)	pH ^e
Buccal	22.78	50.2	418.8	500	6.3
Gingiva	19.54	46.6	263.8	250	6.8
Floor	12.23	13.3	117.6	200	6.5
Palate	15.04	20.1	257.8	200	7.4
Tongue-top	100.61	25.7	701	500	7.4
Tongue-bottom	15.84	13.3	235	250	6.5

^a The same blood flow values are used for humans based on a combination of values found in literature [27, 28]

^b Surface areas for individual compartments in human adults were obtained from literature [29, 30], the surface areas for children can be estimated by scaling adult surface areas based on published information on vocal tract development [31]

^c Values for epithelium thickness in different regions in humans were obtained from literature [12, 22, 32–37]

^d Very limited information for lamina propria thickness is available for humans [32]

^e pH values in individual regions of the oral cavity for human were found in literature [38]

defined by fitting *in vitro* permeability data in porcine buccal and sublingual tissues. From optimal fitting of the results of intraoral permeability assays for nine model molecules, sublayer 1 represents 5% of the total epithelium thickness, and the remaining 95% of epithelium thickness is split evenly among the remaining five layers. The process of drug diffusion through the epithelium is described by Eq. 3:

$$V_j^{\text{epi}} \times \frac{dC_{j,t}^{\text{epi}}}{dt} = \frac{\text{Diff}}{h_j^{\text{epi}}} \times \text{SA} \times (C_{j-1,u}^{\text{epi}} - 2C_{j,u}^{\text{epi}} + C_{j+1,u}^{\text{epi}}) \quad (3)$$

where $C_{j,t}^{\text{epi}}$ and $C_{j,u}^{\text{epi}}$ represent total and unbound drug concentrations in the epithelium sublayer j , respectively; V_j^{epi} is the volume of epithelium sublayer j in a given compartment; and h_j^{epi} is the thickness of the epithelium sublayer j in a given compartment. Further, the current model assumes similar composition of the epithelium and lamina propria tissue layers, so the drug exchange between these two layers is further modeled as a simple diffusion. For modeling purposes, the lamina propria compartment is split into six evenly spaced sublayers. The process of drug diffusion through lamina propria and uptake into systemic circulation is described by Eq. 4:

$$V_j^{\text{lam}} \times \frac{dC_{j,t}^{\text{lam}}}{dt} = \frac{\text{Diff}}{h_j^{\text{lam}}} \times \text{SA} \times (C_{j-1,u}^{\text{lam}} - 2C_{j,u}^{\text{lam}} + C_{j+1,u}^{\text{lam}}) - \text{RateIntoSyst} \quad (4)$$

Systemic circulation uptake is modeled as an instant partitioning between the unbound concentration in plasma and the unbound concentration in each lamina propria layer. The rate of drug uptake into the systemic circulation is dependent on the rate of blood flow through the lamina propria, as described by Eq. 5:

$$\text{RateIntoSyst} = Q \times R_{\text{bp}} \times \left(C_u^{\text{lam}} \times \frac{1}{f_{\text{up}}} - C_p \right) \quad (5)$$

where $C_{j,t}^{\text{lam}}$ and $C_{j,u}^{\text{lam}}$ represent total and unbound drug concentrations in lamina propria sublayer j , respectively; V_j^{lam} is the volume of lamina sublayer j in a given compartment; h_j^{lam} is the thickness of the lamina propria sublayer j ; RateIntoSyst is the rate of uptake into systemic circulation from the lamina propria in a given compartment; Q is the rate of blood flow through the lamina propria layer in a given compartment; R_{bp} is the drug blood/plasma concentration ratio; f_{up} is the fraction of drug unbound in plasma; C_u^{lam} is the unbound drug concentration in lamina propria; and C_p is drug concentration in plasma.

Estimation of Epithelium/Saliva Partition Coefficient (P) and Diffusivity using Drug Physicochemical Properties in Oral Mucosa. As described in Eq. 1, the model assumes no nonspecific binding in buffer or saliva, so the fraction unbound in mucosal tissue will be equal to the reciprocal value of the mucosa/buffer (saliva) partition coefficient. The initial value of f_{ut} for oral mucosa can be estimated using a default theoretical model in the program (Eq. 6). The model was obtained by analysis of *in vitro* permeability measurements through pig buccal and sublingual

tissues for nine drugs (Fig. 2a, see [Supplemental documents](#) for the experiments).

$$f_{\text{ut}} = \frac{1}{P} = \frac{1}{2.12 \times e^{0.523 \times \log D(7.4)}} \quad (6)$$

The oral cavity drug delivery model includes a theoretical model to provide an initial estimate of the drug diffusivity through the oral mucosa (Eq. 7).

For compounds with $\log D_{\text{pH}=7.4} \leq 3$: Diff

$$= 10^{-0.0803 \times (\log D(7.4))^2 + 0.5006 \times \log D(7.4) - 6.7316}$$

For compounds with $\log D_{\text{pH}=7.4} > 3$: Diff = $10^{-5.9514}$ (7)

where $\log D_{\text{pH}=7.4}$ is the log10 of the octanol/water distribution coefficient at pH=7.4. Similar to the f_{ut} estimation, the model was obtained by analysis of *in vitro* permeability measurements through pig buccal and sublingual tissues for nine drugs (Fig. 2b, see [Supplemental materials](#) for detailed experimental results). Experimental data were not available to estimate the diffusivity through keratinized epithelium, so the default values for both diffusivities (soft tissues and keratinized epithelium) currently are considered similar. However, much slower diffusivity would be expected through keratinized epithelium, and these parameters can be modified in the simulation based on available data.

Model Evaluation

Parameter Sensitivity Analysis

A sensitivity analysis was conducted to demonstrate the impact of key IO model parameters on the fraction absorbed via oral mucosa ($F_{\text{a,IO}}$). The key IO model parameters that determine $F_{\text{a,IO}}$ include diffusivity, f_{ut} , drug solubility, particle size of API, and $\log D_{\text{pH}=7.4}$ (*in vitro* results indicate that $\log D_{\text{pH}=7.4}$ is highly correlated with diffusivity, f_{ut}). The sensitivity analysis was performed for a theoretical API administered as a solution or tablet at a dose of 1 mg sublingually without water. Initially, the sensitivity analysis was performed to investigate the effects of the epithelium/saliva partitioning coefficient (P) and diffusivity at a range of 1–100 and 0.001– 1×10^{-6} cm/s, respectively. Because the epithelium/saliva partitioning coefficient (P) and diffusivity can be estimated from the $\log D_{\text{pH}=7.4}$ value according to Eqs. 6 and 7, respectively, the $F_{\text{a,IO}}$ is associated with the lipophilicity of an API. The drug solubility in saliva is another major contributing factor to intraoral absorption. Since solid dosage forms are commonly used in IO drug delivery, the interplay of drug solubility and lipophilicity of an API was further investigated. The sensitivity analysis was then performed to estimate the change in $F_{\text{a,IO}}$ for a sublingual tablet by changing the drug solubility and $\log D_{\text{pH}=7.4}$ values ranging from 0.001 to 1 mg/mL and –2 to 6, respectively. The molecular properties were input as neutral, Mw=400 g/mol, particle radius=10 μm , drug density=1.2 g/mL, and dose=

Fig. 2. Regression curves for **a** oral mucosa f_{ut} and **b** diffusivity through mucosal tissue *versus* $\log_{10}$ of the octanol/water distribution coefficient at pH=7.4 ($\log D_{pH=7.4}$) based on the results obtained from *in vitro* mucosa permeability assays for nine compounds

1 mg. The influence of residence time on $F_{a_{IO}}$ was also investigated at 15 min using the simulation for a sublingual tablet.

Model Compound and Settings

Zolpidem was chosen as the model compound for the OCCAT evaluation. Zolpidem is a nonbenzodiazepine hypnotic agent for the short-term treatment of insomnia. Oral tablets of zolpidem tartrate are available on the market under the brand name Ambien® [16]. Zolpidem has rapid and nearly complete oral absorption, with an absolute oral bioavailability of 70% in humans and moderate first-pass metabolism [17]. Data from a clinical pharmacokinetic study of IO administration of a 3.5-mg zolpidem tartrate sublingual tablet [18] were used to evaluate the performance of the OCCAT model. For the sublingual administration, the subjects ($N=34$) were instructed to move the Intermezzo® tablet under the tongue to facilitate tablet disintegration without swallowing for 2 min after dosing. As a reference, each individual also received a 3.5-mg zolpidem tartrate tablet orally in another study period. The clinical study results showed that IO dosage forms of zolpidem (such as Intermezzo®) provided a faster rise of the plasma concentration *versus* time (Cp-time) profile, as well as significantly earlier sleep initiation compared with the conventional oral tablet [19, 20]. Only the mean plasma concentration *versus* time curves related to the aforementioned clinical study were digitized from the literature to yield the “observed” data, whereas standard error values could not be accurately digitized because some of the error bars were overlapping with the symbols of mean concentrations. The IO-model evaluation was conducted to reasonably match Cp-time and estimate $F_{a_{IO}}$, as well as the relative proportion of IO absorption to total drug absorption. Physicochemical properties of the model API, including pK_a , $\log P$, solubility, and P_{eff} were obtained from the literature or estimated using ADMET Predictor (v6.0; Simulation Plus Inc., CA). The systemic PK parameters (e.g., clearance, volume of distribution, rate constants) were calculated by fitting the intravenous PK data using PKPlus™ (Simulation Plus Inc., CA). The

absorption of API from IO dosage forms can occur across both oral mucosa and the gastrointestinal tract. As a prerequisite model evaluation step, physicochemical properties and systemic PK of the commercial IO product administered orally were used to build the GastroPlus ACAT models to match the Cp-time profiles. Some physicochemical parameters (e.g., P_{eff} , precipitation time) required optimization to fit the Cp-time profile of the oral PK data. Diffusivity and f_{ut} were estimated using Eqs. 6 and 7. For IO modeling, the parameters related to IO-simulation settings (e.g., holding time, dosage forms) were obtained from the reported clinical study design; the OCCAT was then used to simulate the Cp-time profiles. The model performance was evaluated by comparing the simulated *versus* observed mean Cp-time profile judged by visual inspection as well as the correlation coefficient (R^2) between predicted and observed profiles. The accuracy of simulation on the key PK parameters (C_{max} , T_{max} , and AUC) was evaluated by deviation (%) between simulated and observed values. For comparison, a simple one-compartment oral cavity model linked to the GastroPlus ACAT model was used to attempt to simulate the Cp-time profile using the default oral-cavity absorption scaling factor (ASF) value as described previously [8]. The new IO and simple oral cavity model predicted $F_{a_{IO}}$ values for the IO dosage forms, depicted on a regional absorption plot. All input parameters are summarized in Table II.

RESULTS

Parameter Sensitivity Analysis

The parameter sensitivity analysis (PSA) was depicted on three-dimensional surface response plots to investigate the sensitivity of $F_{a_{IO}}$ to key factors (Fig. 3). The PSA assessed the impact of two unique parameters introduced in this IO module, f_{ut} (fraction unbound in oral cavity tissue) and Diff (diffusivity in oral tissue). For an IO solution formulation, an initial gradual increase of $F_{a_{IO}}$ was observed when f_{ut} decreased from 1 to 0.1 and diffusivity increased from 1×10^{-9} to 1×10^{-7} cm²/s. In contrast, a relatively steep increase in

Table II. Summary of input parameters used in the GastroPlus simulation of zolpidem

Parameter	Value	Resource
Molecular weight (Da)	Free base: 307.4 Tartrate salt: 764.9	
pH-dependent solubility (mg/mL)		Merck internal database
1.0	40.0	
2.0	40.0	
3.0	37.0	
4.0	22.0	
5.0	4.6	
6.0	0.61	
7.0	0.18	
8.0	0.14	
$\log D_{\text{pH}=7.4}$	2.42	[17]
$\text{p}K_a$	6.2	[17]
Mean precipitation time (s)	900	Default
Drug particle density (g/L)	1.2	Default
Effective particle radius (μm)	25	Default
Dose (mg)	3.5	From clinical study
Dosage form	Sublingual tablet	From clinical study
Body weight (kg)	71.7	From clinical study
Human P_{eff} ($\times 10^{-4} \text{ cm}^2/\text{s}$)	10	Estimated from oral PK data [18]
Unbound fraction in plasma (%)	8	[17]
Blood/plasma concentration ratio	0.77	[17]
First-pass extraction (%)	30	Based on oral bioavailability
Clearance (L/h/kg)	0.157	Fitted from IV PK of zolpidem
Volume distribution (L/kg)	0.525	Fitted from IV PK of zolpidem
Elimination half-life (h)	2.32	Fitted from IV PK of zolpidem
Fraction unbound in oral tissue	0.134	Generated from Eq. 6
Oral mucosa diffusivity ($\times 10^{-6} \text{ cm}^2/\text{s}$)	1.02	Generated from Eq. 7
Hold time (min)	2	From clinical study design
pH in sublingual	5	Measured in artificial saliva

$F_{a_{\text{IO}}}$ was observed after f_{ut} was further decreased from 0.1 to 0.01 and diffusivity increased from 1×10^{-7} to $1 \times 10^{-6} \text{ cm}^2/\text{s}$. In addition, the plot suggested that a maximum $F_{a_{\text{IO}}}$ of ~60% was predicted by reducing f_{ut} to 0.01 and increasing Diff up to $1 \times 10^{-6} \text{ cm}^2/\text{s}$ for a residence time of 15 min in the oral cavity (Fig. 3a).

For IO use of solid dosage forms, the impact of the two most important physicochemical properties (solubility and $\log D_{\text{pH}=7.4}$) on $F_{a_{\text{IO}}}$ is shown in Fig. 3b and c. $F_{a_{\text{IO}}}$ is predicted to increase with higher solubility and/or increased

a **b**

Sublingual Tablet
(1 μm API particle radius)

c

Sublingual Tablet
(10 μm API particle radius)

Fig. 3. Simulated surface response plot for the theoretical impact on the fraction absorbed via IO mucosa by the **a** oral cavity model parameters of tissue diffusivity and f_{ut} after a single sublingual solution dose versus solubility and $\log D_{\text{pH}=7.4}$ compared with an API particle radius of **b** 1 μm or **c** 10 μm after a single sublingual tablet dose (1 mg)

$\log D_{pH=7.4}$; however, PSA results also predict that a compound with solubility <0.1 mg/mL and $\log D_{pH=7.4} < 2$ would have negligible intraoral absorption ($F_{a_{IO}} < 1\%$). Furthermore, the maximum $F_{a_{IO}}$ of $\sim 50\%$ was predicted when the $\log D_{pH=7.4}$ value was increased from -2 to 6 and the solubility was also increased to 10 mg/mL. It is worth noting that high $\log D_{pH=7.4}$ and high solubility values may not occur simultaneously for the same compound, so based on this model, the maximum achievable $F_{a_{IO}}$ is expected to be lower than 50% . The interplay between solubility and $\log D_{pH=7.4}$ on the predicted IO absorption was also evaluated using a three-dimensional surface response. The PSA results showed that high $\log D_{pH=7.4}$ cannot significantly facilitate the IO absorption process at low solubility despite of high drug partitioning into oral tissues. Similarly, high solubility cannot significantly improve the IO absorption at low $\log D_{pH=7.4}$. Comparing the surface response plots for 1 and 10 μm API particle radius (Fig. 3b, c), $F_{a_{IO}}$ was very similar, indicating that, for certain ranges of solubility and $\log D_{pH=7.4}$, particle size in the range of 1 – 10 μm may not be critical to IO absorption.

Predicting the Plasma Exposure of Intermezzo® Sublingual Tablets

The observed and simulated mean Cp-time profiles for oral and sublingual administration of zolpidem (3.5 mg) are shown in Fig. 4. The goodness of fit for both arms was judged by the correlation coefficient ($R^2 > 0.9$) and deviation (%) between observed and simulated pharmacokinetic parameters. Based on Eqs. 6 and 7, the f_{ut} (fraction unbound in tissue) and Diff (tissue diffusivity) of zolpidem were calculated as 0.133 and $1.022 \times 10^{-6} \text{ cm}^2/\text{s}$, respectively. All other input parameters were either from the clinical study design or from literature as listed in Table II.

The observed mean zolpidem Cp-time profile following sublingual zolpidem tartrate tablet administration showed significantly faster rise in Cp than that from the oral tablet in the first hour. According to the pharmacokinetic parameters shown in the Intermezzo NDA file, the values of $\text{AUC}_{0-20 \text{ min}}$ were 3-fold higher following sublingual 3.5 mg zolpidem ($2.27 \text{ ng/mL} \cdot \text{h}$) than following oral zolpidem ($0.74 \text{ ng/mL} \cdot \text{h}$) [18].

Fig. 4. Simulated and observed mean Cp-time curves for zolpidem after a single 3.5-mg Intermezzo® sublingual tablet using **a** the new GastroPlus physiologically based IO absorption model, **b** a simple one-compartment oral cavity model, compared with simulated and observed PK profiles after **c** a single oral dose of a 3.5-mg zolpidem tablet. The comparison of simulated PK at the early absorption stage up to 1.5 h is shown in panel (**d**)

The OCCAT module well simulated the clinical pharmacokinetics of the sublingual zolpidem tablet, especially for early time points in the plasma concentration profile (Fig. 4a), which is critical for the desirable pharmacodynamic effect. The predicted $C_{\max}$, $T_{\max}$, $AUC_{0-20 \text{ min}}$, and $AUC_{0-\infty}$ were all within $\pm 30\%$ of the observed values (Table III).

In comparison, a simple one-compartment oral cavity model along with the ACAT GI model significantly underestimated the early onset of the zolpidem Cp-time profile following sublingual administration of the zolpidem sublingual tablet using the default oral cavity ASF model (Fig. 4b). However, the conventional ACAT GI model accurately simulated zolpidem clinical pharmacokinetics following oral administration (Fig. 4c). A combined plot including observed and simulated Cp-time profiles following the sublingual/oral administration of zolpidem tablets clearly demonstrated the good fit of the early pharmacokinetic profile with the new OCCAT model (Fig. 4d).

Prediction of Fraction of IO Absorption and Diagnostic Analysis

The extent of absorption of the sublingual zolpidem tablet in different GI regions, including the oral cavity ($F_{a_{\text{IO}}}$), which was predicted to be 18.9%, is shown in the Regional Absorption plot (Fig. 5a). In addition to the significant transmucosal absorption in the oral cavity, the majority of the absorption was predicted to be in the duodenum and upper jejunum regions of the small intestine. Total absorption was predicted to be close to 100%.

The predicted dissolution and absorption behavior of the zolpidem sublingual tablet in the oral cavity and subsequently in the GI tract are shown in Fig. 5b. The dissolution of the sublingual zolpidem tablet was predicted to be complete within 5 min; however, absorption was prolonged up to 1.2 h and could be clearly divided into two sections: a rapid absorption phase in the oral cavity and more gradual absorption in the GI tract. The amount of zolpidem entering into the portal vein from the GI tract was lower than the total absorption of zolpidem. The difference between the total fraction absorbed and the fraction entering the portal vein is transmucosal absorption in the oral cavity (Fig. 5b). Figure 5b also shows the simulated total IO absorption for zolpidem. As expected, the initial absorption rate increased rapidly, reaching its maximal absorption rate within the first 2–3 min. The extent of absorption then gradually decreased because the drug absorbed in the epithelium diffused back

into the fresh saliva after each swallowing to reach a new partition equilibrium.

The new OCCAT model also enabled various diagnostic analyses of dissolution and absorption of zolpidem from the sublingual tablet in the oral cavity (Fig. 5c). As the holding time was fixed at 2 min based on the clinical study design, the zolpidem concentration increased within the first 2 min due to no drug swallowing. After 2 min, the drug amount dissolved in saliva decreased periodically as more dissolved zolpidem was swallowed, resulting in gradually increasing intestinal absorption into the systemic circulation.

DISCUSSION

The objective of developing this OCCAT model was to provide a comprehensive physiologically based *in silico* model for simulating the disposition of drugs administrated into the oral cavity and to predict the overall clinical pharmacokinetics of IO formulations. The model was constructed using built-in physiological factors describing the oral cavity for humans (Table I). Blood flow, saliva pH, and oral cavity tissue surface areas and thicknesses were incorporated into this OCCAT module to provide the default physiological parameters. As described in Fig. 1, the drug mass transfer processes within the oral cavity are reflected in two main pathways: the drug exchange between the perfused layers of individual compartments and systemic circulation and the drug exchange due to salivary flow in the oral cavity. The model is also connected to the ACAT GI absorption model within GastroPlus to account for the swallowed portion of the administered dose.

The kinetic model of drug transfer in the OCCAT module can be described in three stages: (1) instant drug partitioning between saliva and the top layers of the epithelium (partition coefficient determined), (2) drug diffusion between sublayers in the oral cavity epithelium and lamina propria (diffusivity rate-limited), and (3) drug uptake into systemic circulation dependent on instant plasma/lamina propria partitioning and the rate of blood flow through the lamina propria. The kinetics of IO absorption have been discussed in previous reviews [21, 22]. The correlation between transmucosal absorption and the partition coefficient was also widely investigated. Lien *et al.* found that the buccal absorption of 41 compounds was correlated with the log of the octanol-water partition coefficient [23]. Beckett *et al.* also showed a correlation for the partition coefficient in *n*-heptane-aqueous systems (partition properties close to the

Table III. Simulated and observed pharmacokinetic parameters after a single 3.5-mg sublingual dose and a single 3.5-mg oral tablet dose of zolpidem

Formulations	Parameters	$C_{\max}$ (ng/mL)	$T_{\max}$ (h)	$AUC_{0-\infty}$ (ng*h/mL)	$AUC_{0-20 \text{ min}}$ (ng*h/mL)
Zolpidem sublingual tablet (3.5 mg)	Observed	38.7	0.75	170.0	2.27
	Predicted	40.9	0.96	190.1	2.92
	Deviations (%)	5.7	28.0	11.8	28.6
Zolpidem oral tablet (3.5 mg)	Observed	37.1	0.75	161.5	0.74
	Predicted	41.2	1.04	175.5	0.34
	Deviations (%)	11.1	38.6	8.7	45.9

Fig. 5. Simulated **a** total and regional fractions absorbed of zolpidem in Intermezzo® sublingual tablets; **b** time course (up to 1.5 h) of the cumulative amount of zolpidem dissolved, absorbed, entered portal vein, absorbed intraorally, and entered system circulation (SC); **c** amount of zolpidem dissolved in saliva, cumulative amount swallowed (in dissolved and undissolved forms), amount retained in the oral cavity, and the cumulative amount that entered systemic circulation up to 0.5 h after a single 3.5-mg Intermezzo sublingual tablet

oral mucosa) with buccal absorption for a series of amines and acids [24]. Permeation within the oral cavity is dominated by passive diffusion with minimal involvement of drug-metabolizing enzymes and active transport; therefore, permeability/diffusivity is one of the key factors to determine IO absorption [1].

Two unique parameters, f_{ut} (fraction unbound in oral cavity tissue) and Diff (diffusivity in oral tissue), were introduced into this OCCAT model. The value of f_{ut} for oral mucosa was estimated using the default theoretical model in Eqs. 6 and 7. The model was obtained by analysis of *in vitro* permeability measurements through porcine buccal and sublingual tissues for nine compounds (as shown in the Supplemental document). Assuming no nonspecific binding in buffer or saliva, f_{ut} is equal to the reciprocal value of the mucosa/buffer (saliva) partition coefficient (P). Considering that the partition coefficient is usually correlated with $\log D_{pH=7.4}$, a regression curve for epithelium/saliva partition coefficient *versus* $\log D_{pH=7.4}$ was developed. The regression equation was derived from Eq. 6. Similarly, Diff was also correlated with $\log D_{pH=7.4}$, and from that assumption, Eq. 7 was derived. The current default estimates for partition coefficient and diffusivity may not be perfect, considering the limited number of compounds that were used for this correlation, but they should provide close estimates for f_{ut} and Diff based on the physicochemical properties of the compound. A future goal is to refine these equations as additional data become available to better predict f_{ut} and Diff. The program also allows manual input of f_{ut} and Diff to

the model if the predicted default values do not provide a good fit for animal or clinical pharmacokinetic data.

Six physiological compartments (buccal, gingival, palate, top of the tongue, bottom of the tongue, and mouth floor) were implemented in this OCCAT model. Each compartment consists of two sub-compartments, such as epithelium and lamina propria. Each sub-compartment was further split into six sublayers. The sublayer structure not only mimics the real physiology in the human oral cavity (eight to ten cell layers in sublingual tissue and 40–50 layers in buccal tissue) but also accounts well for the delay in IO absorption observed clearly *in vitro* permeation studies (as shown in the Supplemental document). Six sublayers each for the epithelium and lamina propria were chosen, as this achieved a good balance between acceptable simulation accuracy and simulation time.

The sensitivity analysis conducted by this OCCAT model investigated the effects of key factors, such as solubility, diffusivity, partition coefficient, and $\log D_{pH=7.4}$ on the transmucosal absorption of IO formulations. As expected, IO absorption increases with higher diffusivity, solubility, $\log D_{pH=7.4}$, and oral mucosa/saliva partition coefficient, and is inversely correlated with f_{ut} . More importantly, we believe it is the first time that a modeling and simulation tool has provided a quantitative estimate of absolute percent of IO absorption based on these physicochemical properties. This OCCAT model provides a mechanistic understanding of the ranges of solubility and lipophilicity for an API to achieve acceptable IO absorption for formulation development. It was determined that a diffusivity of approximately $1 \times$

Table IV. The $F_{a_{IO}}$ bioavailability for sublingual administrated tablets in a clinic study

Drugs	Dose (mg)	“Observed” $F_{a_{IO}}^a$ (%)	Methods for obtaining the “observed” $F_{a_{IO}}$	OCCAT model predicted $F_{a_{IO}}$ (%)	Reference
Zolpidem	3.5	13.3	F_{PO} : 70%; F_{PO+IO} : 74% Eq. 8 ^b	18.9	[18]
Asenapine	5	35	F_{PO} : 1%; F_{PO+IO} : 35% Eq. 8 ^b	35.9	[39]
Verapamil	40	35	F_{PO} : 35%; F_{PO+IO} : 58% Eq. 8 ^b	31.5	[40]
Propranolol	40	25–40	PBPK model with a single oral cavity compartment	30.9	[8]
Nicotine	2	53	F_{PO} : 25%; F_{PO+IO} : 65% Eq. 8 ^b	14.8	[41, 42]

^a “Observed” $F_{a_{IO}}$ was calculated using Eq. 8 based on the absolute bioavailability of the oral only formulation (F_{PO}) and the absolute bioavailability of intraoral drug products (F_{IO+PO}) reported in literature unless specified (e.g., estimated using PBPK model published in literature)

^b Fraction absorbed in oral cavity calculated by $F_{a_{IO}} + (1 - F_{a_{IO}}) \times F_{PO} = F_{PO+IO}$

10^{-7} cm²/s and f_{ut} of 0.1 could be used as a conservative lower limit to expect an API to achieve significant intraoral absorption (e.g., 10%) if absorption is not limited by dissolution and solubility (e.g., IO solution formulations). For a solid dosage form, acceptable solubility (with at least 10% of dose dissolved in the oral cavity) and $\log D_{pH=7.4}$ (>2) values are the minimum requirements to obtain acceptable IO absorption ($F_{abs,IO}=10\%$) for an API with a high mucosa/saliva partition coefficient and diffusivity. The model also indicates that maximum IO absorption is less than 60% no matter how favorable the solubility and diffusivity values are (limited by residence time in the oral cavity and swallowing). It is also consistent with observed clinical pharmacokinetics for a number of compounds following sublingual administration as shown in Table IV. The relatively lower absorption obtained from the oral cavity compared to intestinal absorption can be attributed to the small volume of saliva, limited absorption window, and low surface area. These findings further reiterated the importance of low dose, high solubility and diffusivity, and suitable $\log D_{pH=7.4}$ for APIs considered for IO formulation development [1].

This OCCAT model clearly demonstrated the capability to prospectively simulate clinical pharmacokinetics for IO formulations that achieve significant transmucosal absorption. Compared with conventional oral delivery, a key advantage of IO delivery is to achieve fast onset *via* transmucosal absorption in the oral cavity and entrance into the systemic circulation through the jugular vein. High patient adherence is also seen as an advantage of IO dosage forms [25, 26]. Therefore, a modeling capability that can predict the rate and extent of plasma concentration is critical for IO formulation development. Pharmacodynamic studies demonstrated that sublingually administered zolpidem has a significant earlier sleep onset compared with oral zolpidem in both healthy and insomnia patients [19, 20]. This indicates that transmucosal absorption of zolpidem in the oral cavity translates into faster onset of action compared with a conventional oral tablet. With the default setting of diffusivity and f_{ut} , the OCCAT model successfully simulated the clinical pharmacokinetics of zolpidem sublingual tablets, especially for the Cp in the first 20 min. The observed $AUC_{0-20\text{ min}}$ is 2.27 ng·h/mL while the simulated $AUC_{0-20\text{ min}}$ is 2.92 ng·h/mL and the prediction deviation is $<30\%$. In comparison, the simple one-compartment oral cavity model using the calculated ASF (within the Opt logD Model SA/V 6.1) underestimated the early Cp. This was mainly due to lack of knowledge of ASF values for the oral cavity for a specific compound. In general, the ASF values in the simple oral cavity model can be only estimated by fitting the observed Cp-time curves. Therefore, the simple oral cavity model is not suitable for providing a prospective prediction for IO drug products.

A slight overprediction of the later phase of the Cp-time curve of the Intermezzo sublingual tablets was observed, which was likely caused by slight overestimation of first-pass metabolism. An approximate 30% first-pass metabolism of zolpidem was assumed in the current model based on its absolute oral bioavailability ($\sim 70\%$) reported in literature. However, the assumption of the extent of first-pass metabolism may slightly vary from different clinical studies (as the subjects in different studies were different). The absolute oral bioavailability for the clinical

study of Intermezzo® sublingual tablets was not reported. In the case of lack of experimental data, it is preferred to use literature reported data as the parameter values for the model as long as the simulated results broadly agree with the observed ones. Thus, further parameter optimization was not necessary in the current IO model for the Intermezzo sublingual tablets.

The decreased extent of API absorbed from the oral cavity simulated by the OCCAT model at around 5 min (Fig. 5b) could be explained by re-equilibrium of drug partitioning between saliva and oral tissues as a result of a decreasing concentration of drug in saliva as the saliva is progressively swallowed. This hypothesis is also consistent with “back-diffusion” observed in a few clinical studies, for example, with propranolol [6].

In clinical studies, bioavailability data generated from IO delivery usually consist of both IO and intestinal absorption. In order to calculate the absolute IO absorption in the oral cavity, a method to estimate intraoral absorption was proposed in this work. The fraction absorbed in the oral cavity ($F_{a,IO}$) was calculated by Eq. (8):

$$F_{PO+IO} = F_{a,IO} + (1 - F_{a,IO}) \times (F_{PO}) \quad (8)$$

where $F_{a,IO}$ is the fraction absorbed in oral cavity and F_{PO+IO} represents the total bioavailability, including both IO and intestinal absorption, and F_{PO} represents the bioavailability only from intestinal absorption. This equation assumes that there is no first-pass metabolism after IO absorption and that the swallowed drug portion undergoes complete intestinal absorption. Using this approach, we estimated the absolute IO absorption ($F_{a,IO}$) of zolpidem to be 13% based on the available F_{PO+IO} and F_{PO} values, which represented the “observed” $F_{a,IO}$ of zolpidem for Intermezzo® sublingual tablets. The model-simulated $F_{a,IO}$ by the OCCAT model was 18.9% (Table IV), which was in reasonable agreement with the “observed” $F_{a,IO}$ values calculated from clinical results using Eq. 8. Similarly, the “observed” $F_{a,IO}$ values were obtained for four other IO drug delivery products, including asenapine sublingual tablets, verapamil sublingual solution, propranolol sublingual tablets, and nicotine sublingual tablet (Table IV). Correspondingly, the $F_{a,IO}$ values for these drug products were simulated using the OCCAT models. The key IO absorption parameters, such as f_{ut} and diffusivity, were calculated using the generic equations described above (Eqs. 6 and 7) based on their Log P , pK_a , and solubility values measured in house or obtained from literature (Table S2). Overall, the $F_{a,IO}$ values simulated by the OCCAT model were comparable with the observed values estimated from the clinical results using Eq. 8 (Table IV), except for the nicotine sublingual tablet. This good agreement between projected IO absorption and observed in clinics demonstrated the validity of this OCCAT model applied for IO delivery in clinical studies. However, the OCCAT model only predicted $\sim 15\%$ of $F_{a,IO}$ for nicotine sublingual tablets, which was much lower than the “observed” value estimated using Eq. 8 ($\sim 53\%$). In the current model, the key parameters of f_{ut} and diffusivity were assumed to correlate to the lipophilicity of the compound. Because nicotine is a

highly water-soluble small molecule with low lipophilicity, the model predicted f_{ut} was highest, whereas predicted diffusivity was lowest for nicotine, compared with other simulated compounds. The case example of nicotine indicated that the correlation between $\log D_{pH=7.4}$ with f_{ut} and diffusivity may have a larger variation for very low molecular weight compounds (such as nicotine with a MW of 162), which exhibits much faster diffusion in oral mucosa than the prediction. It is not completely unexpected, as the diffusion rate is not only associated with $\log D_{pH=7.4}$ but also with molecular weight. In the generic equation presented in this model (Eq. 8), molecular weight is not included in the regression equation for simplification purposes. Further optimization of this generic equation could be explored by including more data for low molecular compounds when they become available.

CONCLUSION

Overall, the novel GastroPlus physiologically based IO absorption model is well designed with valid assumptions and satisfactory prediction capability. Theoretically, IO absorption is associated with tissue diffusivity and epithelium/saliva partitioning, as well as API lipophilicity and aqueous solubility. The OCCAT model well captured the observed clinical pharmacokinetics for the zolpidem tartrate sublingual tablet. Predicted C_{max} , T_{max} , and AUC were within $\pm 30\%$ compared with the observed values. We expect this new modeling capability will be helpful to guide the development of future intraoral formulations.

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REFERENCES

- Mathias NR, Hussain MA. Non-invasive systemic drug delivery: developability considerations for alternate routes of administration. *J Pharm Sci*. 2010;99(1):1–20.
- Patel VF, Liu F, Brown MB. Advances in oral transmucosal drug delivery. *J Control Release*. 2011;153(2):106–16.
- Hearnden V, Sankar V, Hull K, Juras DV, Greenberg M, Kerr AR, et al. New developments and opportunities in oral mucosal drug delivery for local and systemic disease. *Adv Drug Deliv Rev*. 2012;64(1):16–28.
- Sugano K. Introduction to computational oral absorption simulation. *Expert Opin Drug Metab Toxicol*. 2009;5(3):259–93.
- Kostewicz ES, Aarons L, Bergstrand M, Bolger MB, Galetin A, Hatley O, et al. PBPK models for the prediction of *in vivo* performance of oral dosage forms. *Eur J Pharm Sci*. 2013 Sep 21.
- Kates RE. Absorption kinetics of sublingually administered propranolol. *J Med*. 1977;8(6):393–402.
- Beckett ABR, Triggs EJ. Kinetics of buccal absorption of amphetamines. *J Pharm Pharmacol*. 1968;20(2):92–7.
- Wang Y, Wang Z, Zuo Z, Tomlinson B, Lee BT, Bolger MB, et al. Clinical pharmacokinetics of buffered propranolol sublingual tablet (Promptol)—application of a new “physiologically based” model to assess absorption and disposition. *AAPS J*. 2013;15(3):787–96.
- Shankaran H, Adeshina F, Teegarden JG. Physiologically-based pharmacokinetic model for Fentanyl in support of the development of provisional advisory levels. *Toxicol Appl Pharmacol*. 2013;273(3):464–76.
- Bartlett JA, van der Voort MK. Understanding the oral mucosal absorption and resulting clinical pharmacokinetics of asenapine. *AAPS PharmSciTech*. 2012;13(4):1110–5.
- Zhang H, Zhang J, Streisand JB. Oral mucosal drug delivery: clinical pharmacokinetics and therapeutic applications. *Clin Pharmacokinet*. 2002;41(9):661–80.
- Squier CA, Wertz PW. Permeability and the pathophysiology of oral mucosa. *Adv Drug Deliv Rev*. 1993;12:13–24.
- Goswami T, Kokate A, Jasti BR, Li X. *In silico* model of drug permeability across sublingual mucosa. *Arch Oral Biol*. 2012;58(5):545–51.
- Agoram B, Woltosz WS, Bolger MB. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. *Adv Drug Deliv Rev*. 2001;50 Suppl 1:S41–67.
- Lagerlof F, Dawes C. The volume of saliva in the mouth before and after swallowing. *J Dent Res*. 1984;63(5):618–21.
- Ramirez E, Laosa O, Guerra P, Duque B, Mosquera B, Borobia AM, et al. Acceptability and characteristics of 124 human bioequivalence studies with active substances classified according to the biopharmaceutic classification system. *Br J Clin Pharmacol*. 2010;70(5):694–702.
- Durand A, Thenot JP, Bianchetti G, Morselli PL. Comparative pharmacokinetic profile of two imidazopyridine drugs: zolpidem and alpidem. *Drug Metab Rev*. 1992;24(2):239–66.
- FDA. Intermezzo NDA files. 2011.
- Staner L, Eriksson M, Cornette F, Santoro F, Muscat N, Luthinger R, et al. Sublingual zolpidem is more effective than oral zolpidem in initiating early onset of sleep in the post-nap model of transient insomnia: a polysomnographic study. *Sleep Med*. 2009;10(6):616–20.
- Staner C, Joly F, Jacquot N, Vlasova ID, Nehlin M, Lundqvist T, et al. Sublingual zolpidem in early onset of sleep compared to oral zolpidem: polysomnographic study in patients with primary insomnia. *Curr Med Res Opin*. 2010;26(6):1423–31.
- Ho NFH. Biophysical kinetic modeling of buccal absorption. *Adv Drug Deliv Rev*. 1993;12(1–2):61–97.
- Rathbone MJ, Hadgraft J. Absorption of drugs from the human oral cavity. *Int J Pharm*. 1991;74:9–24.
- Lien EJCK, Tong RT, George L. Physicochemical properties, bioavailability of drugs: buccal and percutaneous absorptions. *Drug Intelligence*. 1971;5(2):38–41.
- Beckett AH, Moffat AC. Correlation of partition coefficients in n-heptane-aqueous systems with buccal absorption data for a series of amines and acids. *J Pharm Pharmacol*. 1969;21(Suppl):144S.
- Greenblatt DJ, Harmatz JS, Roth T, Singh NN, Moline ML, Harris SC, et al. Comparison of pharmacokinetic profiles of zolpidem buffered sublingual tablet and zolpidem oral immediate-release tablet: results from a single-center, single-dose, randomized, open-label crossover study in healthy adults. *Clin Ther*. 2013;35(5):604–11.
- Green R, Hicks RW. Orally disintegrating vardenafil tablets for the treatment of erectile dysfunction: efficacy, safety, and patient acceptability. *Patient Prefer Adherence*. 2011;5:181–5.
- Heckmann SM, Heckmann JG, Hilz MJ, Popp M, Marthol H, Neundorfer B, et al. Oral mucosal blood flow in patients with burning mouth syndrome. *Pain*. 2001;90:281–6.
- Atasever NE, Ercan MT, Naldoken S, Ulutuncel N. Effect of wearing complete dentures on human palatal mucosal blood flow measured by 133-Xe clearance. *Arch Oral Biol*. 1991;36(9):627–30.
- Collins LMC, Dawes C. The surface area of the adult human mouth and thickness of the salivary film covering the teeth and oral mucosa. *J Dent Res*. 1987;66(8):1300–2.
- Sudhakar Y, Kuotsu K, Bandyopadhyay AK. Buccal bioadhesive drug delivery—a promising option for orally less efficient drugs. *J Control Release*. 2006;114(1):15–40.
- Vorperian HK, Wang S, Chung MK, Schimek EM, Durtschi RB, Kent RD, et al. Anatomic development of the oral and

- pharyngeal portions of the vocal tract: an imaging study. *J Acoust Soc Am.* 2009;125(3):1666–78.
32. Feldchtein FI, Gelikonov GV, Gelikonov VM, Iksanov RR, Kuranov RV, Sergeev AM, et al. In vivo OCT imaging of hard and soft tissue of the oral cavity. *Opt Express.* 1998;3(6):239–50.
 33. Prestin S, Rothschild SI, Betz CS, Kraft M. Measurement of epithelial thickness within the oral cavity using optical coherence tomography. *Head Neck.* 2012;34(12):1777–81.
 34. Klein-Szanto AJP, Schroeder HE. Architecture and density of the connective tissue papillae of the human oral mucosa. *J Anat.* 1977;123(1):93–109.
 35. Muller HP, Schaller N, Eger T, Heinecke A. Thickness of masticatory mucosa. *J Clin Periodontol.* 2000;27:431–6.
 36. Valentine JA, Scott J, West CR, Hill CAS. A histological analysis of the early effects of alcohol and tobacco usage on human lingual epithelium. *J Oral Pathol.* 1985;14:654–65.
 37. Sasaki M. Histomorphometric analysis of age-related changes in epithelial thickness and Langerhans cell density of the human tongue. *Tohoku J Exp Med.* 1994;173:321–36.
 38. Aframian DJ, Davidowitz T, Benoliel R. The distribution of oral mucosal pH values in healthy saliva secretors. *Oral Dis.* 2006;12:420–3.
 39. FDA. Asenapine FDA NDA file. 2009.
 40. Berk SI, Beckman K, Hoon TJ, Hariman RJ, Hu D, Siegel FP, et al. Comparison of the pharmacokinetics and electrocardiographic effects of sublingual and intravenous verapamil. *Pharmacotherapy.* 1992;12(1):33–9.
 41. Hukkanen J, Jacob 3rd P, Benowitz NL. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev.* 2005;57(1):79–115.
 42. Molander L, Lunell E. Pharmacokinetic investigation of a nicotine sublingual tablet. *Eur J Clin Pharmacol.* 2001;56(11):813–9.