From in vitro dissolution testing to in vivo clinical pharmacokinetic prediction using PBPK models for oral cavity drug products

M1430-05-30

AUTHORS: Fiona Plait[1], Priyata Kalra[1], Maxime Le Merdy[1], Saima Subhami[1], Viera Lukacova[1], Pankaj Dwivedi[2], Khondoker Alam[3], Eleftheria Tsakalozou[3], Giovanni Pauletti[2], Haiying Zhou[1]

AFFILIATIONS: [1] Simulations Plus, Inc., Research Triangle Park, NC, USA; [2] University of Health Sciences and Pharmacy in St. Louis, St. Louis, MO; [3] U.S. Food and Drug Administration, 10903 New Hampshire Avenue, Silver Spring, USA

CONTACT INFORMATION: fiona.plait@simulations-plus.com

PURPOSE

This work develops a novel *in vitro* to *in vivo* extrapolation (IVIVE) method for the prediction of *in vivo* pharmacokinetic (PK) for oral cavity drug products (DP). This IVIVE uses *in vitro* dissolution measurements in artificial saliva; *in vitro* permeability measurements from EpiOral™ assays [1,2]; and physiologically based PK (PBPK) modelling to bridge the critical gap between laboratory testing and clinical performance for sublingual (SL) DPs.

OBJECTIVE

- To predict systemic PK profiles of sufentanil (SUF) and zolpidem (ZOL) after SL administration of Dsuvia® [Sufentanil sublingual tablet, Eq. 0.03 mg base] and Edluar® [Zolpidem sublingual tablet, Eq. 10 mg base].
- To estimate the intraoral fraction absorbed (F_{a_IO}) and the bioavailability (F%) of those 2 active pharmaceutical ingredients (APIs) following SL administration of Dsuvia® and Edluar®.

METHODS

Clinical Data

Collected clinical PK data for SUF and ZOL following intravenous (IV), oral (PO) and SL administration from literature [3, 4, 5, 6, 7].

Baseline PBPK Models

Developed in **GastroPlus® v9.9** (Simulation Plus Inc., Research Triangle Park, North Carolina, USA) and validated against the clinical data previously collected.

Oral Cavity Model

Enhanced with Oral Cavity Compartmental Absorption and Transit (OCCAT™) models to simulate SL administration of Dsuvia® [Sufentanil sublingual tablet, Eq. 0.03 mg base] (SUF) and Edluar® [Zolpidem sublingual tablet, Eq. 10 mg base] (ZOL).

Permeability Parameters

Diffusivity (D_m) and unbound fraction (f_{uM}) of selected model APIs were deconvoluted from EpiOral™ assay measurements in MembranePlus™ [2].

In Vitro Dissolution Parameters

Measurements in artificial saliva (pH 6.7, 60 mL, 37°C) of Dsuvia® and Edluar® (DPs) for 24 hours. The Z-factor method was used to capture DP-specific dissolution.

Clinical Design Parameters

Incorporated intraoral holding time and dosage form behavior.

Figure 1: Modeling strategy: OCCAT IVIVE workflow

RESULTS

Table 1 summarizes the key outcomes from the simulation of Dsuvia® and Edluar® DPs.

Integrating *in vitro* dissolution data measured in artificial saliva (Figure 2) into PBPK models enabled accurate IVIVE predictions for both DPs (Figure 3, Table 2). PBPK modelling also provided additional insights on differences in intraoral (IO) absorption (Figure 4) and bioavailability between Dsuvia® (SUF) and Edluar® (ZOL).

Table 1: Summary of SUF and ZOL SL simulations results

Aspect	SUF - Dsuvia®	ZOL - Edluar®
IVIVE Outcome	Acceptable prediction of PK metrics (Table 2, Figure 3)	Acceptable prediction of PK metrics (Table 2, Figure 3)
Intraoral Absorption (F_{a_IO})	~30% of total absorption (Figure 4)	Negligible (Figure 4)
Effect on Bioavailability (F%)	**Enhanced** (oral F% ~9%, increased to ~35% with SL)	**Unchanged** (oral F% ~70%)
Sensitivity Analysis	Mucosa thickness, holding time critical (Figure 5)	Minimal sensitivity (due to high baseline (i.e., oral) F%)
Route Comparaison	Greater systemic exposure for SL (oral cavity) route vs swallowed (oral) route due to transmucosal absorption	SL Edluar® shows same systemic PK to oral route; differences vs SL tablet Intermezzo® observed from formulation and IO hold time

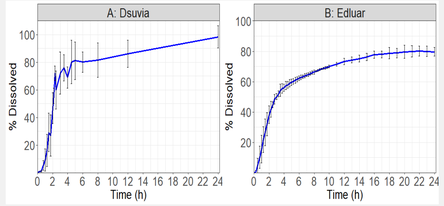

Figure 2: Mean *in vitro* dissolution measurements for Dsuvia (A) and Edluar (B) DPs over a course of 24 hours (n = 4; error bars = standard deviation).

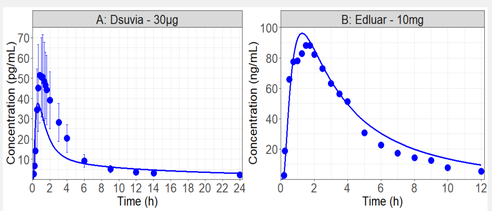

Figure 3: Observed (circles) and simulated (line) SUF (A) and ZOL (B) plasma concentration-time courses in healthy subjects following a single sublingual administrations of Dsuvia (A) and Edluar (B) DPs. [4, 7] (n = 35; Error bars = Standard deviation).

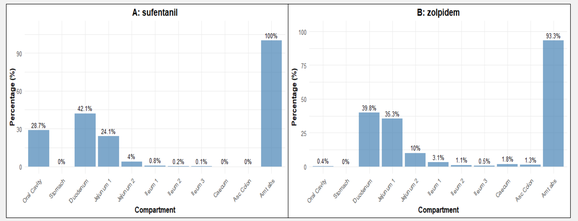

Figure 4: Predicted compartmental absorption in the oral cavity and the different gastrointestinal segments following SL administration (30 µg dose for SUF (A); 10 mg dose for ZOL (B)) in healthy subjects.

Table 2: Predicted/Observed ratios of SUF and ZOL PK parameters for SL simulations captured in Figure 3. [4, 7]

Drug Product	Cmax Ratio	AUCt Ratio	AUCinf Ratio
SUF (30 µg)	0.73	0.81	0.89
ZOL (10 mg)	1.09	1.13	1.18

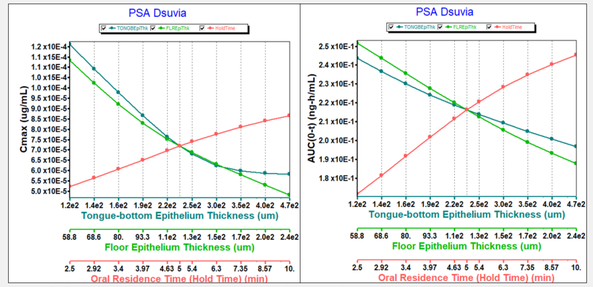

Figure 5: PSA on mucosal thickness and oral hold time following SL administration of Dsuvia® and their impact on systemic Cmax and AUCt parameters

CONCLUSION

- The integration of *in vitro* dissolution measurements with PBPK models enabled reasonable prediction of PK profiles after SL administration, establishing an IVIVE methodology for oral cavity DPs.
- **Clinical Significance:** This approach will help formulators explore excipient impact on *in vitro* dissolution and critical biopharmaceutical parameters potentially affecting *in vivo* PK performance to accelerate the development of both innovator and generic oral cavity DPs.
- **Future Applications:** Extension to other sublingual/buccal formulations and integration with regulatory science initiatives for enhanced drug development efficiency.

REFERENCES

1. Kalra, P., Le Merdy, M., Lukacova, V., Dwivedi, P., Alam, K., Tsakalozou, E., Pauletti, G.M., and Zhou, H. PBPK Oral Absorption Model to Predict Mucosal Permeability of Oral Cavity Drug Products. AAPS Poster. 2023
2. Kalra P, Lukacova V, Dwivedi P, Alam K, Tsakalozou E, Zhou H. Mechanistic Model of in vitro Intraoral Absorption of Buprenorphine for the Buccal and Gingival Mucosa. AAPS Poster. 2024
3. Willsie SK, Evashenk MA, Hamel LG, Hwang SS, Chiang YK, Palmer PP. 2015.
4. Fisher DM, Chang P, Wada DR, Dahan A, Palmer PP. 2018.
5. Andreas CJ, Pepin X, Markopoulos C, Vertzoni M, Reppas C, Dressman JB. 2017.
6. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022328Orig1s000MedR.pdf
7. Staner, P. Danjou, R. Luthringer. Expert Rev. Neurother. 12(2), 141–153 (2012)
8. Xia B, Yang Z, Zhou H, et al. AAPS J. 2015.

FUNDING

The project was funded by a contract from the U.S. Food and Drug Administration (Contract # 75F40120C00150).