APPLICATIONS OF PHYSIOLOGICALLY-BASED PHARMACOKINETIC MODEL TO SMOKEABLE / INHALABLE TOBACCO PRODUCTS

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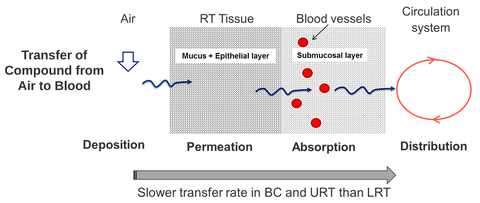
ABSTRACT

Mathematical modeling is a non-invasive approach for predicting the time course concentration of compounds within human tissues. We have developed and validated a physiologically based pharmacokinetic (PBPK) model with physiological and biological components to describe nicotine pharmacokinetics using tobacco products [1]. The previous model [2-3] has been enhanced to divide the uptake route in the model into three regions; Buccal Cavity (BC), Upper Respiratory Tract (conducting airways, URT) and Lower Respiratory Tract (transitional airways and alveolar region, LRT). Our PBPK model was validated for various tobacco products, including cigarette, smokeless tobacco, E-vapor, and nicotine inhaler. Based on regional deposition and permeation rate of nicotine within each region, the PBPK model predicts the product specific nicotine PK profile. In this study, a sensitivity analysis was carried out in an attempt to examine the effect of nicotine level in smokeable/inhalable products, aerosol mass and regional deposition of nicotine within different regions of human respiratory tract on nicotine PK profile. The results demonstrated that higher nicotine deposition in BC, and URT leads to a lower nicotine C_{max} (maximum plasma concentration), due to the slower uptake in these regions compared to LRT. Additionally, higher aerosol mass results in higher nicotine delivery, and hence, a higher level of nicotine concentration in plasma over time. Increasing the nicotine delivery increased C_{max}, proportionately, however, did not significantly affect t_{max} (time to reach C_{max}) ,as t_{max} mainly depends on type of product along with the use conditions. In addition to the aforementioned validation cases, capability of the model for predicting PK profile of Tobacco Heating System (THS) is also tested, and the results demonstrate good agreement between PK data from the experiment and prediction by the model. We report here a robust PBPK model that can be used to predict nicotine pharmacokinetics from a wide variety of tobacco products.

OBJECTIVES

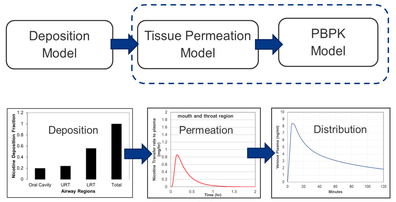
Expand the understanding of internal exposure to nicotine through a parametric study, examining the effect of various parameters such as nicotine concentration, smoking topography and regional absorption of nicotine within different regions of human respiratory tract on nicotine pharmacokinetic profile.

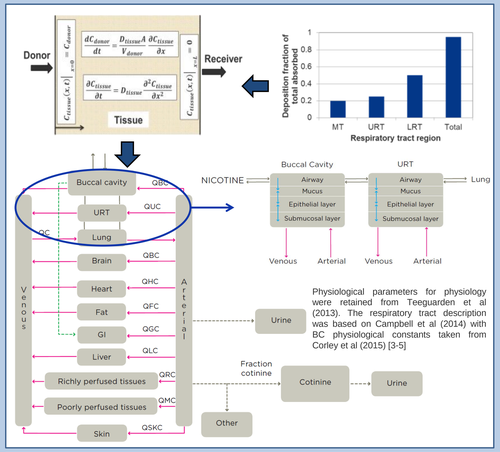
KEY FEATURES OF MODEL



- Within each region, the model includes product specific descriptions of the flux of nicotine into plasma, as well as the flux of nicotine from the BC and URT to the Gastrointestinal (GI) tract. These descriptions are based on regional absorption and permeation models of nicotine into plasma.
- Mucous diffusion in URT is based on water diffusivity.
- Epithelial layer diffusion in URT estimated to provide the best fit to the permeation model expected flux of nicotine and the plasma time-course across all product types.
- Diffusion coefficients were scaled to tissue width and surface area.
- Nicotine reaching the lower respiratory tract is assumed to be transferred to the plasma immediately.
- The model results are compared with the available data only.

METHOD





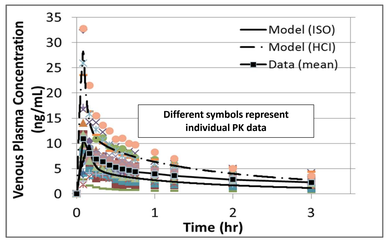
Physiological parameters for physiology were retained from Teeguarden et al (2013). The respiratory tract description was based on Campbell et al (2014) with BC physiological constants taken from Corley et al (2015) [3-5]

VALIDATION

The model was validated for various tobacco products [6], including cigarette, smokeless tobacco, E-vapor, as well as Nicotrol® Inhaler.

EXAMPLE 1:

Cigarette: Model, Mean and Individual Data

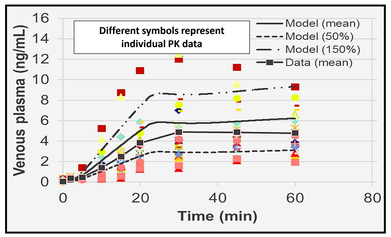


***Study**: Subjects took up to 10 inhalations of the cigarette at 30-sec intervals, with the inhalation duration as desired by the subject

*Altria Client Services LLC Study No. ALCS-RS-15-05-MST

EXAMPLE 2:

Nicotrol® Inhaler : Model, Mean and Individual Data



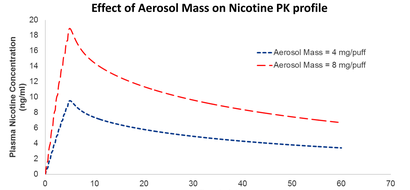
***Study**: Each product administration consisted of using one unit of the product, with puffs taken approximately every 15 seconds for 20 minutes

*Altria Client Services Inc., Study No. CEL-LIQ-01-12, Celerion Project AA98611

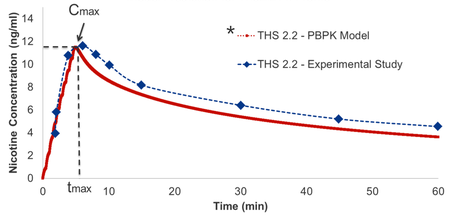
RESULTS

Cases	Aerosol Mass (mg/puff)	Nicotine %	Nicotine (mg/puff)	BUCF	URTF	LRTF
1a (Device 1)	4	3	0.12	0.125	0.0625	0.7625
1b (Device 2)	8	3	0.24	0.125	0.0625	0.7625

Effect of Aerosol Mass on Nicotine PK profile



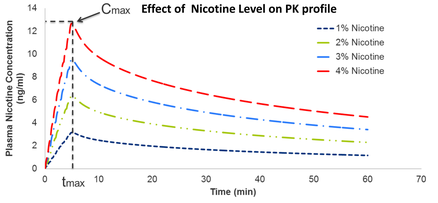
Model Prediction for THS2.2 PK Profile



* Nicotine Pharmacokinetic Profiles of the Tobacco Heating System 2.2, Cigarettes and Nicotine Gum in Japanese Smokers, Patrick Brossard et al. PMI R&D [7]

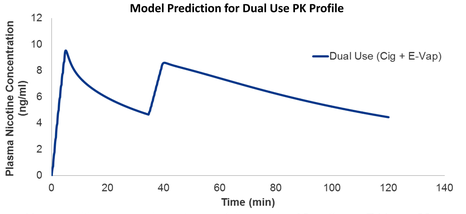
Cases	Aerosol Mass (mg/puff)	Nicotine %	Nicotine (mg/puff)	BUCF	URTF	LRTF
2a	4	1	0.04	0.125	0.0625	0.7625
2b	4	2	0.08	0.125	0.0625	0.7625
3b	4	3	0.12	0.125	0.0625	0.7625
4b	4	4	0.16	0.125	0.0625	0.7625

Effect of Nicotine Level on PK profile



Case	Aerosol Mass (mg/puff)	Nicotine %	Nicotine (mg/puff)	BUCF	URTF	LRTF
Dual Use	4	3%	0.12	0.5	0.25	0.2

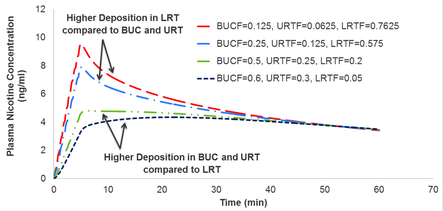
Model Prediction for Dual Use PK Profile



Use conditions: one cigarette use followed by 10 puffs on E-Vapor 30 min later

Cases	Aerosol Mass (mg/puff)	Nicotine %	Nicotine (mg/puff)	BUCF	URTF	LRTF
3a	4	3	0.12	0.125	0.0625	0.7625
3b	4	3	0.12	0.25	0.125	0.575
3c	4	3	0.12	0.5	0.25	0.2
3d	4	3	0.12	0.6	0.3	0.05

Effect of Regional Deposition of Nicotine in Respiratory Tract on PK profile



SUMMARY

- We report here a robust PBPK model that can predict the experimental PK profile for a number of tobacco products. Comparisons with experimental data for other products and formulations are further due.
- We observed that higher nicotine deposition in BC, and URT leads to a lower nicotine C_{max} (maximum plasma concentration), due to the slower uptake in these regions compared to LRT.
- Based on the range of tested conditions, we observed that a higher aerosol mass results in higher nicotine delivery, and a higher level of nicotine concentration in plasma over time.
- We observed that increasing the nicotine delivery increased C_{max}, proportionately, however, did not significantly affect t_{max} (time to reach C_{max}) ,as t_{max} mainly depends on type of product along with the use conditions.
- The model is capable of predicting the dual use (Cig+E-Vap) PK profile. However, due to the lack of available experimental data, comparison of the results with the individual PK data could not be conducted.

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