Estimation of Nicotine Uptake from Oral Nicotine-Containing Pouch Products in Human Buccal Tissue using Physiologically-Based Pharmacokinetic (PBPK) Modeling

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INTRODUCTION

Oral tobacco-derived nicotine (OTDN)[1] products like nicotine pouches are tobacco leaf-free and contain pharmaceutical grade tobacco-derived nicotine, flavors, and excipients. Because they are smoke-free and do not contain tobacco leaf, most of the harmful and potentially harmful constituents (HPHCs) are either absent or present at substantially lower levels.[2]

Therefore, completely switching to these products presents a harm reduction opportunity for ~30 million adults in the U.S. that smoke cigarettes[3]

- Nicotine pouches are growing in popularity among users of moist smokeless tobacco products (MST) due to familiarity of use behavior. While MST use is not as prevalent as cigarette smoking, approximately 5.7 million adults in the United States (2.3%) reported current use of MST[3]
- Since MST products contain several HPHCs, some of them being potent carcinogens, switching from MST to nicotine pouches may also present a harm reduction opportunity to users of MST
- Pharmacokinetics (PK) of nicotine in humans—notably outcomes such as the maximum venous plasma concentration, C_{max} [ng/mL]—inform abuse liability assessments of nicotine-containing products such as OTDN pouch products
- Nicotine absorbed in the gastrointestinal (GI) tract undergoes first pass metabolism while it can directly be absorbed in the systemic circulation if absorbed through the buccal cavity (BC) tissue[4]
- Therefore, nicotine release and uptake in BC tissue and transfer to the GI tract are the key determinants of the PK outcomes besides physiological parameters
- Nicotine release can be simply measured by tracking the nicotine content of nicotine pouches before and after use. However, little quantitative information on nicotine uptake in BC tissue and transfer to the GI tract is available as they are difficult to measure in practice

AIMS

- The aim of this study was to quantify the nicotine buccal cavity (BC) tissue uptake and transfer to the GI tract in individual subjects using a variety of OTDN pouch products by leveraging a previously published human Physiologically-Based Pharmacokinetic (PBPK) model[4,5]

METHODS

OTDN Pouches:

- Nicotine release and PK profiles for individuals in two clinical studies using different brands, nicotine strength, and flavors were considered. Table 1 and Table 2 list the OTDN pouches and corresponding actual and nominal nicotine contents prior to use for two studies. In study 1, 5 different on! PLUS™ nicotine pouches were used for 45 minutes[6] and coded A-E in Table 1. In study 2, 5 commercially available OTDN pouches were used for 30 minutes[7] and coded F-J in Table 2

PBPK Model:

- The BC tissue uptake fraction, denoted by $0 \leq f_{tiss} \leq 1$, is defined as *the fraction of experimentally measured nicotine extraction* from the OTDN pouches denoted by $0 \leq R \leq 1$ that is taken up by the BC tissue and eventually absorbed by the BC circulation over the duration of use. f_{tiss} is expected to vary with time, given that diffusion through tissue is a transient process. We assumed f_{tiss} varies linearly during the use period. Reverse PBPK modeling is used to regress individual subjects' PK profiles against the individual intercept and slope of the f_{tiss} linear function over the use duration. Root-mean-square-error (RMSE) was selected as the objective function. Cumulative f_{tiss} averaged over the use duration is calculated for every individual subject. The subject's extent of nicotine extraction and body weight (denoted by BW [kg]) are known quantities and are taken from published clinical studies.[6,7] Pre-use (Actual) nicotine content of nicotine pouches is denoted by A0 [mg] and listed in Tables 1 & 2. We follow our previous modeling approach,[4,5] accounting for the release of nicotine from pouches, subsequent permeation through the BC tissue, absorption by the BC blood circulation, saliva secretion, swallowing and transfer to the GI tract as a function of time

Limitations:

- The PBPK model utilized here[4,5] is well validated against mean PK data for a range of nicotine products, but it does not explicitly account for inter-individual variability in clearance parameters, nor does it factor in covariates other than BW. However, we have previously demonstrated that variability in use, which results in a distribution of nicotine release and BC tissue uptake among users, has a more pronounced effect on PK outcomes than variability in clearance rate constants[5]
- Regression of PK data for individuals with high C_{max} values and low nicotine extraction lead to RMSE, exceeding 30% of C_{max} and/or BC tissue uptake fractions outside the interval [0, 1]. These data were dropped from our analysis

RESULTS

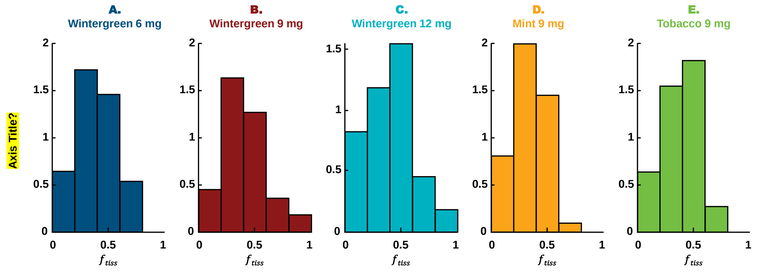
- Distribution of BC tissue uptake among individuals for the OTDN pouches are plotted in the histograms depicted in Figure 1 (products A-E) for Study 1 and in Figure 2 (products F-J) for Study 2. The corresponding mean and standard deviations are listed in Tables 1 and 2. Mean BC tissue uptakes range from 33% to 57% and indicate only a partial absorption of released nicotine from OTDN pouches by the BC tissue, with the balance transferred to the GI tract. on! PLUS™ products share a similar formulation and pouch properties, but for the nicotine content and flavor. The strength and flavor does not appreciably impact the BC tissue uptake fraction nor the release profile for the on! PLUS™ products in Study 1. However, both tissue uptake and nicotine release are impacted in Study 2 where different pouch brands differ in formulation and pouch properties. f_{tiss} is the highest and lowest for the products with the highest and lowest pH in Study 2 – J and I, respectively. Pouch pH has been known to affect the PK profile of nicotine products, with higher pH linked to higher uptake and C_{max}[8]
- Extent of nicotine extraction, R from OTDN pouches is a poor predictor of C_{max} even when scaled by the pre-use nicotine content, A0 and individuals' BW for all the products we considered, see Figure 3A and 4A. However, the total uptake fraction of pre-use nicotine, $R \times f^{tiss}$ shows a strong correlation with the scaled C_{max} values with linear fit correlation coefficient R2 of approximately 0.9 for Study 1 and 0.75-0.93 for Study 2, as shown in Figures 3B and 4B. The y-intercepts of the linear regression lines in Figure 3B and 4B reflect the contribution of nicotine absorption in the GI tract while the variability of regressions likely arises from inter-individual variability in the clearance parameters. The variability is more pronounced in Study 2 where subjects used different brands with different formulations
- Interestingly, a generally negative correlation is observed between nicotine release, R and BC tissue uptake, f_{tiss} in Figure 5. Linear regression analysis revealed negative slopes for 7 out of 10 products, while the slopes for products D, G, H were not statistically different from 0. Although this trend is not conclusive, it suggests that subjects with higher nicotine extraction tend to transfer more of the released nicotine to the GI tract. Since nicotine permeation through the BC tissue is a slower process than swallowing. If a large amount of nicotine is released during use, there may be insufficient time for BC absorption, and the unabsorbed nicotine in saliva is available to be swallowed and transferred to the GI tract

Study 1: Products A-E

Table 1. on! PLUS™ Nicotine Pouches in Study 1 – 45 min use

Flavor	Code	Labelled (Actual, A0) Nicotine	*R*, Measured Mean Nicotine %Release (SD)	f_{tiss} ,Calculated Mean %Buccal Uptake (SD)	pH[9]
Wintergreen	A	6 (5.73) mg	68% (18)	39% (17)	8.4-8.6
Wintergreen	B	9 (8.63) mg	65% (17)	40% (18)	8.4-8.6
Wintergreen	C	12 (11.53) mg	68% (18)	39% (22)	8.4-8.6
Mint	D	9 (8.55) mg	73% (15)	36% (16)	8.4-8.6
Tobacco	E	9 (8.69) mg	67% (16)	38% (18)	8.4-8.6

Figure 1. Normalized Distribution of BC Tissue Uptake Fraction (f_{tiss}) for Individuals Using Different on! PLUS™ Flavors (Codes A-E, Table 1)



Study 2: Products F-J

Table 2. Commercial Nicotine Pouches in Study 2 – 30 min use

Brand	Code	Labelled (Actual, A0) Nicotine	*R*, Measured Mean Nicotine %Release (SD)	f_{tiss} ,Calculated Mean %Buccal Uptake (SD)	pH
on!® Mint	F	8 (7.81) mg	63% (20)	38% (19)	8.1
Lyft™ Mint	G	Medium (4.26) mg	48% (15)	33% (16)	7.8
Zyn® Cool Mint	H	6 (5.69) mg	60% (22)	40% (16)	7.9
Velo® Mint	I	2 (1.76) mg	45% (35)	33% (23)	7.3
Dryft® Spearmint	J	7 (5.58) mg	47% (20)	57% (28)	8.3

Figure 2. Normalized Distribution of BC Tissue Uptake Fraction (f_{tiss}) for Individuals Using Different Brands (Codes F-J, Table 2)

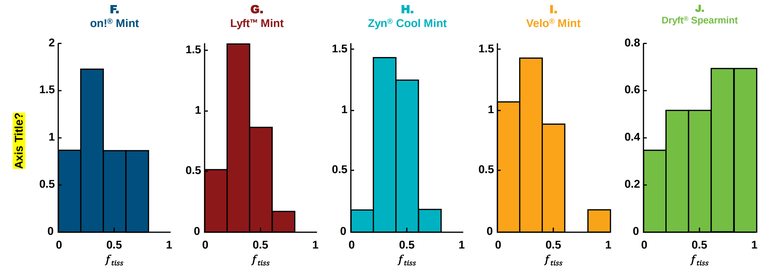


Figure 3. Normalized Individual C_{max} versus (A) Extent of Release (R); and (B) Extent of Release Times Tissue Uptake (R x f_{tiss})

Symbols and lines represent subject's data and the best-fit linear regression for each flavor, respectively.

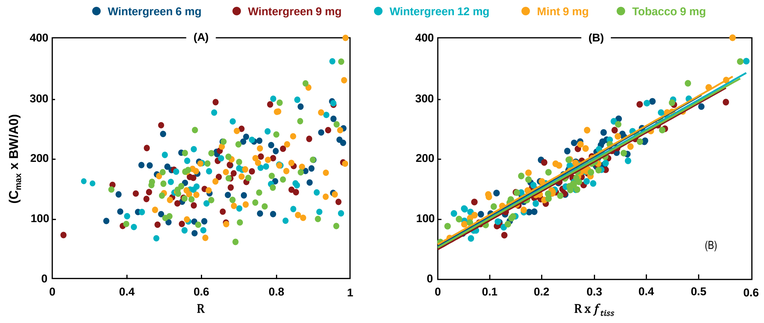


Figure 4. Normalized Individual C_{max} versus (A) Extent of Release (R); and (B) Extent of Release Times Tissue Uptake (R x f_{tiss})

Symbols and lines represent subject's data and the best-fit linear regression for each flavor, respectively.

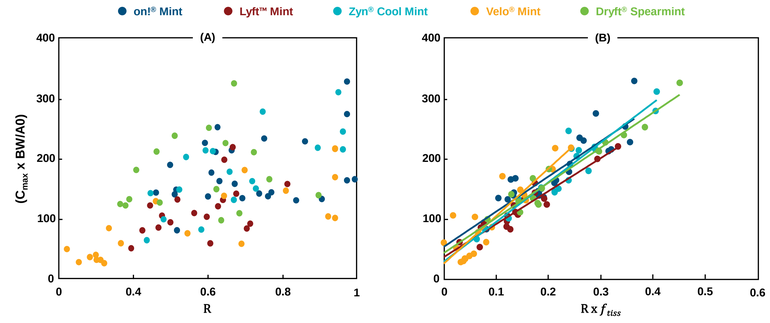
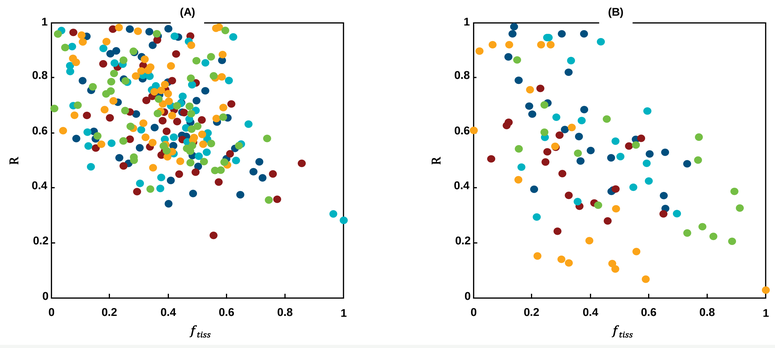


Figure 5. Extent of Release (R) versus BC Tissue Uptake (f_{tiss})



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CONCLUSIONS

- Fractional nicotine release, R, is a poor predictor of a key pharmacokinetic outcome, C_{max}, even when scaled by nicotine strength and body weight
- Only a portion, f_{tiss} of fractional nicotine release, R from OTDN pouches is taken up by the systemic circulation in the BC tissue with the balance transferred to the GI tract upon swallowing
- f_{tiss} ranges between ~ 30%-60% depending on product formulation, pH and use duration and exhibits significant inter-individual variability
- Overall fractional uptake of nicotine by the BC tissue – $R \times f_{tiss}$ – is a strong predictor of C_{max} scaled by actual nicotine content and body weight
- A higher nicotine release may be accompanied by increased transfer to the GI tract due to elevated swallowing

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