

Development of a Model to Predict Nicotine Pharmacokinetics from Oral Nicotine Pouches

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INTRODUCTION

Rising awareness of smoking-related health risks has driven a shift toward non-combustible nicotine products, including oral nicotine pouches (ONPs), which deliver nicotine via the buccal mucosa while bypassing first-pass hepatic metabolism. In the U.S., ONPs require FDA authorization through the Premarket Tobacco Product Application process, demanding extensive supporting data.

While traditional pharmacokinetic (PK) studies rely on costly clinical trials, predictive models incorporating physiological understanding and *in vitro* data could streamline development and regulatory review. Existing FDA-recognized dissolution methodologies support product comparison and equivalence assessments, however their potential for *in vitro-in vivo* correlation remains underexplored.

AIM

To develop a simple PK model specifically designed to predict the buccal absorption of nicotine from ONPs based on a simple mathematical convolution approach using only experimental *in vitro* data (nicotine dissolution and dynamic pH profiles), average participant weight, and well-established nicotine PK parameters (apparent volume of distribution, and plasma half-life) as input.

METHODS

Clinical Study

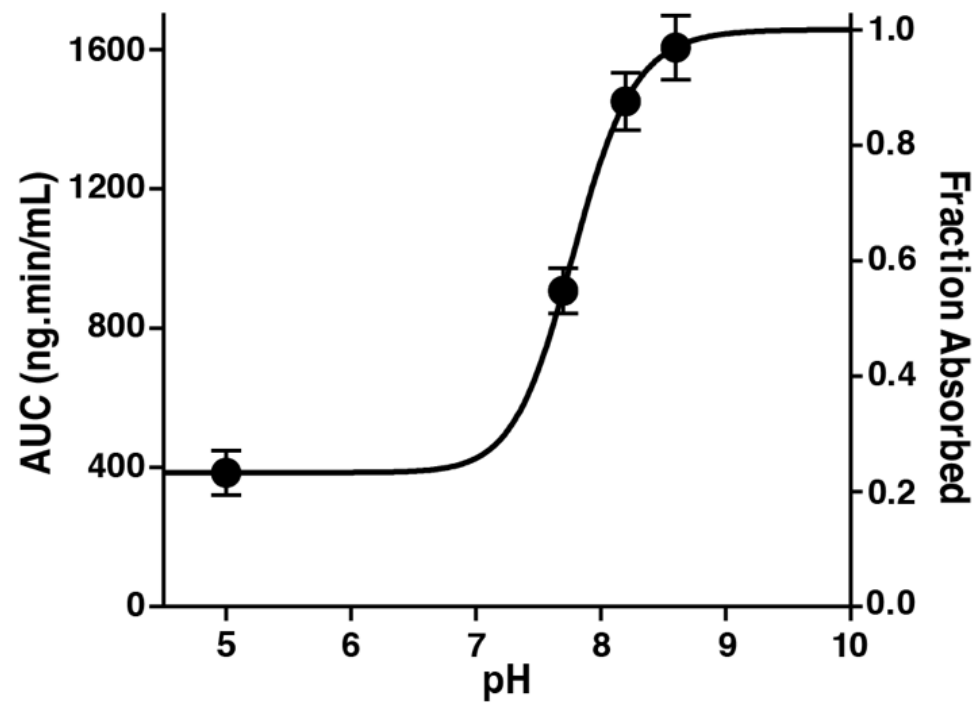
An Advarra IRB-approved, randomized 7-way crossover PK study enrolled 34 healthy adult combustible cigarette smokers (21–45 years) to compare nicotine absorption from three pouches (ZYN[®] Cool Mint 6 mg, DRYFT[™] Spearmint 7 mg, VELO[®] Mint 4 mg), conducted per FDA regulations and ICH-GCP guidelines. Following acclimation and daily *ad libitum* use sessions, participants used each product under controlled conditions (one pouch for 30 min) after overnight abstinence. Blood samples were collected at baseline and multiple timepoints through the total length of time 120 min post-placement, with nicotine concentrations measured under GLP conditions by a third-party laboratory.

In vitro Nicotine Dissolution

Dissolution testing, adapted from a previously published method [1], used a µDISS Profiler mini bath with pouches loaded into custom sinkers, which were submerged in 10 mL of pH-adjusted Orthana artificial saliva (37 °C, stirred at 150 rpm). Six units per product were tested across all three pouches, with pH measurements and samples collected at 5, 10, 15, 30 min and replaced with fresh medium. Samples were diluted, centrifuged, and analyzed by HPLC-UV. The plasma concentration-time profiles were estimated by convolution of the nicotine dissolution and pH profiles based on literature values for nicotine volume of distribution, V_d , and plasma half-life, $T_{1/2}$, of 2.0 ± 0.3 L/kg and 2.0 h, respectively.

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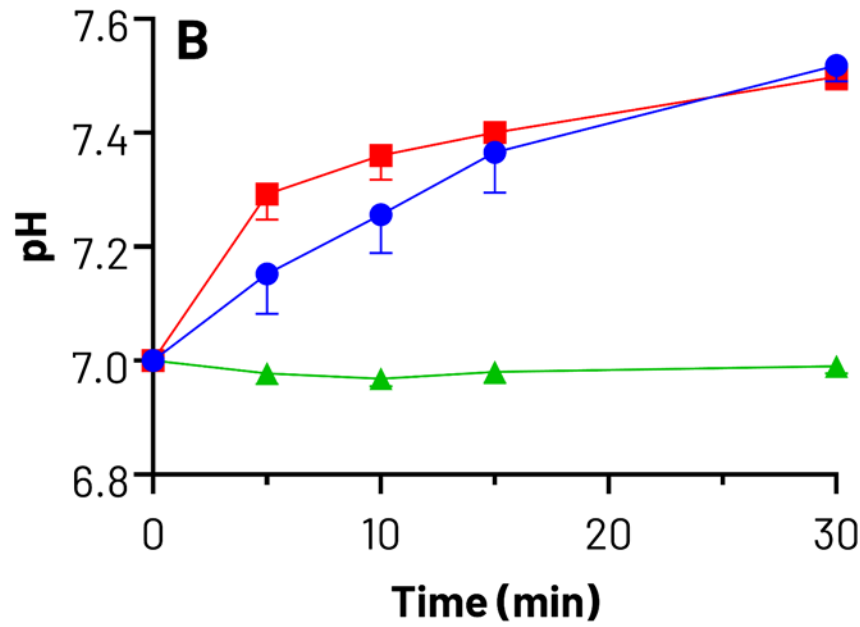
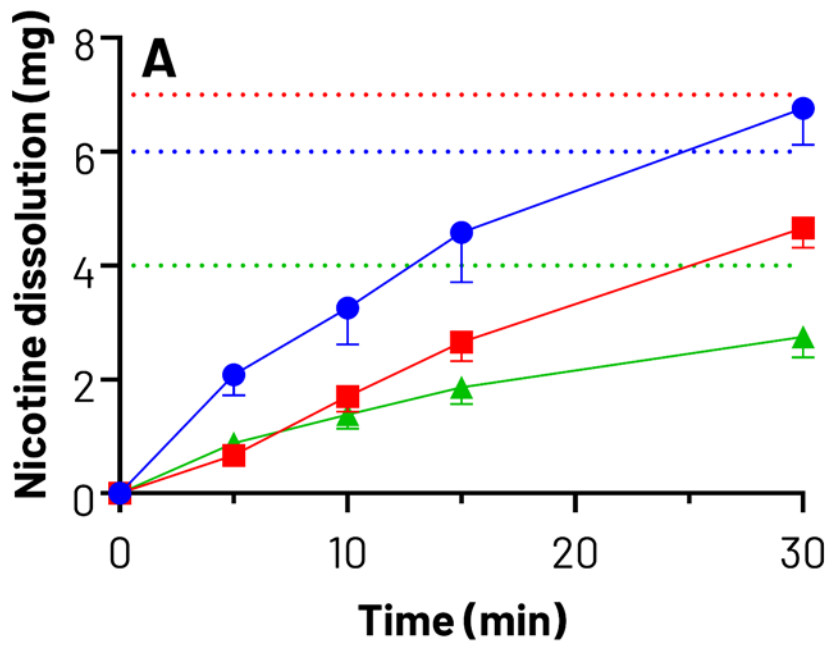
PK PREDICTION MODEL



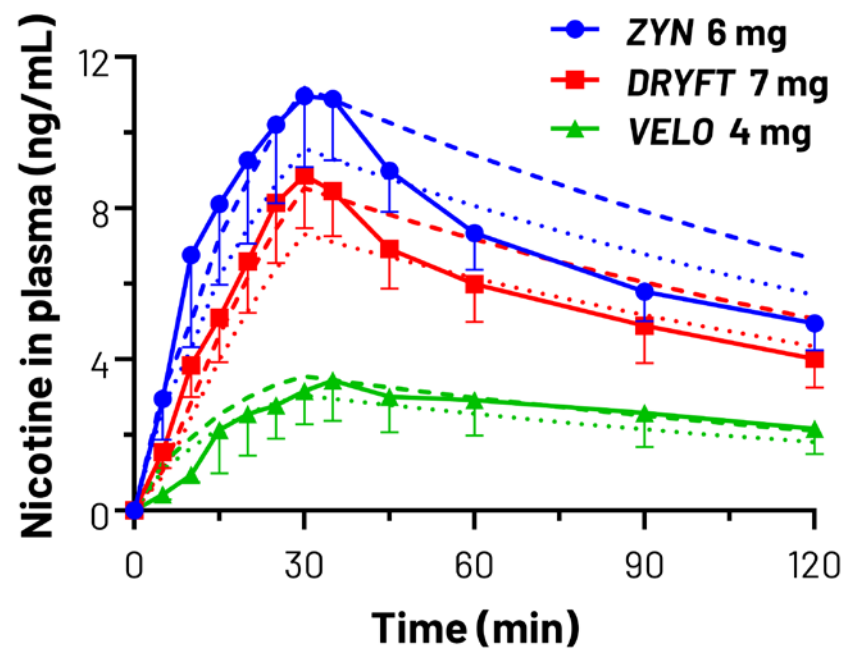
Left: Area under the curve (AUC) of nicotine plasma concentrations from 0-240 min following 30 min exposure to a pH-manipulated oral tobacco-derived nicotine product. Data represent mean $\pm$ SE (n = 40) based on data reported in [2]. **Right:** Equation for calculating plasma concentration-time profile, $C(t)$, based on *in vitro* dissolution ($I(t)$) and the fraction absorbed, F_a , which is further calculated based on the dynamic *in vitro* pH profiles.

$$C(t) = \int_0^t \frac{I(\tau) \cdot F_a \cdot 0.5^{\frac{t-\tau}{T_{1/2}}}}{V_d} d\tau$$
$$F_a = 0.23 + \frac{0.77}{1 + e^{-4.1(pH-7.8)}}$$

RESULTS



Nicotine *in vitro* dissolution (A) and dynamic pH profiles (B) in artificial saliva at 37 °C of three oral nicotine pouches (ONPs). Dotted lines indicate 100% of product label claim. Data represent mean - SD (n = 6).



Left: Predicted nicotine pharmacokinetic (PK) profiles (dashed and dotted lines) and clinical PK profiles (symbols with solid lines) of the three ONPs. Predicted profiles are based on an apparent volume of distribution of 2.0 - 0.3 L/kg corresponding to mean - SE. **Right:** Clinical and predicted PK parameters presented as mean (95% CI).

	Clinical		Prediction	
	AUC _{0-120min} (ng·min/mL)	C _{max} (ng/mL)	AUC _{0-120min} (ng·min/mL)	C _{max} (ng/mL)
ZYN [®] 6 mg	849 (686 - 1013)	12.4 (10.4 - 14.4)	985 (926 - 1043)	11.2 (9.8 - 12.5)
DRYFT [™] 7 mg	663 (492 - 833)	9.7 (8.4 - 11.0)	732 (687 - 777)	8.5 (7.5 - 9.6)
VELO [®] 4 mg	300 (147 - 451)	3.9 (2.7 - 5.1)	319 (300 - 337)	3.6 (3.1 - 4.0)

CONCLUSIONS

The PK model developed in this study marks a significant step forward in understanding and predicting buccal nicotine absorption from ONPs. By integrating experimental *in vitro* data with established PK parameters in a clinical study, the model provides a reliable framework for evaluating nicotine dissolution and absorption dynamics across different ONPs. Notably, the study highlights the influence of product-specific factors, such as nicotine dose, nicotine dissolution, and product pH that could impact salivary pH and nicotine uptake.

The ability of the model to accurately predict PK outcomes achieved in clinical settings, including AUC, C_{max} , and T_{max} , underscores its utility as a cost-effective alternative to traditional clinical studies. Beyond its immediate application in product development, this approach also has the potential to streamline regulatory approval processes, reduce reliance on human studies, and enhance the scientific foundation for evaluating ONPs and other oral nicotine delivery systems.

REFERENCES

- [1] Knopp, M. M. et al. Introducing a Novel Biorelevant In Vitro Dissolution Method for the Assessment of Nicotine Release from Oral Tobacco-Derived Nicotine (OTDN) and Snus Products. Separations 9, 52 (2022).
- [2] Wilhelm, J. et al. The pH of Smokeless Tobacco Determines Nicotine Buccal Absorption: Results of a Randomized Crossover Trial. Clin. Pharmacol. Ther. 111, 1066-1074 (2022).



This scientific research is presented by Altria Client Services LLC (ALCS). ALCS affiliate companies are tobacco product manufacturers.