Tobacco-Free Nicotine Pouches: Nicotine Release Profile can be Used to Estimate User Exposure. A Comparative Analysis of *In Vitro* Dissolution and *In Vivo* Pharmacokinetics

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INTRODUCTION

Over the past decade, alternative nicotine delivery systems, such as Electronic Nicotine Delivery Systems (ENDS), heated tobacco products (HTPs), and more recently, tobacco-free nicotine pouches (TFNPs), have emerged as potentially reduced harm alternatives to cigarettes [1, 2]. TFNPs are oral nicotine pouches which do not contain any tobacco leaf or burn tobacco. As such, research demonstrates that they contain significantly fewer and substantially lower levels of harmful chemicals compared to cigarettes [3,4]. *In vitro* toxicological assessments support this, TFNP extracts show reduced biological activity relative to cigarettes and snus, highlighting their potential role in tobacco harm reduction (THR) [5,6]. To support their use as smoking alternatives, TFNPs must not only reduce toxicant exposure but also effectively deliver nicotine and offer a satisfying user experience to adult smokers, thereby increasing the likelihood of switching away from cigarettes. This requires robust evaluation of nicotine pharmacokinetics (PK). While PK studies are essential for evaluating nicotine absorption and exposure, comprehensive clinical testing is resource-intensive, in terms of both time and cost. Moreover, such studies typically require invasive procedures (e.g., repeated blood sampling), which carry associated risks and burden for participants. Therefore, given the growing diversity of nicotine products, physiologically based PK (PBPK) modelling offers a mechanistic, cost-effective alternative and risk-reduced alternative as it does not require invasive technique. PBPK models integrate *in vitro* data and human physiological parameters to simulate plasma concentration profiles. This study aimed to develop a simplified PK model, informed by *in vitro* data, to predict nicotine exposure from TFNP use in humans.

DATA and METHODS

- A simplified, population-level PK model was developed to predict systemic nicotine exposure from TFNPs. The model assumes correct product use (sublabial placement) and treats nicotine absorption as a first-order transfer to the bloodstream. While a dual-pathway (buccal + gastrointestinal) was considered, the final model focused solely on buccal absorption, due to the buccal route of exposure [7](**Figure 1**).

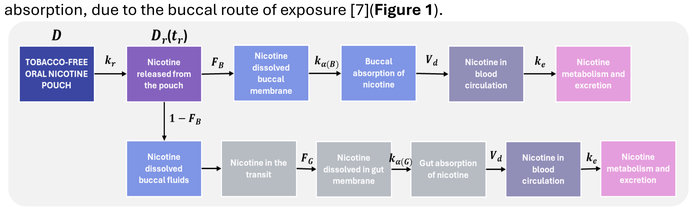

Figure 1: Schematic representation of the pharmacokinetics of sublabial administration of nicotine. The product is placed between the lip and gingiva, allowing for mucosal absorption and potential secondary gastrointestinal uptake.

- The total plasma nicotine concentration following use of a TFNP could be modelled by the following equation:

$$C_{tot}(t) = F_B \sum_{t_r=0}^{max\ use} \frac{k_{a(B)}}{V_d \times (k_{a(B)} - k_e)} D_r(t_r)\left(e^{-k_e(t-t_r)} - e^{-k_{a(B)}(t-t_r)}\right) + (1 - F_B) \sum_{t_r=0}^{max\ use} \frac{F_G \cdot k_{a(G)}}{V_d \times (k_{a(G)} - k_e)} D_r(t_r)\left(e^{-k_e(t-t_r)} - e^{-k_{a(G)}(t-t_r)}\right)$$

Equation 1: Predictive model for total plasma concentration over time. $C_{tot}(t)$ total plasma nicotine concentration at time t (ng.mL-1), $D_r(t_r)$ released dose of nicotine per time unit (mg.min-1), $k_{a(B)}$ and $k_{a(G)}$ first-order rate constants for buccal and gut absorption, respectively (min-1), k_e first-order nicotine elimination rate constant (min-1), V_d apparent volume of distribution (mL.kg-1), F_B and F_G fractions of nicotine absorbed via buccal and gastrointestinal route, respectively.

- Nicotine release data were quantified using the USP-4 flow-through apparatus. Although this method overestimates nicotine release due to high flow rates in lab settings, a strong linear correlation was observed between *in vitro* and *in vivo* data across five TNFPs (these products are not available for sale in USA). A machine learning model was trained to map *in vitro* release profiles to *in vivo* absorption, forming the basis for the PK model (**Figure 2**).

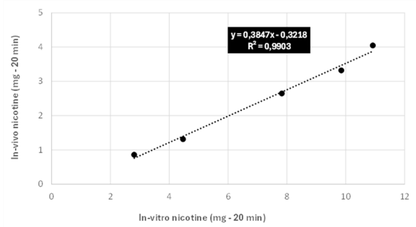

Figure 2: Relationship between *in-vitro* and *in-vivo* nicotine release from TFNP.

- Nicotine elimination was modelled separately using a first-order decay equation, based on an average half-life ($T_{1/2}$) of 2 hours ($k_e \approx 0.00578$ min^{-1}):

$$k_e = \frac{\ln(2)}{T_{1/2}}$$

- The resulting plasma nicotine concentration is computed as:

$$For\ t > t_{max}\ :\ C(t) = C(t_{max})e^{-k_e.t}$$

C(t) nicotine plasma concentration at time t (ng.mL^{-1}), $C(t_{max})$ predicted absorbed nicotine concentration at time t_{max}, estimated form the in-vitro release curve, via the trained model (ng.mL^{-1}), $e^{-ke.t}$ the decline in nicotine plasma concentration due to elimination after time t.

- Our previous clinical PK data shows that nicotine absorption continues after nicotine pouch removal with time to maximum plasma concentration (T_{max}) occurring on average ~2.7 minutes post-use. Once T_{max} is determined, we can then calculate the maximum plasma concentration (C_{max}).

- The model also incorporated a post-use absorption window to reflect delayed T_{max}, accounting for residual nicotine in the oral cavity and mucosa as observed in clinical studies (**Figure 3**).

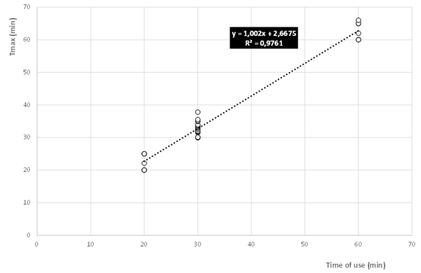

Figure 3: Relationship between Time of use and T_{max} from clinical studies on TFNP

RESULTS

- Plasma nicotine concentration-time profiles (PK curves) were simulated for TFNP products using the developed model, based on *in vitro* release data (obtained via the USP-4 method) (**Figure 4**).

- PK curves were modelled by convolving *in vitro* derived absorption profiles with the first-order elimination function. The short post-use absorption phase was also added to reflect delayed T_{max} observed in clinical data.

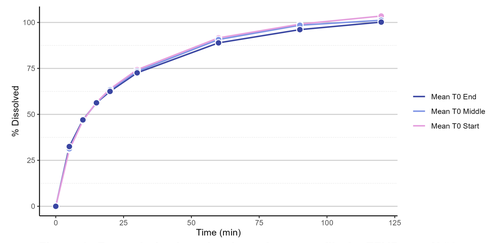

Figure 4: Example *in vitro* nicotine release profile for TFNP zoneX #3.

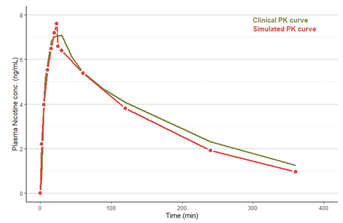

Figure 5: Comparison between clinical (green) and simulated (red) pharmacokinetic curves for TFNP zoneX #3, showing strong alignment in curve shape and magnitude.

A strong agreement was observed between simulated and observed PK curves for TNFP zoneX #3, demonstrating the model's accuracy using only *in vitro* release data (**Figure 5**).

- Simulated results were evaluated against clinical data using key PK parameters, T_{max}, C_{max} (maximum concentration) and AUC (area under the curve). Observed and predicted data align closely, as shown in **Table 1**.

Table 1: Comparison of simulated and observed PK parameters for IMB's TFNP

Product	Parameter	Simulated Value	Observed Clinical Value Mean (SD)	Relative Difference (%)
Zone X #2	C_{max} (ng/mL)	5.3	5.2 (1.7)	2%
	T_{max} (min)	23	26 (9)	-12%
	AUC_{0-90} (ng.h/mL)	5.7	5.2 (1.6)	10%
Zone X #3	C_{max} (ng/mL)	7.62	7.9 (2.4)	-4%
	T_{max} (min)	23	22 (8)	5%
	AUC (ng.h/mL)	8.2	7.9 (2.3)	4%
Zone X #5	C_{max} (ng/mL)	13.0	13.4 (4.9)	-3%
	T_{max} (min)	23	25 (5)	-8%
	AUC_{0-90} (ng.h/mL)	14.1	13.1 (3.9)	8%
Zone X #5 Slim	C_{max} (ng/mL)	12.1	15.0 (5.0)	-19%
	T_{max} (min)	23	25 (5)	-8%
	AUC_{0-90} (ng.h/mL)	13.1	14.8 (4.1)	-11%
Zone X #6	C_{max} (ng/mL)	16.8	19.3 (6.6)	-13%
	T_{max} (min)	23	25 (5)	-8%
	AUC_{0-90} (ng.h/mL)	17.8	19.8 (6.3)	-10%

CONCLUSIONS

- A simplified PK model was developed to predict plasma nicotine concentration following use of TFNPs.
- The model integrates *in vitro* nicotine release data (USP-4 method) and use duration to estimate systemic exposure.
- Strong alignment with clinical data for C_{max}, T_{max}, and AUC supports model validity.
- This approach offers a resource-efficient alternative to extensive clinical testing and supports:
  1. Early product development
  2. Toxicological risk assessment
  3. Regulatory evaluation of novel nicotine products
- Further model validation is needed. Therefore, publicly available TNFP data will be explored for potential use, although only a few studies provide both *in vitro/in vivo* data, limiting direct applicability.

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