Characterization of on!® Nicotine Pouches – Part 2: Nicotine Dissolution Release Profiles

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ABSTRACT

on!® is an oral tobacco-derived nicotine pouch product that does not contain cut, ground, powdered or leaf tobacco. In order to issue market authorization, FDA must determine whether the on!® nicotine pouches are appropriate for the protection of public health (APPH). We characterize the nicotine release profiles for the portfolio of on!® nicotine pouches to inform the determination of APPH. Evaluating nicotine release profiles through dissolution testing is valuable for product assessment and for product-to-product comparisons. We used a robust dissolution method to study the *in vitro* release of nicotine from on!® products into artificial saliva using the U.S. Pharmacopeia flow-through cell dissolution apparatus 4 (USP-4). Additionally, we validated a UPLC-UV method for the determination of nicotine in dissolution fractions. Nicotine release profiles were compared by calculating the difference factor (f_1) and similarity factor (f_2) by adopting methodology referenced in Guidance for Industry from FDA's Center for Drug Evaluation and Research (CDER).

on!® nicotine pouches are marketed in a variety of flavors and nicotine strengths. Nicotine release rates, based on percent released, were comparable across nicotine strengths and flavor variant. Furthermore, nicotine release rate for on!® nicotine pouches was found to be equivalent to Skoal Bandits™ (a traditional pouched moist smokeless tobacco product) based on FDA's criteria.[2,3]

STUDY OVERVIEW

- on!® is an oral tobacco-derived nicotine pouch product that does not contain cut, ground, powdered or leaf tobacco.
- We adopted a robust nicotine release method utilizing the USP-4 flow-through cell apparatus.[1]
- We performed product-to-product comparisons on the 35 varieties of on!® nicotine pouches (seven flavors with five nicotine strengths each).
- We calculated the difference factor (f_1) and similarity factor (f_2) using the 4 mg on!® nicotine pouches as a reference to the other nicotine strengths for each flavor variant.[2,3]

CUMULATIVE AND % RELEASE PROFILES

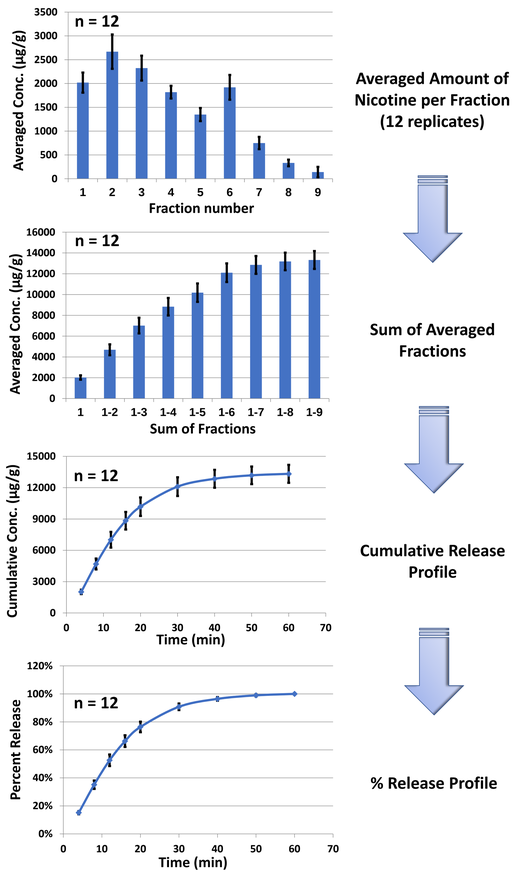


Figure 2. Calculation of nicotine cumulative and % release profiles from 4 mg Mint on!® nicotine pouches. Error bars represent ± 1 standard deviation.

DISSOLUTION METHODOLOGY

Figure 1. SOTAX CE7 Smart flow-through system (USP-4) including cells holder, pump, fractions collector, and flow-through cell.[5]

Table 1. Artificial saliva composition.[4]

Ingredient	Amount per 1 L (g)
Magnesium Chloride Hexahydrate ($MgCl \cdot 6H_2O$)	0.17 g
Potassium Hydrogen Phosphate anhydrous ($K_2HPO_4 \cdot H_2O$)	0.68 g
Sodium Chloride (NaCl)	0.33 g
Potassium Chloride (KCl)	0.75 g
Calcium chloride dihydrate ($CaCl \cdot 2H_2O$)	0.15 g
Potassium Carbonate (K_2CO_3)	0.53 g
Type 1 Water (De-ionized)	1000 mL
Hydrochloric acid	2 mL
5N sodium hydroxide	Adjust to pH 6.8 ± 0.1

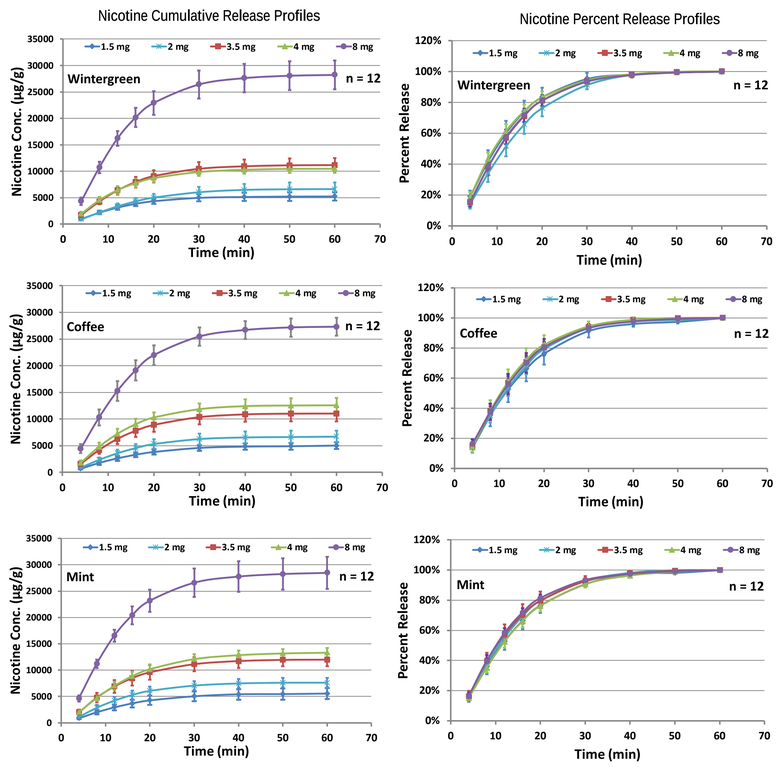
f_1 & f_2 Models

$$f_1 = \left\{\left[\sum_{t=1}^{n}|R-T|\right] / \left[\sum_{t=1}^{n}R\right]\right\} \text{ X } 100 \qquad f_2 = 50 \cdot \log\left[\frac{100}{\sqrt{1+\frac{\sum_{t=1}^{t=n}[R_t - T_t]^2}{n}}}\right]$$

R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the two products.

f_1 values up to 15 (0-15) and f_2 values of 50 or greater (50-100) ensure similarity or equivalence between two products.

NICOTINE CUMULATIVE AND PERCENT RELEASE PROFILES FOR *on!*® NICOTINE POUCHES



Similar release profiles were observed for Berry, Cinnamon, Citrus, and Original on!® nicotine pouches at different nicotine strengths (see f_1 and f_2 values in Table 2).

Figure 3: Nicotine cumulative and percent release profile profiles from on!® nicotine pouches (n=12). Error bars represent ± 1 standard deviation.

Table 2. Product-to-product comparisons using f_1 and f_2 model

Comparison	f_1	f_2	Equivalency
on!® Wintergreen			
4 mg vs 1 mg	1.1	94.3	Yes
4 mg vs 2 mg	11.2	56.3	Yes
4 mg vs 3 mg	4.8	72.8	Yes
4 mg vs 8 mg	4.6	73.7	Yes
on!® Coffee			
4 mg vs 1 mg	6.6	67.2	Yes
4 mg vs 2 mg	4.5	74.8	Yes
4 mg vs 3 mg	1.7	91.1	Yes
4 mg vs 8 mg	2.6	86.1	Yes
on!® Mint			
4 mg vs 1 mg	0.8	97.4	Yes
4 mg vs 2 mg	3.9	79.0	Yes
4 mg vs 3 mg	5.9	71.5	Yes
4 mg vs 8 mg	7.4	67.1	Yes
on!® Original			
4 mg vs 1 mg	8.5	62.2	Yes
4 mg vs 2 mg	4.0	77.3	Yes
4 mg vs 3 mg	8.4	62.6	Yes
4 mg vs 8 mg	3.0	82.8	Yes
on!® Citrus			
4 mg vs 1 mg	6.5	72.2	Yes
4 mg vs 2 mg	5.7	71.3	Yes
4 mg vs 3 mg	6.5	73.2	Yes
4 mg vs 8 mg	6.3	72.8	Yes
on!® Berry			
4 mg vs 1 mg	8.6	63.0	Yes
4 mg vs 2 mg	4.1	76.4	Yes
4 mg vs 3 mg	1.5	92.3	Yes
4 mg vs 8 mg	6.4	67.6	Yes
on!® Cinnamon			
4 mg vs 1 mg	8.1	63.8	Yes
4 mg vs 2 mg	2.3	87.3	Yes
4 mg vs 3 mg	2.3	86.9	Yes
4 mg vs 8 mg	4.0	79.4	Yes

COMPARASON TO SKOAL BANDITS™ POUCH

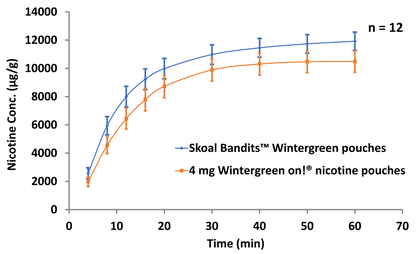


Figure 4: Cumulative release profile of nicotine from 4 mg Wintergreen on!® nicotine pouches and Skoal Bandits™ Wintergreen pouch. Error bars represent ± 1 standard deviation.

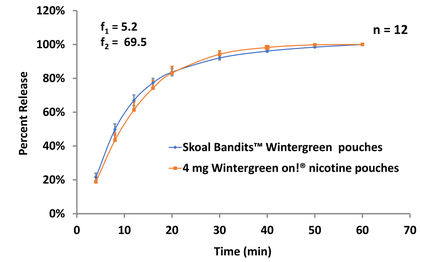


Figure 5: Total release profile of nicotine from 4 mg Wintergreen on!® nicotine pouches and Skoal Bandits™ Wintergreen. Error bars represent ± 1 standard deviation.

CONCLUSIONS

- Following FDA guidance, we applied a robust USP-4 dissolution method to determine the nicotine release profiles for a variety of on!® nicotine pouches.[2,3]
- Nicotine release rate for each flavor variant is equivalent based on f_1 and f_2 criteria.[3]
- Demonstrated a dose-dependent response for the cumulative nicotine release profiles for all nicotine strengths.
- The nicotine release rate for 4 mg Wintergreen on!® nicotine pouches was found to be equivalent to Skoal Bandits™ Wintergreen (a traditional pouched moist smokeless tobacco product).

STRENGTHS & LIMITATIONS

- We applied an accurate and reproducible tool to perform product to product comparisons using cumulative and percent nicotine release profiles.
- This methodology was not developed to serve as a direct surrogate to clinical studies for evaluating human usage or exposure. Additional work would need to be conducted to establish *in vitro*/*in vivo* correlations.

REFERENCES

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