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Randomized studies assessing the effect of flavor on pharmacokinetic and subjective parameters for dry and moist nicotine pouches

Mikael Staaf, Anna E. Masser [1], Camilla Pramfalk [2], Robert Pendrill, Sara Moses, Johan Lindholm, Tryggve Ljung *

Regulatory & Scientific Affairs, Swedish Match North Europe AB, Box 17037, Stockholm SE-104 62, Sweden

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ABSTRACT

Background: Nicotine pouches (NPs) have different formulations (e.g., dry or moist), and the vast majority are flavored. However, it is unclear if flavors exert any effect on nicotine pharmacology and subjective parameters.
Methods: Data from two, open-label, randomized, nine-way cross-over, single-dose administration, pharmacokinetic and subjective effects studies were analyzed, evaluating dry 6-mg and moist 9-mg NPs, respectively. The studies included unflavored and flavored varieties (flavor characteristics: traditional [tobacco], cooling, minty, fruit, beverage). All participants were adults who currently used snus and/or NPs daily (n = 38 for moist, n = 39 for dry).
Results: Maximum plasma concentrations (C_{max}) of nicotine were observed at NP removal at ~60 min (T_{max}), with overlapping geometric least squares mean (GLSM) values for the dry and moist products (12.08–15.07 ng/mL). The total nicotine exposure (calculated as area under the curve from time point 0 to infinity, AUC_{inf}) was 40.84–50.86 h*ng/mL, with overlapping GLSM values for dry and moist varieties. Equivalence testing for AUC_{inf} and C_{max} between unflavored and flavored varieties showed equivalence for all varieties except two of the moist minty NPs. For subjective parameters, the effect of flavor was more pronounced for moist NPs, with participants rating the flavored varieties higher for satisfaction, product liking, and intent to use again.
Conclusions: For dry varieties, flavor had no effect on C_{max} and AUC_{inf}, but two moist varieties were different from moist unflavored. Flavor did not affect T_{max} for dry or moist NPs. Considerable variation in participant preferences suggest a need for diverse varieties and product types.

1. Introduction

Sweden has the lowest prevalence of smoking in the European Union (EU), but the prevalence of tobacco use is close to the EU average (European Union, 2021). An important factor underlying this trend is that snus has replaced cigarettes as the tobacco product of choice among many males and some females (Sjodin et al., 2024). This has likely contributed to the record-low tobacco-related morbidity and mortality rates among Swedish males compared to males in the rest of the EU (Global Burden of Disease Collaborative Network, 2020), where snus has been banned since 1992.

Swedish snus is a smokeless tobacco product that contains low levels of tobacco-specific nitrosamines (TSNAs) and trace levels of polycyclic aromatic hydrocarbons (PAHs), which are two of the main classes of harmful and potentially harmful constituents in tobacco products classified as human carcinogens (Lawler et al., 2020). Using Swedish snus instead of smoking cigarettes avoids exposure to the thousands of combustion compounds in tobacco smoke, many of which are highly carcinogenic and may induce systemic inflammation or chronic irritation in the upper and lower airways (Fowles and Dybing, 2003). Despite the vast risk differential between snus and cigarettes in terms of adverse long-term health effects (Murkett et al., 2022; Nutt et al., 2014) snus remains a controversial product as it contains tobacco, is intended for recreational use, and its addictive potential due to the presence of nicotine (Benowitz, 2010; National Center for Chronic Disease Prevention and Health Promotion US Office on Smoking and Health, 2014).

Nicotine pouches (NPs) intended for recreational use are a fairly recent development (Robichaud et al., 2020) and have been

* Corresponding author.
E-mail addresses: anna.masser@pmi.com (A.E. Masser), tryggve.ljung@pmi.com (T. Ljung).
[1] 0000–0001-6065–8216
[2] 0000–0003-4928–1256

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commercially available in many markets for the past decade (e.g., the United States and Sweden). They typically contain fillers, stabilizers, pH adjusters, nicotine (tobacco-derived or synthetic), food-grade flavorings, and sweeteners. Depending on the moisture content, they are considered as dry (~3 % moisture) or moist (~45 % moisture). Given the novelty of the category, there is considerable regulatory variability, ranging from complete bans to requiring a prescription to availability at gas stations and convenience stores (Duren et al., 2023). NPs are intended to be used in the same way as snus (*i.e.,* placed under the upper lip), and they have some similar features. Most notably, they deliver nicotine to systemic circulation through the oral mucosa. As tobacco-derived NPs can be manufactured in a way that virtually eliminates the presence of PAHs and TSNAs (Azzopardi et al., 2021; Back et al., 2023; Jablonski et al., 2022; Mallock et al., 2022), the health effects are predicted to be substantially lower for people who use NPs compared to those who smoke cigarettes (BfR, 2022), and also reduced relative to snus consumption (Back et al., 2023). Although most of the harmful and potentially harmful constituents found in emissions or extractions from other tobacco and nicotine products are not found in NPs, it is important to assess pharmacokinetic, pharmacodynamic, and subjective parameters related to nicotine exposure.

Nicotine induces several biological effects in humans, and these are generally correlated with the amount and speed of nicotine delivery. The nicotine delivery profile of a product is an important determinant (among others such as taste, sensory, and ritual) of its ability to decrease craving and therefore affects the product's acceptability as an alternative to cigarettes among people who smoke (Benowitz, 2009; Liu et al., 2022; Palmer et al., 2022). Although numerous NP products are commercially available, only a few studies have investigated their nicotine pharmacokinetics (PK) and pharmacodynamics (PD)/subjective effects (Azzopardi et al., 2022; Chapman et al., 2022; Kanobe et al., 2025; Liu et al., 2022; Lunell et al., 2020; McEwan et al., 2021, 2023; Rensch et al., 2021). A 2022 review highlighted the importance of flavors in helping people who smoke cigarettes transition to e-cigarettes with potentially lower health risks (Gades et al., 2022), and those who use flavored e-cigarettes are more likely to successfully quit smoking (Mok et al., 2023). Others have hypothesized that flavor, including menthol may influence a product's misuse potential by enhancing nicotine uptake and increasing its appeal (St Helen et al., 2017; Wickham, 2020). For NPs, this hypothesis has only been tested in three studies. Rensch and colleagues assessed six NPs (one unflavored and five flavored varieties with similar nicotine contents) and found no effect of flavors on nicotine exposure (Rensch et al., 2021). McEwan et al. investigated the PK and subjective effects of nine flavored products and also found no effect of flavor on nicotine exposure, but no unflavored NPs were included for comparison (McEwan et al., 2023). Kanobe and colleagues evaluated nicotine uptake and subjective effects in NPs with different nicotine contents, sizes, and flavors (Kanobe et al., 2025). Overall, there are limited clinical data regarding any possible effect of flavoring on PK and PD parameters and subjective effects. It also remains unclear whether flavors have different effects across product types, such as variations in moisture content.

In the present work, PK and subjective parameters, and nicotine extraction were assessed for unflavored and flavored varieties of moist and dry NPs. The primary objective of both studies was to evaluate the effect of flavor on nicotine exposure after the administration of single doses of unflavored and flavored NPs. The secondary objectives were to evaluate the effect of flavors on subjective parameters and to compare *in vivo* extracted amounts and fractions between unflavored and flavored NPs.

2. Methods

2.1. Ethical and regulatory requirements

The data were obtained from two separate clinical studies, evaluating dry and moist NP, respectively. Both were approved by the Swedish Ethical Review Authority (approval numbers 2020–06740 [NP moist] and 2021–05945–01 [NP dry]) and registered in the International Standard Randomized Controlled Trial Number (ISRCTN) clinical trial registry as ISRCTN66329631 (09/02/2021) and ISRCTN91637022 (13/12/2021), respectively. Clinical study protocols were submitted to the same database. The studies were conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki (The World Medical Association, 2018) and adhere to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) E6 (R2) guidance (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human, 2002), the European Union (EU) Clinical Trials Directive 2001/20/EC (European Commission, 2001), and applicable local regulatory requirements. All participants provided written informed consent before any study procedures were initiated.

2.2. Participants

Participants were recruited between 11/02/2021 and 23/03/2021 (NP moist) and 10/01/2022 and 16/02/2022 (NP dry). They were healthy males and females aged $\geq$ 19 years who had been using snus and/or NPs for at least 1 year (the legal age for using these products in Sweden is 18 years), with a minimum daily consumption of five pouches. Females of child-bearing potential were required to use a sufficient contraceptive method for the study duration.

The main exclusion criteria were a history of diagnosed hypertension or any cardiovascular disease; any surgical or medical condition that may interfere with nicotine absorption, distribution, metabolism, or excretion; pregnancy or breastfeeding, or an intention to become pregnant during the study; plasma donation within 1 month of screening; or blood donation/blood loss during the 3 months prior to screening. Participants who intended to change their nicotine consumption, including the intention to stop using nicotine products within the next 3 months from the screening visit, were also excluded.

Participants were free to discontinue study involvement at any time and for whatever reason without affecting their right to an appropriate follow-up investigation or their future care.

2.3. Investigational products

Each study tested one unflavored and eight flavored NPs that were specifically manufactured for research purposes (Swedish Match, Stockholm, Sweden; Table 1). The varieties are labeled A-I and categorized according to their flavor characteristic (unflavored, fruit, cooling, minty, traditional (tobacco), and beverage). Within each product type (dry/moist), none of the varieties had the exact same flavor. The moist NPs contain 1.1 % nicotine (9 mg/pouch) and have a moist matrix with ~40 % moisture and a pH of 8.5; the pouches measure 13.5 × 34 mm and weigh 0.8 g. The dry NPs contain 1.5 % nicotine (6 mg/pouch) and have a dry matrix with around 3 % moisture and a pH of 8.3; the pouches measure 14 × 28 mm and weigh 0.4 g. All moist minty

Table 1
Study NPs.

NP moist 9 mg varieties	NP dry 6 mg varieties
A unflavored	A unflavored
B fruit	B traditional (tobacco)
C cooling	C traditional (tobacco)
D minty	D beverage
E minty	E beverage
F minty	F fruit
G minty	G fruit
H minty	H fruit
I minty	I fruit

products, except moist F minty, and moist B fruit contain menthol. None of the dry varieties contained menthol.

2.4. Study design and procedures

The data summarized herein were from two open-label, randomized, nine-way cross-over, single-dose administration studies carried out at a single site in Uppsala, Sweden. Both studies followed similar protocols (ISRCTN, 2023, 2024). The primary objective was to assess the effect of flavors on nicotine exposure in the NPs indicated above. No changes to the methods or outcomes were made after the studies had started.

Participants visited the clinic 10 times, including 1 screening visit (visit 1) and 9 study visits (visits 2–10) (Fig. 1). Computer-generated randomization (SAS Proc Plan, Version 9.4, SAS, Cary, NC, USA) took place on visit 2, when participants were randomized to six sequences. Participants were required to abstain from any tobacco/nicotine products and beverages containing alcohol for at least 12 h before each study visit and were self-reported abstinent, being only allowed to use the single NP administered during each visit. No eating, drinking, or any other mouth-related procedures (e.g., toothbrushing, gum chewing) were allowed for 30 min prior to NP administration, during NP use, and for 30 min after NP removal.

For each participant, all administrations were conducted at the same time during each study visit, with all participants receiving their administrations in the morning. Participants were instructed to keep the NP between the upper lip and gum for 60 min and not to manipulate it with their tongue or lips. NPs were collected after 60 min. Thereafter, participants had to abstain from nicotine products for 5 h while PK and subjective effects were monitored.

2.5. Study endpoints

The primary endpoint in both studies was to determine the PK of nicotine in plasma after administering single unflavored and flavored NPs and assessing the equivalence (90 % confidence interval [CI] between 0.8 and 1.25) in the baseline-adjusted areas under the curve from time point 0 to infinity (AUC_{inf}) based on nicotine plasma concentrations.

Secondary endpoints included differences in subjective parameters, equivalence in C_{max}, differences in the time of occurrence of C_{max} (T_{max}), differences in the extracted amounts and fractions of nicotine, and differences in maximum effect (E_{max}) for self-reported craving and satisfaction after the administration of single doses of unflavored and flavored NPs.

2.6. Plasma nicotine concentration

Venous blood samples (~3 mL) to measure plasma concentrations of nicotine and calculate PK parameters after NP administration were collected through an indwelling venous catheter at pre-defined time points: pre-administration (within 15 min prior to dose) and 5, 10, 15, 30, 45, 60, 75, 90, 120, 240, and 360 min post-administration. The samples were centrifuged to separate plasma and frozen at −20°C. Plasma concentrations of nicotine were analyzed using a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method. Analyses were carried out by Lablytica Life Science AB (Uppsala, Sweden).

Many participants had quantifiable plasma nicotine concentrations prior to NP administration; baseline-adjusted parameters are reported herein. No differences in equivalence testing were seen when comparing baseline-adjusted and -unadjusted data.

2.7. Nicotine extraction

Used NPs were collected after 60 min (±1 min) and stored at −20°C prior to measuring residual nicotine. For each variety, ten unused NPs from the same production batch as the used pouches were retained as reference products to determine total nicotine content. The coefficient of variation (CV) for the nicotine content of the ten unused reference pouches per variety ranged from 1.2 % to 5.0 %, indicating low variability within batches. NPs were analyzed using an adaptation of CORESTA's recommended method No. 62 "Determination of nicotine in tobacco and tobacco products by gas chromatographic analysis" (Cooperation Centre for Scientific Research Relative to Tobacco, 2021).

2.8. Subjective effects

The self-reported parameters "craving," "satisfaction," "product liking," and "intent to use again" were rated using a 100-mm visual analog scale (VAS), anchored with "not at all" to "extremely" (or "very likely" for the "intent to use again" parameter) as suggested in U.S. Food and Drug Administration (FDA) guidance for industry (FDA, 2017).

"Craving" was assessed with the question "Right now, how strong is your urge to snus?" at pre-administration (-10 min prior to dose, used as baseline), and at 5, 10, 15, 30, 45, 60, 75, 90, 120, 240, and 360 min post-administration. The change from baseline was calculated. "Satisfaction" was assessed with the question "Right now, is the product satisfying?" at 5, 10, 15, 30, 45, 60, 75, 90, 120, 240, and 360 min post-administration. E_{max} (i.e., how much the NPs were able to reduce cravings or give satisfaction) and time to E_{max} (i.e., when the highest craving relief or satisfaction occurred) were reported.

"Product liking" and "intent to use again" were assessed at 60-min post-administration with the respective questions "How much did you like the product?" and "How likely are you to use this product again in the future?" "Product liking compared to the participants' usual product of choice" was evaluated with the multiple-choice question "How much did you like the product compared with your usual product of choice? To a greater extent? To a lesser extent? To the same extent?" The best-liked

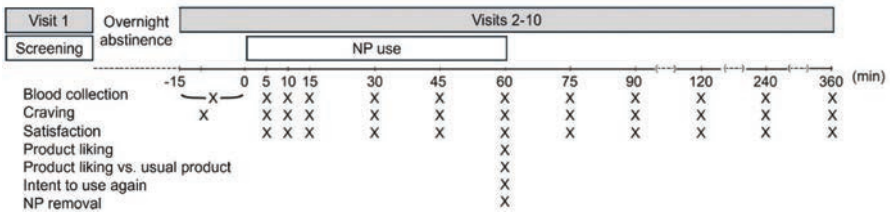

Fig. 1. Study design for both studies. All participants attended a screening visit (Visit 1) to ensure that they were in good health and met all inclusion criteria and none of the exclusion criteria. Following overnight abstinence, visits 2–10 began with determining baseline craving and drawing blood for plasma nicotine measurements. A single NP was administered from time point 0–60 min. Blood sampling and measurements of craving and satisfaction were taken at pre-defined time points during NP use and up to 360 min post-NP use. Product liking, product liking vs. participants' usual product, and intent to use again were evaluated after 60 min (in conjunction with NP removal). NP, nicotine pouch.

Table 2
Participants' baseline characteristics and demographics.

Characteristic		NP moist study (n = 44)	NP dry study (n = 42)
Age (years)			
	Mean (SD)	28.3 (10.1)	30.1 (10.5)
	Median (Min, Max)	26.0 (19, 77)	26.0 (21, 78)
Height (cm)			
	Mean (SD)	177.7 (8.0)	175.1 (7.3)
	Median (Min, Max)	178.0 (160, 194)	175.0 (162, 188)
Weight (kg)			
	Mean (SD)	83.3 (23.2)	78.0 (14.5)
	Median (Min, Max)	77.1 (57, 148)	79.0 (51, 108)
Body mass index (kg/m^2)			
	Mean (SD)	26.2 (6.4)	25.4 (4.3)
	Median (Min, Max)	23.8 (19, 46)	24.8 (19, 35)
Sex			
	Female	9 (20 %)	16 (38 %)
	Male	35 (80 %)	26 (62 %)
Race			
	American Indian or Alaska Native	0	0
	Asian	2 (4.5 %)	1 (2.4 %)
	Black or African American	2 (4.5 %)	2 (4.8 %)
	Multiple	0	1 (2.4 %)
	Native Hawaiian or Other Pacific Islander	1 (2.3 %)	0
	White	39 (89 %)	38 (90 %)
Ethnicity			
	Hispanic or Latino	1 (2.3 %)	4 (9.5 %)
	Not Hispanic or Latino	43 (98 %)	38 (90 %)
	Not Reported	0	0
	Unknown	0	0

product was calculated from each participant's rating of the NPs.

2.9. Safety assessments

Any adverse events (AEs), including serious AEs (SAEs), were collected through interviews and spontaneously reported by the participants from the start of NP administration until the last study visit. The grading of the severity/intensity (grade 1–5) of AEs followed the common terminology criteria for AEs (CTCAE) v5.0 (National Cancer Institute Division of Cancer Treatment and Diagnosis, 2017). Reported AEs were assessed as unlikely, possibly, or probably related to the NPs.

2.10. Statistical methods

The sample sizes were determined based on the CV for the extracted fraction of nicotine in previous studies (31–33 %) (Lunell et al., 2020). Assuming no difference between products, defining equivalence as a 90 % CI of least squares means entirely in the range of 0.8–1.25, and using a CV of 32.5 %, a power of 80 %, and a significance level of 10 %, 36 evaluable participants were required. To account for a 15 % discontinuation rate, 42 participants would need to be randomized for each study. For both C_{max} and AUC_{inf} PK parameters, comparisons between flavored NPs (test) and the unflavored NP (reference) for both dry and moist NPs were assessed using a mixed model with the natural log of the PK parameter as the dependent variable, treatment as a fixed effect, and subject as a random effect. All NPs in the study were included in this model. Kenward-Rogers approximation for degrees of freedom was used. The results of this analysis are presented as geometric least squares mean ratios (GLMRs) and 90 % CIs for each variety of flavored NP against the corresponding unflavored NP. Equivalence was assessed by comparing each 90 % CI of GLMR of both PK parameters to the bioequivalence range of 80–125 % as detailed in FDA guidance for industry (FDA, 2001). No adjustments for multiple comparisons were applied, so CIs are reported without correction for multiplicity and should be interpreted as unadjusted. The same approach was followed for the nicotine extraction endpoints.

Significance testing for differences in parameters on an ordinal scale (such as subjective ratings using a VAS) or a discontinuous scale (E_{max}/time to E_{max}) was performed using Wilcoxon's signed-rank test. Adjustment for multiple testing was performed, within each set of evaluations, following Holm's stepdown procedure (Holm, 1979), and a 5 % significance level was used.

3. Results

3.1. Participants

In total, 60 and 55 participants were screened for the NP moist and NP dry studies, respectively. For the NP moist study, 44 participants were randomized and 38 completed the study. Dropouts were due to withdrawal of consent (n = 4), loss to follow up (n = 1), and removal due to a positive drug test (n = 1). Of the 42 randomized participants in the NP dry study, 39 completed the study, and 3 withdrew consent prior to study completion.

The study population (Table 2) included 20 % and 38 % females for the NP moist and dry studies, respectively. The participants were predominantly white with a mean age of 28.3 (moist study) and 30.1 (dry study) years. All reported current, daily use of flavored snus and/or NPs.

3.2. Nicotine pharmacokinetics

The mean plasma-nicotine concentration time-profiles for unflavored and flavored NP moist varieties were similar, and all varieties increased plasma-nicotine concentrations until NP removal at 60 min (Fig. 2a). The mean C_{max} values were observed ~1 h after the start of administration for all NPs, except for moist C cooling, where C_{max} was observed at 75 min. C_{max} was 12.22 ng/mL for moist A unflavored and ranged from 12.08 ng/mL (moist C cooling) to 15.07 ng/mL (moist H minty) for the flavored moist varieties (Table 3). At 360 min (5 h after 60-min NP use), plasma nicotine concentrations had returned close to baseline levels. The total mean nicotine exposure (AUC_{inf}) was 42.48 h*ng/mL for moist A unflavored and ranged from 40.84 h*ng/mL

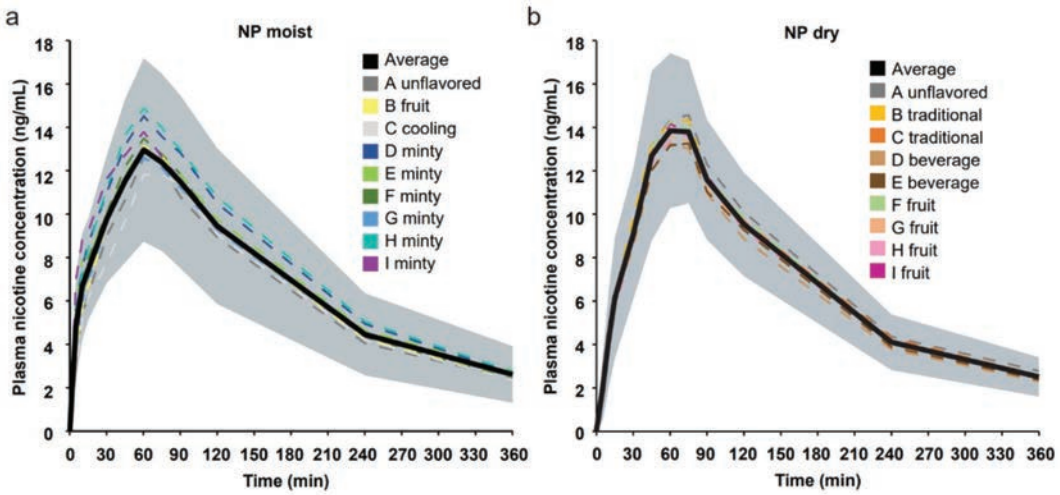

Fig. 2. Pharmacokinetic profiles for (a) nine moist 9 mg varieties and (b) nine dry 6 mg varieties. Baseline-adjusted mean plasma nicotine concentrations (ng/mL) over time when using an NP for 60 min. The black line shows the mean for all variants and all participants using moist (a) and dry (b). Dashed lines show means for each variety. The gray shading depicts the standard deviation between individuals. NP, nicotine pouch.

Table 3
Analysis of baseline-adjusted nicotine PK parameters for moist varieties used for 60 min.

Parameter	Test NP	Test NP GLSM (CV%)	Reference NP	Reference NP GLSM (CV %)	90 % CI lower bound	GLMR	90 % CI upper bound
Baseline-adjusted $AUC_{0\text{-inf}}$ (h*ng/mL)	Moist B fruit	43.92 (43.8 %)	Moist A unflavored	42.48 (40.3 %)	0.98	1.05	1.13
	Moist C cooling	40.84 (47.7 %)			0.89	0.95	1.03
	Moist D minty	49.90 (35.5 %)			1.11	1.19	1.28
	Moist E minty	49.50 (38.4 %)			1.07	1.15	1.24
	Moist F minty	45.89 (35.9 %)			0.99	1.07	1.15
	Moist G minty	43.41 (38.2 %)			0.96	1.03	1.11
	Moist H minty	50.86 (38.6 %)			1.12	1.20	1.30
	Moist I minty	47.10 (40.3 %)			1.05	1.13	1.22
Baseline-adjusted C_{max} (ng/mL)	Moist B fruit	12.87 (41.3 %)	Moist A unflavored	12.22 (36.6 %)	0.98	1.05	1.13
	Moist C cooling	12.08 (39.3 %)			0.91	0.98	1.05
	Moist D minty	14.82 (33.6 %)			1.12	1.20	1.29
	Moist E minty	13.84 (28.8 %)			1.06	1.13	1.22
	Moist F minty	13.72 (28.6 %)			1.04	1.12	1.20
	Moist G minty	12.57 (38.2 %)			0.96	1.03	1.10
	Moist H minty	15.07 (34.5 %)			1.14	1.22	1.31
	Moist I minty	14.00 (34.7 %)			1.07	1.14	1.23

Note. AUC_{inf}, area under the curve from time 0 to infinity; C_{max}, maximum observed concentration; CI, confidence interval; CV, coefficient of variation; GLSM, geometric least squares mean; GLMR, geometric least squares mean ratio; NP, nicotine pouch; PK, pharmacokinetic.

(moist C cooling) to 50.86 h*ng/mL (moist H minty) for the flavored moist products. Equivalence testing for AUC_{inf} and C_{max} between NP moist A unflavored and each flavored variety showed equivalence for all varieties except moist D minty and moist H minty.

The mean plasma-nicotine concentration time-profiles were similar for all dry varieties (Fig. 2b). Use of all varieties resulted in increasing plasma-nicotine concentrations until NP removal. After removal, concentrations remained steady or increased somewhat over the next 15 min, then declined and returned close to baseline levels after 360 min. C_{max} was 14.47 ng/mL for dry A unflavored and ranged from

Table 4
Analysis of baseline-adjusted nicotine PK parameters for dry varieties used for 60 min.

Parameter	Test NP	Test NP GLSM (CV%)	Reference NP	Reference NP GLSM (CV%)	90 % CI lower bound	GLMR	90 % CI upper bound
Baseline adjusted $AUC_{0\text{-}inf}$ (h*ng/mL)	Dry B traditional	46.24 (35.0 %)	Dry A unflavored	48.13 (37.3 %)	0.89	0.95	1.02
	Dry C traditional	46.20 (28.9 %)			0.90	0.96	1.03
	Dry D beverage	42.20 (33.0 %)			0.82	0.88	0.94
	Dry E beverage	43.38 (31.5 %)			0.85	0.90	0.96
	Dry F fruit	46.36 (30.4 %)			0.90	0.96	1.03
	Dry G fruit	44.50 (34.2 %)			0.87	0.92	0.99
	Dry H fruit	44.10 (34.7 %)			0.86	0.92	0.98
	Dry I fruit	45.71 (32.2 %)			0.89	0.95	1.01
Baseline adjusted C_{max} (ng/mL)	Dry B traditional	14.23 (29.0 %)	Dry A unflavored	14.47 (34.9 %)	0.95	1.01	1.08
	Dry C traditional	14.65 (30.9 %)			0.92	0.98	1.05
	Dry D beverage	13.54 (28.3 %)			0.88	0.94	1.00
	Dry E beverage	13.58 (26.8 %)			0.89	0.94	1.00
	Dry F fruit	14.45 (31.4 %)			0.94	1.00	1.07
	Dry G fruit	13.70 (34.2 %)			0.89	0.95	1.01
	Dry H fruit	13.82 (33.9 %)			0.90	0.96	1.02
	Dry I fruit	14.27 (31.5 %)			0.93	0.99	1.05

Note. AUC_{inf}, area under the curve from time point 0 to infinity; C_{max}, maximum observed concentration; CI, confidence interval; CV, coefficient of variation; GLSM, geometric least squares mean; GLMR, geometric least squares mean ratio; NP, nicotine pouch; PK, pharmacokinetic.

Table 5
Summary of T_{max} for moist and dry varieties used for 60 min.

	T_{max} (hh:mm)
NP	Median (Q1, Q3)
Moist A unflavored	01:00 (01:00, 01:15)
Moist B fruit	01:01 (01:00, 01:15)
Moist C cooling	01:15 (01:00, 01:17)
Moist D minty	01:00 (00:45, 01:08)
Moist E minty	01:00 (00:45, 01:15)
Moist F minty	01:00 (00:45, 01:15)
Moist G minty	01:00 (01:00, 01:15)
Moist H minty	01:00 (00:46, 01:15)
Moist I minty	01:00 (00:45, 01:15)
Dry A unflavored	01:14 (01:00, 01:15)
Dry B traditional	01:15 (01:00, 01:15)
Dry C traditional	01:15 (01:00, 01:15)
Dry D beverage	01:01 (01:00, 01:15)
Dry E beverage	01:15 (01:00, 01:15)
Dry F fruit	01:00 (01:00, 01:15)
Dry G fruit	01:00 (01:00, 01:15)
Dry H fruit	01:15 (01:00, 01:15)
Dry I fruit	01:01 (01:00, 01:15)

Note. T_{max}, time of maximum concentration; Q, quartile.

13.54 ng/mL (dry D beverage) to 14.65 ng/mL (dry C traditional) for the flavored dry products; C_{max} was observed between 60 and 75 min (Table 4). AUC_{inf} was 48.13 h*ng/mL for dry A unflavored and ranged from 42.20 h*ng/mL (dry D beverage) to 46.36 h*ng/mL (dry F fruit) for the flavored dry varieties. Equivalence testing for AUC_{inf} and C_{max} between dry A unflavored and flavored dry varieties showed equivalence for all varieties. T_{max} was reached around pouch removal at 60 min, or the following time point (Table 5).

3.3. Nicotine extraction

Despite different nicotine contents (9 mg/moist NP and 6 mg/dry NP), the mean extracted amounts of nicotine were similar between both product types (Table 6). They ranged from 3.39 to 4.12 mg in moist varieties and from 3.29 to 3.80 mg in dry varieties. This corresponded with a higher mean extracted fraction of nicotine for dry varieties (56.99–63.90 %) compared to moist varieties (38.85–45.98 %).

Equivalence testing for the *in vivo* extracted amounts and fractions of nicotine between the flavored moist varieties and moist A unflavored showed that all flavored varieties—except moist H minty—were equivalent to moist A unflavored (Supplementary Table 1). The results showed equivalence for the *in vivo* extracted amounts and fractions of nicotine between all flavored dry varieties and dry A unflavored (Supplementary Table 2).

Table 6
Summary of estimated nicotine content, extracted amount, and extracted fraction of nicotine from moist and dry varieties.

NP	Content pre-use (mg/unit)*	Extracted amount (mg/unit)	Extracted fraction (%)
	Mean (SD)	Mean (SD)	Mean (SD)
Moist A unflavored	8.73 (0.12)	3.45 (1.40)	39.5 (16.0)
Moist B fruit	8.89 (0.13)	3.61 (1.45)	40.6 (16.5)
Moist C cooling	8.73 (0.11)	3.39 (1.50)	38.9 (17.1)
Moist D minty	8.91 (0.14)	3.81 (1.32)	42.8 (15.0)
Moist E minty	8.89 (0.15)	3.60 (1.36)	40.5 (15.4)
Moist F minty	8.87 (0.16)	3.65 (1.46)	41.1 (16.2)
Moist G minty	8.86 (0.16)	3.68 (1.62)	41.6 (18.5)
Moist H minty	8.99 (0.15)	4.12 (1.54)	46.0 (16.9)
Moist I minty	8.74 (0.14)	3.59 (1.40)	41.1 (16.0)
Dry A unflavored	5.95 (0.04)	3.80 (0.91)	63.9 (15.4)
Dry B traditional	5.72 (0.06)	3.50 (0.83)	61.2 (14.5)
Dry C traditional	5.81 (0.05)	3.58 (0.89)	61.6 (15.3)
Dry D beverage	5.77 (0.06)	3.29 (0.85)	57.0 (14.8)
Dry E beverage	5.82 (0.04)	3.40 (0.90)	58.4 (15.4)
Dry F fruit	5.82 (0.05)	3.45 (0.76)	59.3 (13.1)
Dry G fruit	5.78 (0.05)	3.46 (0.95)	59.9 (16.5)
Dry H fruit	5.75 (0.04)	3.40 (0.83)	59.2 (14.4)
Dry I fruit	5.76 (0.06)	3.55 (0.87)	61.7 (15.1)

* The nicotine content of 10 unused pouches was used as a reference to calculate content pre-use and the extracted amount from used NPs. Data are presented as mean and standard deviation (SD).

3.4. Subjective effects

3.4.1. Craving

Prior to moist NP administration, the average self-reported craving rating was 80 mm. A rapid reduction in reported craving was observed after administration (Fig. 3a). The E_{max} ranged from −56 mm (moist C cooling) to −73.5 mm (moist I minty) and occurred after 12–30 min (Table 7). After E_{max} was reached, median craving remained low until NP removal at 60 min. Post NP removal, reported craving increased rapidly at first and then at a declining rate, returning to pre-NP administration levels after around 300 min for median craving. Minimal differences in reported craving were observed between the

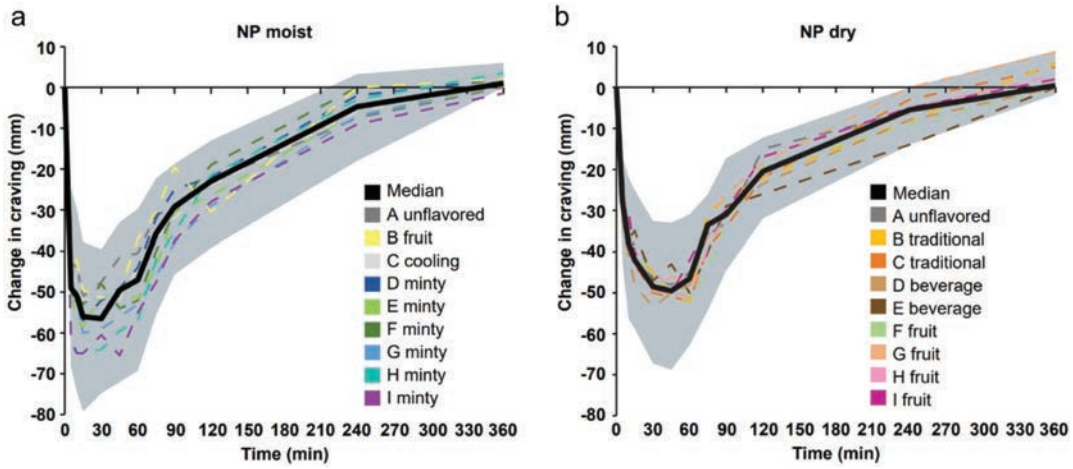

Fig. 3. Changes in self-reported craving ("urge to snus") related to (a) moist and (b) dry NP use. Craving was reported at pre-defined time points before NP administration (baseline, 0), during 60 min of use, and up to 360 min. The black lines show the median change from baseline for all participants using (a) moist and (b) dry varieties. Dashed lines show medians for each variety, respectively. The gray shading depicts quartile (Q1-Q3) ranges between individuals. NP, nicotine pouch.

unflavored and flavored moist varieties.

In participants using dry varieties, average craving was 74 mm prior to NP administration, reduced after NP administration, and remained low until NP removal at 60 min (Fig. 3b). Median E_{max} values were similar for all varieties, ranging from −52.5 mm (dry D beverage) to −61 mm (dry F fruit), and occurred after 30–45 min (Table 7). After NP removal, reported craving followed the same pattern as with moist varieties. Minimal differences in reported craving were observed between the unflavored and flavored dry varieties.

3.4.2. Satisfaction

All NP varieties provided acceptable satisfaction as reflected by the median E_{max}, which ranged from 65 to 81 mm for moist varieties and from 71 to 78 mm for dry varieties (Table 7). Among the moist varieties, the unflavored product was the least satisfying during the first 120 min (Fig. 4a) with a median E_{max} of 64.5. All flavored moist varieties were more satisfying, having a significantly larger median E_{max} than the moist A unflavored variety (all adjusted $p \leq 0.05$) (Supplementary Table 3). For dry NPs, the dry F fruit (adjusted $p < 0.05$) variety had significantly higher median E_{max} value than the dry A unflavored variety (Supplementary Table 4).

As for self-reported craving, median maximum satisfaction generally occurred slightly later for participants using dry varieties, after 30–45 min, compared to 12–30 min in participants using moist varieties (Fig. 4b). No significant differences were seen for time to E_{max} when comparing flavored moist varieties with moist A unflavored (Supplementary Table 3) or flavored dry varieties with dry A unflavored.

3.4.3. Product liking

All flavored moist varieties had higher median scores for the "product liking" parameter than moist A unflavored (Fig. 5a). The median VAS scores for moist B-I ranged from 52 mm (moist B fruit and moist C cooling) to 67 mm (moist E minty) for the flavored varieties, whereas the median score for moist A unflavored was 31 mm.

The presence of flavor had less effect on product liking of dry varieties (Fig. 5b). The median VAS scores for dry B-I ranged from 37 mm (dry C traditional) to 57 mm (dry I fruit), with a score of 49 mm for dry A unflavored.

3.4.4. Product liking compared to usual product of choice

Moist G minty and moist H minty were the most liked varieties, being "liked" to the same or to a greater extent by almost half (47 %) of the participants compared to their usual product of choice (Fig. 5c). Moist A unflavored was the least liked product, with 79 % of participants liking it to a lesser extent. The most-liked dry variety was dry H fruit, being "liked" to the same or to a greater extent by 34 % of the participants (Fig. 5d). Dry A unflavored was the third most-liked variety, and the only variety that more than one participant liked to a greater extent compared to their usual product of choice.

Based on product liking compared to each participant's usual product of choice, the best "liked" variety was calculated. For moist varieties, 9 (24 %) participants liked all varieties to a lesser extent, 20 (53 %) had at least one variety that they liked to the same extent, and 9 (24 %) found one or more varieties that they liked to a greater extent compared to their usual product of choice. For dry varieties, 13 (34 %) participants liked all varieties to a lesser extent, 21 (55 %) found one or more varieties that they liked to the same extent, and 4 (11 %) found at least one variety that they liked to a greater extent compared to their usual product of choice.

The highest fraction of participants "liking" a variety to the same or to a greater extent compared to their usual product of choice was 47 % and 34 % for the best-liked dry and moist varieties, respectively. Broadening the portfolios to include more than one variety of each product increased these numbers to 66 % and 76 % for dry and moist, respectively.

3.4.5. Intent to use again

All flavored moist varieties had higher median scores for the "intent to use again" parameter than moist A unflavored (Fig. 5e). The median VAS scores ranged from 48 mm (moist B fruit) to 67 mm (moist D minty) for the flavored varieties, whereas the median score for moist A unflavored was 24 mm.

As with product liking, the flavors in dry NPs had less influence on intent to use again (Fig. 5 f). The median VAS scores for NP dry varieties ranged from 25 mm (dry A unflavored and dry C traditional) to 54 mm (dry H fruit).

3.5. Adverse events

No SAEs were reported in any of the studies, and no participants were discontinued because of AEs. In the NP moist study, 25 AEs were reported, of which all but one (nausea) were assessed as unlikely related

Table 7
Summary of E_{max} and time to E_{max} for self-reported craving and satisfaction for moist and dry varieties.

NP	Craving		Satisfaction	
	E_{max} Median (Q1, Q3)	Time to E_{max} Median[a] (min, max)	E_{max} Median (Q1, Q3)	Time to E_{max} Median[a] (min, max)
Moist A unflavored	-63.5 (-81, −38)	00:15 (00:10, 00:53)	64.5 (48.5, 77)	00:15 (00:10, 00:45)
Moist B fruit	-59 (-85.5, −27)	00:15 (00:05, 00:30)	76 (61.5, 88.5)	00:12 (00:05, 00:30)
Moist C cooling	-56 (-83, −47)	00:15 (00:10, 00:45)	76 (61, 86)	00:15 (00:10, 00:45)
Moist D minty	-68 (-82, −35)	00:15 (00:05, 00:45)	81 (66, 89)	00:15 (00:05, 00:30)
Moist E minty	-68 (-83, −40)	00:15 (00:05, 00:30)	81 (73, 89)	00:15 (00:05, 00:30)
Moist F minty	-62 (-86, −46)	00:15 (00:05, 00:45)	79 (68, 89)	00:15 (00:05, 00:45)
Moist G minty	-67 (-87, −45)	00:15 (00:10, 00:30)	81 (70, 90)	00:30 (00:10, 00:45)
Moist H minty	-73 (-85, −54)	00:12 (00:05, 00:30)	80 (65, 90)	00:15 (00:10, 00:30)
Moist I minty	-73.5 (-88, −55)	00:30 (00:10, 00:45)	79.5 (70, 90)	00:15 (00:05, 00:30)
Dry A unflavored	-55 (-76, −32)	00:45 (00:10, 01:00)	73 (42,80)	00:45 (00:15, 01:00)
Dry B traditional	-53 (-77, −42)	00:30 (00:15,01:00)	75 (60, 83)	00:30 (00:10, 01:00)
Dry C traditional	-60 (-78, −40)	00:45 (00:10, 01:00)	71 (59, 82)	00:30 (00:10, 00:45)
Dry D beverage	-52.5 (-75, −30.5)	00:30 (00:10, 00:53)	71 (55.5, 79.5)	00:30 (00:15, 01:00)
Dry E beverage	-56 (-73, −38.5)	00:30 (00:10, 00:45)	73.5 (63, 81.5)	00:30 (00:10, 00:45)
Dry F fruit	-61 (-73.5, −37.5)	00:45 (00:15, 01:00)	78 (65, 90)	00:37 (00:15, 00:53)
Dry G fruit	-53 (-75, −32)	00:30 (00:10, 01:00)	76 (58, 88)	00:30 (00:15, 00:45)
Dry H fruit	-54 (-80, −40)	00:30 (00:15, 00:45)	78 (61, 85)	00:30 (00:15, 00:45)
Dry I fruit	-55 (-74, −40)	00:30 (00:10, 00:53)	73.5 (63, 83.5)	00:37 (00:15, 01:00)

[a] Time presented as (hh:mm). E_{max}, maximum effect; NP, nicotine pouch; Q, quartile.

to NP administration. In the NP dry study, 29 AEs were reported, of which 21 were assessed as unlikely related to the NPs; 5 were assessed as possibly related (2 cases of headache, abdominal distension, tachycardia, and diarrhea), and 3 were assessed as probably related (1 case of feeling hot and 2 cases of nausea) to NP administration. All AEs assessed as possibly or probably related to the NPs were mild and transient.

4. Discussion

Both clinical studies were designed to assess the effect of flavors on PK and subjective parameters using nine unflavored and flavored varieties of each product type (moist and dry) in adults who reported current, daily use of snus and/or NP. Most of the studied parameters were similar between the unflavored and flavored varieties, although subjective flavor preferences were found, highlighting the importance of offering a variety of products for individuals to choose from. To our knowledge, this is the first study to evaluate these parameters in flavored and unflavored varieties of a moist NP product. We previously published PK and PD data on unflavored NP dry products containing 3, 6, or 8 mg of nicotine per pouch, with comparisons to traditional smokeless tobacco products (Lunell et al., 2020).

Equivalence testing is a statistical method used to determine if two products are similar enough in their effects or characteristics to be considered equivalent (FDA, 2001). For moist NPs, equivalence for AUC_{inf} and C_{max} was shown for all flavored varieties compared to moist A unflavored, except for two of the minty varieties (D and H), which both demonstrated higher nicotine exposure. However, these two varieties also had the highest nicotine content, which likely contributed to these discrepancies. After adjusting for nicotine content, the AUC_{inf} for moist D minty meets the equivalence criteria (90 % CI lower bound: 1.08 90 %, CI upper bound: 1.25).

Menthol in cigarettes has been shown to not significantly affect PK parameters (Dimova et al., 2024), but it is unclear if menthol influences nicotine uptake when delivered via the oral mucosa. The moist A unflavored NP was shown to be equivalent to NP moist I minty, although the latter contains more than twice the menthol content of moist D minty and moist H minty, which fell outside of the equivalence criteria. This indicates that there is no dose-response relationship between menthol content and the parameters tested in this type of NP product.

Equivalence was shown between all flavored dry varieties compared with dry A unflavored for both AUC_{inf} and C_{max}, demonstrating that flavoring had no relevant effect on nicotine exposure or uptake in this

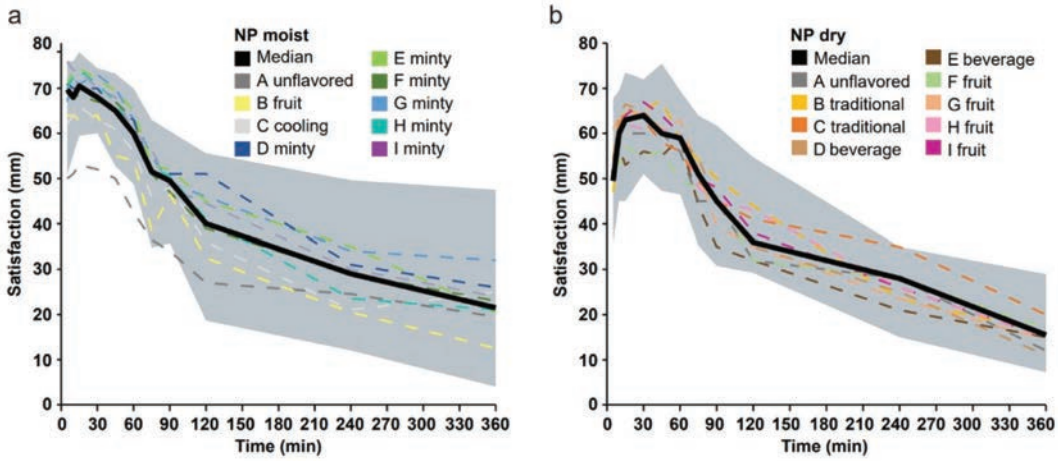

Fig. 4. Satisfaction related to moist and dry use. Satisfaction was rated using a 100-mm visual analog scale at pre-defined time points from 5 min to 360 min. The products were used for 60 min. The black lines show median satisfaction for all participants using (a) moist and (b) dry varieties. Dashed lines show median values for each variety, respectively. The gray shading depicts quartile (Q1-Q3) ranges between individuals. NP, nicotine pouch.

type of NP product. These results are in line with a previous study reporting that flavor had little effect on PK and PD parameters in varieties of the dry NP on!™ when used by individuals who smoke cigarettes daily (Rensch et al., 2021).

A study determining the PK profiles of NPs from several different manufacturers showed that the nicotine content of an NP provides limited information on its nicotine delivery in terms of C_{max} and $AUC_{0–6h}$ (McEwan et al., 2021). In line with these findings, the two product types studied herein contained 9 mg (moist) and 6 mg (dry) of nicotine and showed similar values for C_{max} and AUC_{inf}. Additionally, the extracted amount of nicotine after 60 min of usage was almost identical for both types. This suggests that other factors than nicotine content (e.g., pouch size, product matrix) affect nicotine delivery.

The present results show that flavors did not substantially influence nicotine extraction or PK parameters but are important to the participants' liking of a particular product. All varieties in both studies reduced self-reported cravings and provided satisfaction. However, great variability was observed for the subjective parameters "product liking" and "intent to use again." No product variety appealed to everyone, but each variety appealed to someone. This variability may have implications for misuse liability in two directions: greater appeal can support switching from more harmful products (Gades et al., 2022), but it may also lower barriers for nicotine-naïve individuals to initiate use.

The results should be considered in the context of their limitations. Since they are from two separate clinical studies, no direct comparisons between the moist and dry could be made. A wide array of varieties was evaluated. However, apart from the unflavored variety, no other variety was tested in both product types, and it remains unclear if flavors have different effects in moist and dry products. No dry minty variety was tested, which could have been of interest as we found a potential difference in moist minty varieties. The variation in nicotine content was larger for moist varieties than dry varieties, which may have affected the equivalence testing. Subjective effects might also be different in a real-world setting with external stimuli compared to a controlled clinical environment. Another limitation of this study is that all participants regularly used snus and/or NP products. No comparator group of people who smoke cigarettes , use other nicotine products, or nicotine-naïve individuals was included. As the experience of people using the product can influence both mucosal absorption efficiency and subjective responses (e.g., craving, satisfaction), the findings may not fully reflect the variability expected in broader populations. This limits the generalizability of the results to individuals considering switching from other nicotine products or initiating use.

5. Conclusions

To our knowledge, these are the first studies to compare the effects of unflavored and flavored varieties on nicotine PK, subjective parameters, and nicotine extraction in dry and moist NPs. In general, flavors did not have a substantial effect on nicotine extraction or uptake in either product type for most of the products tested, but they were important for subjective parameters such as product liking. The unflavored and flavored varieties reduced craving in both studies, but the variation in participant preferences supports the need for a diverse NP portfolio.

CRediT authorship contribution statement

Anna E. Masser: Writing – review & editing, Writing – original draft, Visualization. **Camilla Pramfalk:** Writing – review & editing, Project administration. **Robert Pendrill:** Writing – review & editing, Formal analysis. **Sara Moses:** Writing – review & editing. **Johan Lindholm:** Writing – review & editing, Conceptualization. **Tryggve Ljung:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Mikael Staaf:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Informed consent statement

Written informed consent was obtained from all participants.

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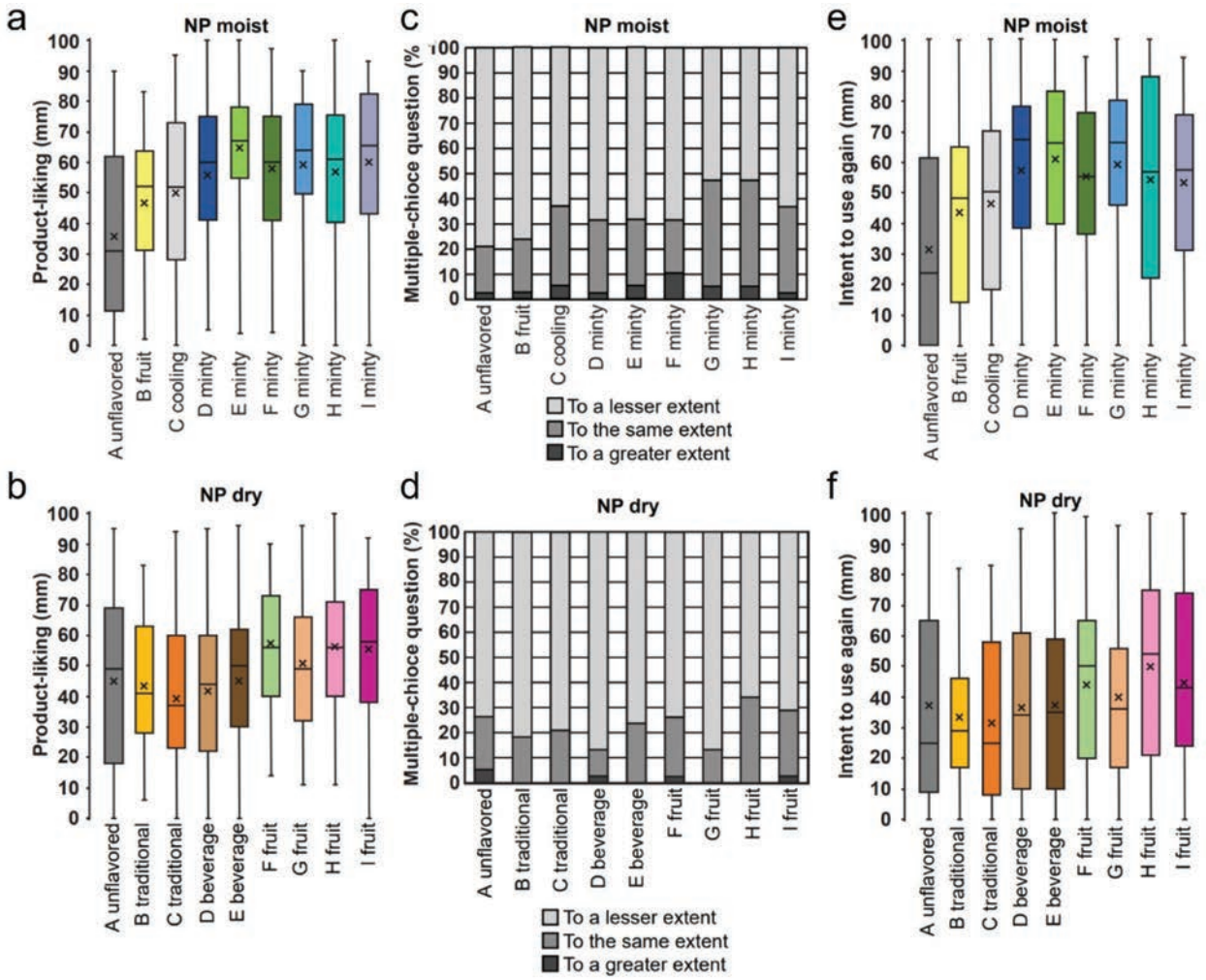

Fig. 5. "Product liking" and "intent to use again" for moist and dry varieties. Product liking was rated using a 100-mm VAS (a-b). After NP use, participants were asked if they liked the variety "to a lesser extent," "to the same extent," or "to a greater extent" compared to their usual product of choice (c-d). Intent to use again was rated using a 100-mm VAS (e-f). Boxes show interquartile ranges with a median line and an "X" indicating the mean. Whiskers show minimum and maximum values. NP, nicotine pouch; VAS, visual analog scale.

Institutional Review Board Statement

Both studies were conducted in accordance with the Declaration of Helsinki and its later amendments. Study ISRCTN66329631 was approved by the Swedish Ethical Review Authority (approval number 2020–06740, 13 January 2021). Study ISRCTN91637022 was approved by the Swedish Ethical Review Authority (approval number 2021–05945–01, 29 November 2021).

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: All authors are employees of Swedish Match AB (a subsidiary of Philip Morris International), which markets the nicotine pouch products described in the article. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2026.113050.

Data Availability

The data presented herein are available upon request from the corresponding author.

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