

Evaluating Intra- and Inter-Brand Nicotine Dissolution Profiles in Nicotine Pouches

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- Nicotine release rate appeared to be largely brand-specific, with strength and flavor showing little effect on dissolution kinetics.
- Differences tracked more closely with inter-brand variation in product design and formulation.

INTRODUCTION

- Nicotine pouches are smoke-free, tobacco leaf-free oral products that deliver nicotine through oral mucosal absorption and are rapidly growing in popularity among adult tobacco users.
- These products typically contain tobacco-derived or synthetic nicotine, flavorings, and fillers enclosed within a permeable pouch that enables nicotine and flavor release.
- Characterizing nicotine dissolution-release profiles is essential for product development, formulation optimization, quality assessment, manufacturing consistency, and product-to-product comparisons.
- Dissolution testing is an important regulatory tool and can provide supporting evidence for FDA evaluations, including Substantial Equivalence (SE) and Premarket Tobacco Product Applications (PMTA).
- A validated USP-4 flow-through cell dissolution method has been shown to effectively differentiate and compare nicotine release profiles across oral nicotine products and nicotine pouch brands.

AIMS

- Characterize nicotine dissolution-release profiles across a broad market sample of nearly 100 nicotine pouch products representing 21 commercial brands.
- Evaluate the impact of nicotine level and flavor variants on nicotine release behavior within individual brands.
- Assess dissolution profile equivalency using FDA-recommended difference (f1) and similarity (f2) factors.
- Compare nicotine release profiles between brands to identify similarities and differences in release kinetics.
- Investigate the role of product design and formulation attributes in driving nicotine release behavior across nicotine pouch products.

METHODS

- Products evaluated: 97 commercial nicotine pouch products representing 21 brands, encompassing a wide range of nicotine strengths and flavor variants.
- Dissolution testing: Nicotine release was assessed using a validated USP-4 flow-through cell dissolution method with artificial saliva at $37 \pm 0.5^\circ\text{C}$ and a flow rate of 4 mL/min.
- Experimental design: Twelve replicates were analyzed per product, and dissolution profiles were generated over 60 minutes with nine collection time points.
- Nicotine quantification: Nicotine concentrations were measured using UPLC-PDA, and cumulative nicotine release was calculated as mg/pouch and normalized to percent of total nicotine released.
- Profile comparison: Brand-specific reference profiles were generated by averaging normalized dissolution profiles across all products within each brand. Individual product profiles were then compared against the corresponding brand reference profile using the difference factor (f1) and similarity factor (f2). Profile equivalence was established when predefined acceptance criteria were met ($f1 \leq 15$ and $f2 \geq 50$).

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CONCLUSIONS

- Nicotine dissolution-release profiles were equivalent within individual brands, regardless of nicotine strength or flavor variant, as demonstrated by FDA equivalency criteria ($f1 \leq 15$ and $f2 \geq 50$).
- Nicotine level and flavor did not alter the intrinsic release kinetics of nicotine pouches within a given brand.
- Distinct differences in nicotine release profiles were observed between brands, indicating that release behavior is brand-dependent.
- Product design and formulation characteristics — rather than nicotine content or flavor alone — appear to be important drivers of nicotine release dynamics.
- Brand-specific nicotine release signatures may serve as valuable benchmarks for product development, quality assurance, lifecycle management, and regulatory product-to-product comparisons.

RESULTS

Table 1. List of all analyzed nicotine pouch products, detailing for each: the brand name, flavor variant, nicotine level, the percentage of nicotine released from label claim after 60 minutes of dissolution, and the calculated f1 and f2 values based on the brand's average percent of total nicotine dissolution release profile as a reference.

Brand	Flavor	Nicotine Level (mg/Pouch)	% Nicotine Released in 60 min	f1 (vs. Brand Average)	f2 (vs. Brand Average)
Brand-A	Glacier Mint	8	40 ± 3.7	2.11	89.09
	Very Berry	8	43 ± 4.1	2.11	89.09
	Chilled Mint	3	74 ± 7.1	6.55	69.64
	Chilled Mint	6	62 ± 2.7	0.98	95.82
	Chilled Mint	9	66 ± 5.2	0.98	96.72
Brand-B	Mountain Wintergreen	3	66 ± 1.4	3.82	80.44
	Mountain Wintergreen	6	63 ± 6.2	1.12	95.77
	Refreshing Chill	3	66 ± 6.0	0.3	99.44
	Refreshing Chill	9	61 ± 2.1	1.44	92.73
	Tropical Fruit	3	70 ± 4.7	2.51	84.7
Brand-C	Tropical Fruit	9	56 ± 1.0	3.04	84.38
	Lush	9	64 ± 5.6	4.58	76.25
	Mint	6	70 ± 6.1	1.25	94.32
	Mint	9	57 ± 6.3	1.85	92.62
	Mint	15	76 ± 4.9	7.28	66.79
Brand-D	Wintergreen	9	63 ± 3.3	2.3	87.91
	Ice Mint Strong	11.2	58 ± 2.5	0.92	96.45
	Ice Mint Super Strong	17.5	78 ± 5.8	5.68	72.85
	Sally Raspberry	4	78 ± 2.8	4.76	75.64
	Mint	9	62 ± 5.6	7.21	66.11
Brand-E	Mint	12	58 ± 2.9	4.58	75.89
	Peppermint	7	92 ± 9.2	6.51	70.09
	Spearmint	7	81 ± 15.9	8.15	67.6
	Wintergreen	7	77 ± 1.7	2.89	82.74
	Extra Extra Strong	15	93 ± 5.7	2.53	84.06
Brand-F	Extra Strong	11.55	89 ± 0.5	2.53	84.06
	Raspberry Lemonade Mint	6	122 ± 1.2	3.25	83.63
	Raspberry Lemonade Mint	12	106 ± 1.4	3.25	83.63
	Mint Mania	9	38 ± 1.8	2.14	90.89
	Smooth Mint	9.4	45 ± 0.6	2.14	90.89
Brand-G	Freeze X-Strong	11.2	41 ± 0.0	2.32	87.77
	Ice Cool	10	67 ± 0.0	1.59	91.41
	Mint	6	55 ± 0.0	0.63	98.33
	Cool Mint Moist	9.6	89 ± 0.3	1.02	96.85
	Dragonfruit Moist	8.9	95 ± 1.0	1.02	96.85
Brand-H	Cinnamon	2	101 ± 2.7	1.39	93.05
	Cinnamon	4	95 ± 2.8	8.19	62.95
	Cinnamon	8	93 ± 5.2	11.72	56.38
	Citrus	2	92 ± 2.4	7.51	64.78
	Citrus	4	91 ± 3.0	1.9	88.4
Brand-I	Citrus	8	94 ± 2.7	8.58	58.52
	Mint	2	94 ± 2.1	3.34	80.74
	Mint	4	95 ± 2.1	2.67	84.21
	Mint	8	99 ± 2.4	2.38	85.44
	Original	2	94 ± 3.1	6.35	68.75
Brand-K	Original	4	97 ± 3.8	5.2	74.15
	Original	8	98 ± 2.1	6.05	67.76
	Wintergreen	2	93 ± 1.7	3.45	79.48
	Wintergreen	4	102 ± 2.8	8.64	62.73
	Wintergreen	8	102 ± 2.9	2.06	89.5
Brand-L	Wintergreen	6	72 ± 3.3	99.65	99.65
	Mint	9	74 ± 5.5	1.29	95.7
	Mint	12	71 ± 3.7	1.43	93.77
	Tobacco	6	62 ± 2.4	1.24	95.67
	Tobacco	9	71 ± 3.2	2.42	88.19
Brand-M	Wintergreen	12	77 ± 2.8	6.47	72.1
	Wintergreen	6	77 ± 2.6	1.37	94.91
	Wintergreen	9	74 ± 3.2	2.08	90.9
	Wintergreen	12	76 ± 3.6	0.16	99.85
	Wintergreen	3	71 ± 1.6	4.77	77.31
Brand-N	Wintergreen	6	75 ± 2.9	4.77	77.31
	Mango	3	69 ± 2.3	11.07	56.93
	Mango	6	54 ± 3.8	2.15	87.34
	Peppermint	6	46 ± 1.8	7.22	65.71
	Spearmint	6	74 ± 5.0	5.42	67.96
Brand-O	Wintergreen	3	53 ± 0.9	5.01	73.97
	Classic	8	78 ± 0.0	4.18	76.07
	True North	10	56 ± 0.0	4.46	76.16
	True North	11	60 ± 0.0	1.59	91.85
	Virginia Classic	6	70 ± 0.0	7.53	65.06
Brand-P	Freezing Peppermint	10.9	62 ± 2.7	3.84	81.25
	Freezing Peppermint	14	75 ± 1.4	77.52	81.25
	Freezing Peppermint	17	68 ± 0.9	1.16	95.96
	Wintergreen	7	82 ± 0.8	3.77	77.11
	Citrus Chill	6	50 ± 3.2	3.02	85.74
Brand-Q	Dragonfruit	6	58 ± 1.6	8.94	65.19
	Mint	9	52 ± 2.1	4.06	78.79
	Peppermint	6	63 ± 4.3	3.14	84.72
	Peppermint	9	48 ± 4.2	2.67	85.01
	Spearmint	6	63 ± 3.1	2.42	86.3
Brand-R	Wild Berry	6	54 ± 3.6	5.68	73.72
	Wintergreen	6	60 ± 1.4	2.77	86.98
	Wintergreen	9	58 ± 1.3	3.04	85.02
	Black	20	55 ± 1.3	2.66	87.95
	Tell Charge	18	48 ± 2.9	2.66	87.95
Brand-S	Berry Moonlight	9	28 ± 2.5	1.59	92.55
	Watermelon Wave	9	39 ± 5.6	1.59	92.55
	Black Cherry	6	100 ± 2.9	8.83	62.26
	Citrus	6	99 ± 2.3	8.26	62.45
	Coffee	3	104 ± 3.5	7.42	65.14
Brand-T	Coffee	6	95 ± 1.0	10.45	56.97
	Cool Mint	3	96 ± 2.1	5.62	68.46
	Cool Mint	6	100 ± 3.1	2.9	82.15
	Wintergreen	6	103 ± 2.2	0.8	97.36
	Wintergreen	6	95 ± 1.5	4.99	73.12
Brand-U	Cool Mint	9	65 ± 2.2	5.29	73.14
	Ice Mint	9.5	72 ± 4.6	6.29	71.98

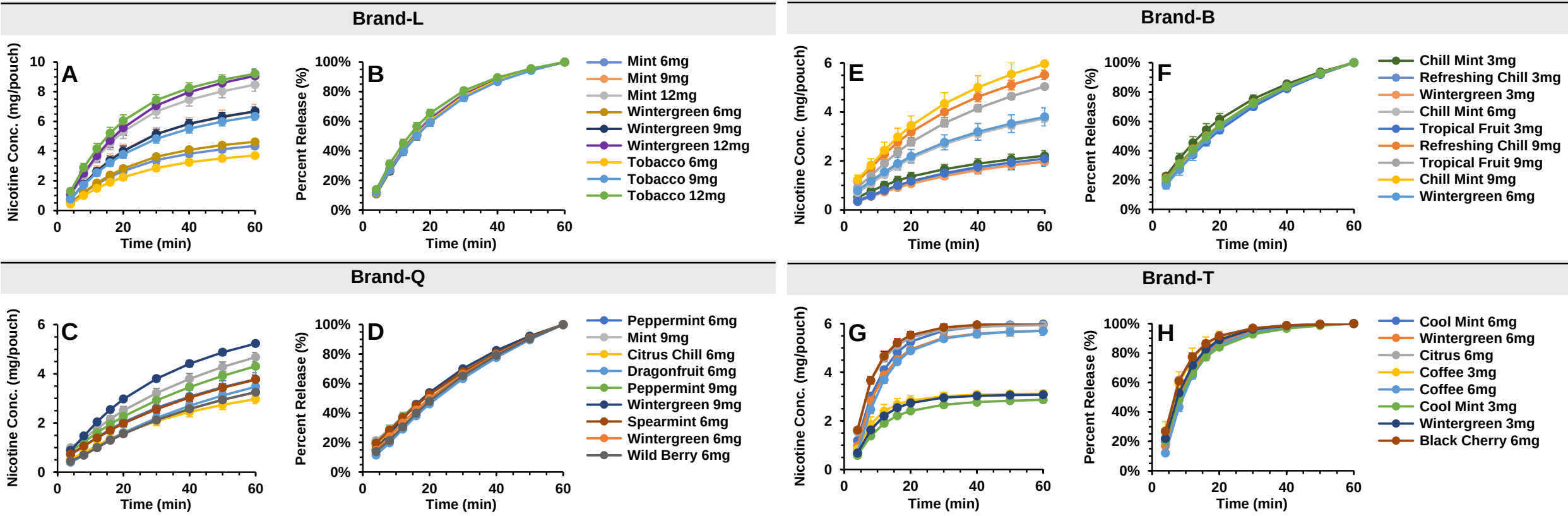


Figure 1. Nicotine dissolution-release profiles for representative nicotine pouch brands. While cumulative nicotine release increased with nicotine strength, normalized release profiles overlapped across nicotine strengths and flavors within each brand, indicating equivalent release kinetics. Data are presented as mean $\pm$ SD (n = 12).

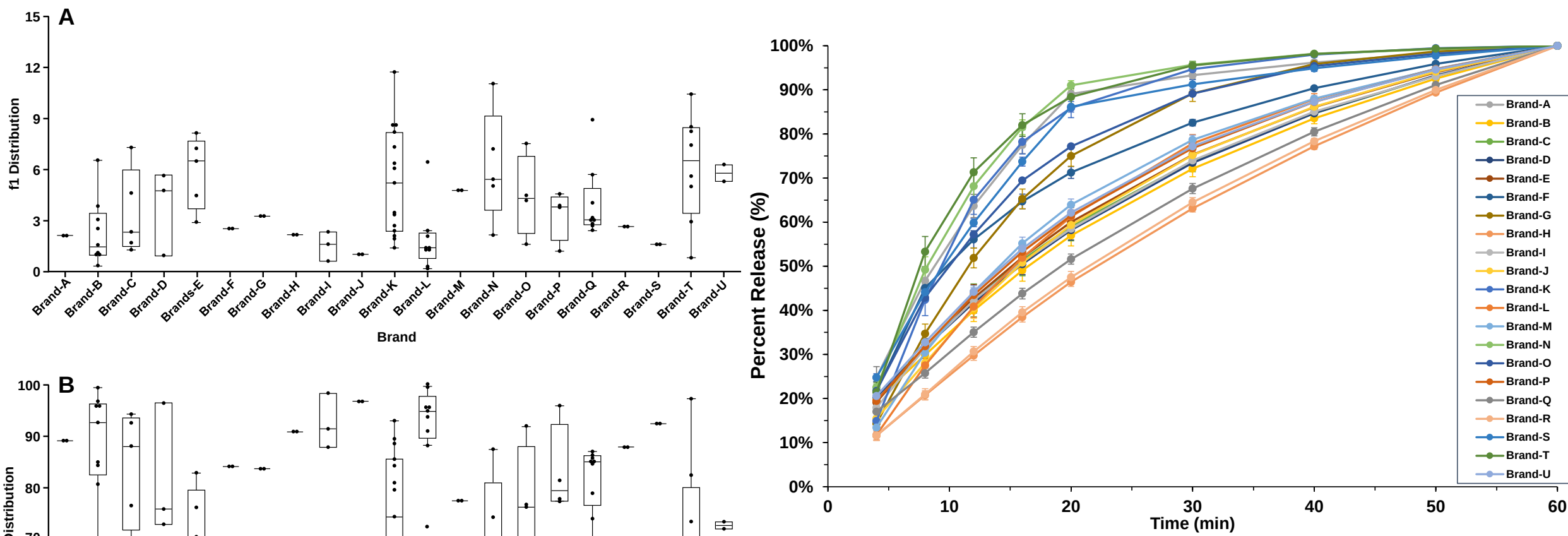


Figure 2. Box and whisker plots of the calculated (A) Difference (f1) and (B) Similarity (f2) factor for nicotine dissolution profiles across select 21 nicotine pouch brands.

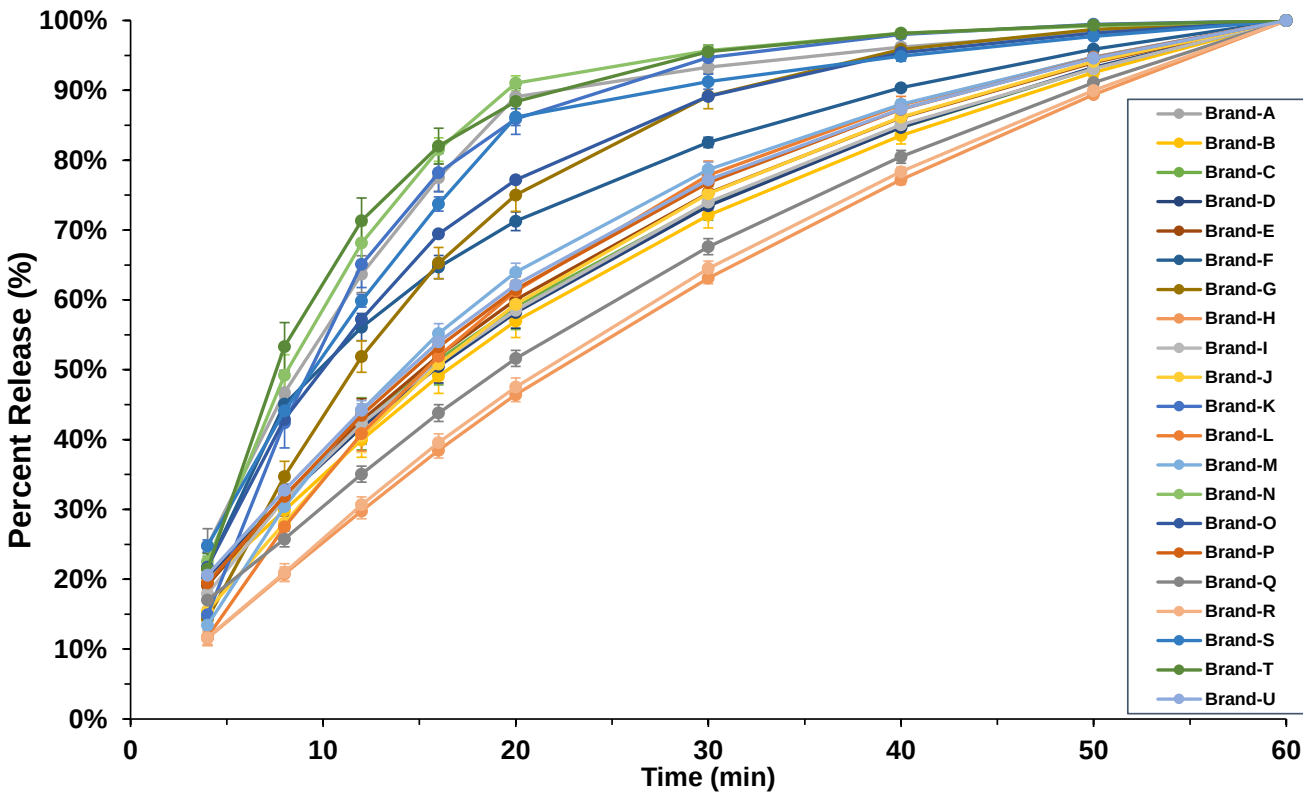


Figure 3. Percent of total dissolution nicotine release profiles of all 21 nicotine pouch brands. Each curve represents the averaged percent of total nicotine release of all products tested within each brand over 60 minutes of dissolution. Results are reported as mean $\pm$ standard deviation (n = 12).

