Science Journal of Analytical Chemistry
2022; 10(3): 32-39
http://www.sciencepublishinggroup.com/j/sjac
doi: 10.11648/j.sjac.20221003.11
ISSN: 2376-8045 (Print); ISSN: 2376-8053 (Online)

Nicotine Gums Mastication: Method Development and Product Comparisons

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To cite this article:
Fadi Aldeek, Vanessa Lopez, John H. Miller, Feng Gao. Nicotine Gums Mastication: Method Development and Product Comparisons. *Science Journal of Analytical Chemistry*. Vol. 10, No. 3, 2022, pp. 32-39. doi: 10.11648/j.sjac.20221003.11

Received: June 13, 2022; **Accepted**: June 28, 2022; **Published**: July 5, 2022

Abstract: Nicotine gums are a class of oral tobacco products that are tobacco-leaf free and come in a variety of flavors and different nicotine strengths. The release of nicotine from these gums is mainly triggered by a chewing process to create new surfaces for the continuous release of nicotine. The rate of nicotine release from these products strongly depends on the nicotine form, product physicochemical characteristics, and mastication parameters used to chew the products. In this work, we developed a discriminatory mastication method to study the release of nicotine from a variety of nicotine gum products using the European Pharmacopoeia (Ch. 2. 9. 25, apparatus B), DRT3 chewing apparatus. Mastication parameters including chewing stroke frequency and jaw gapping distance were systematically investigated. The optimized mastication method was used to characterize the release profiles of nicotine from three commercially available nicotine gum products, including Nicorette, Lucy, and Rogue gums. The cumulative percent nicotine release rates were found to be dependent on the product characteristics, showing differences when comparing Rogue to Lucy and Nicorette gums, and similarities when comparing Nicorette to Lucy gum products. Furthermore, the nicotine release profiles obtained from the same product brand at different nicotine strengths and flavors were found to be equivalent. These observations were further confirmed by analyzing the nicotine release profiles to calculate the difference factor (f_1) and similarity factor (f_2). The developed mastication method can be used as an important tool for product-to-product comparison, guiding product design, determining relative product performance, ensuring consistency during the manufacturing process, and supporting regulatory reporting.

Keywords: Nicotine Gums, Mastication, UPLC-PDA, Nicotine Release Rates, Method Development

1. Introduction

In recent years, oral tobacco-derived nicotine (OTDN) chewing gums have emerged as a new oral tobacco product category [1]. They are available in a variety of flavors at various nicotine strengths and do not contain cut or ground tobacco leaf. They are typically made with gum based with elastomers, sugar alcohol, and coating. The use of these OTDN gums is considered by many to have potentially reduced risk of harm compared to smoking cigarettes [2-4]. These products provide adult smokers who are unable or unwilling to stop smoking with a reduced risk alternative. Currently, there are several OTDN gum products commercialized under different brand names such as Lucy and Rogue [1, 5-8]. Although the intent of use is not the same, the use patterns of these OTDN gums are similar to nicotine replacement therapy (NRT) gums (e.g., Nicorette) [9]. They rely on a process called chew and park, allowing the release of nicotine from the gum and absorption by the oral mucosa [10].

The performance of these products strongly depends on the rate at which nicotine solubilizes into saliva, while they are masticated. Although commercially available mastication apparatuses do not mimic the likely experience of users, they do provide consistent release of active ingredients under the same laboratory conditions, which allows for comparison of nicotine release across products. These apparatuses can only model the nicotine dissolution release from these products and are not necessarily predictive of human exposure and absorption of active ingredients into the blood stream.

To date, standardized mastication methods for

reproducible generation of nicotine from nicotine gum products for product-to-product comparisons have still not been established. The European Pharmacopoeia describes two different mastication instruments to study the dissolution release profile of active ingredients from chewing gums [11]. However, no such methods exist in the United State Pharmacopeia (USP) [12, 13].

The two instruments described in European Pharmacopoeia are referred to as Apparatus A and Apparatus B. Apparatus A consists of a non-transparent metal chamber, two horizontal oscillatory testing device pistons to simulate mastication, and one vertical piston to keep the chewing gum in place during release testing. Apparatus B consists of a double walled glass chamber, including one vertical oscillatory piston and one stationary rotating piston with removable chewing jaws [11, 14, 15]. Unlike Apparatus A, Apparatus B is commercially available and commonly used by many laboratories [16].

Most mastication methods described in the literature have been used to study the *in vitro* release profile of nicotine from NRT gums [17]. For example, Morjaria and co-workers have compared the release of nicotine from two compressible gum formulations and a commercial NRT gum (Nicorette 4 mg) product using the European Pharmacopoeia Apparatus A [18]. The compressible gum formulations exhibited nicotine release profiles which were similar to each other but demonstrated a more rapid release of nicotine compared to the Nicorette gum products. Gajendran and co-workers have studied several of the mastication parameters that could be modified to optimize the nicotine release profiles for two NRT gums using the European Pharmacopoeia Apparatus B [19]. Faster nicotine release was observed when the mastication frequency increased from 40 to 60 strokes per minute and the amount of nicotine released was a function of the number of strokes. In addition, a faster release profile was correlated with decreased jaw gapping distance. Berglund and co-workers reported on the development of a mastication method using the European Pharmacopoeia, Apparatus B, to study the dissolution of nicotine from NRT gums, Nicorette 2 mg Classic and Nicotinell 2 mg [20]. In this report, multiple mastication settings were evaluated for their effects on the release profile of nicotine from these commercial NRT gums. They determined that the stroke frequency, distance between the chewing surfaces, and mastication twist angles influenced the rate of nicotine release. The authors demonstrated that the release profiles from these two commercially available NRT products were similar using their optimized parameters [20].

No international standardized mastication method has been established for controlled release tests of nicotine gums. In addition, methods that have been used to study the mastication release profile of nicotine for comparison of the recently marketed oral tobacco-derived nicotine (OTDN) gums are not well-known. A recent memo from the Food and Drug Administration Center for Tobacco Products (FDA/CTP) presented an excellent discussion on the background and framework for how dissolution methodologies can be employed for comparing the performance of oral tobacco products to demonstrate similarities or differences [21]. In this memo, Apparatus B from the European Pharmacopoeia was recommended to provide acceptable mastication results for nicotine gum products. However, the FDA did not provide guidelines on dissolution testing of nicotine gum products using this apparatus. The FDA stated that dissolution methods are generally developed by the manufacturers in pharmaceutical applications and the applicability and validity of the methods is evaluated as part of the application process FDA [21].

The objective of this work is to provide a comprehensive evaluation of the mastication parameters of the European Pharmacopoeia (Ch. 2. 9. 25, Apparatus B), DRT3 chewing apparatus using OTDN gum products, that would allow for reproducible product-to-product comparisons. We evaluated three nicotine gum products and demonstrated the performance of our method to discriminate between the release of nicotine from these products. We also presented a sensitive Ultra Performance Liquid Chromatography coupled to Photodiode-Array detector (UPLC-PDA) method for the accurate quantitation of nicotine released from these products into artificial saliva. We characterized and compared the mastication release of nicotine from commercially available NRT (Nicorette) and OTDN (Lucy and Rogue) gums using the optimized methodology. The nicotine release profiles were further analyzed by calculating the difference factor (f_1) and similarity factor (f_2) [22]. Furthermore, we evaluated the nicotine release profiles from OTDN gum products with different flavor variants and nicotine levels. The proposed mastication and analytical methods described herein are valuable for the scientific community and regulatory agencies to reproducibly measure and compare the release rate of nicotine and other constituents from gum products.

2. Materials and Methods

2.1. Reagents

Optima grade methanol, water, acetonitrile, ACS grade potassium hydrogen phosphate anhydrous (K_2HPO_4), sodium chloride (anhydrous), calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$), potassium chloride (anhydrous), potassium carbonate (anhydrous), magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$), hydrochloric acid, 5N sodium hydroxide solution, and caffeine (98.5+%) internal standard were purchased from Acros Organics (Geel, Belgium). 6N Ammonium Hydroxide was acquired from Ricca chemicals, (Pocomoke, MD), and 1M Acetic Acid was procured from Fluka Analytical (Pittsburgh, PA). ISO 17034 certified nicotine solution (10 mg/mL) was purchased from Restek Corporation (Bellfonte, PA).

2.2. Instrumentation

The mastication of gums was performed using the European Pharmacopoeia (Ch. 2. 9. 25, apparatus B), DRT3 chewing apparatus [23]. The mechanical jaw gapping distance was set at 1.4 mm with a chewing frequency of 60 strokes per minute

and a 20° twisting angle of rotation. Three 60 mL glass cuvette chewing cells were used for each of the chewing pistons. The DRT3 chewing apparatus was purchased from AB FIA (Vinkelhaken, SÖDRA SANDBY). The quantitation of nicotine in all samples was performed using a Waters (Milford, MA) Acquity I-Class UPLC-PDA. The UPLC was equipped with a binary solvent manager, temperature-controlled autosampler, temperature-controlled column compartment, Waters BEH C18 analytical column (2.1 x 100 mm, 1.7 µm), and Waters BEH C18 VanGuard pre-column (2.1 x 5 mm, 1.7 µm).

2.3. Artificial Saliva Preparation

The artificial saliva was prepared according to the method described in the German Institute for Standardization (DIN) Recipe listed in the German standard DIN V Test Method 53160-1 2002-10 [23]. Briefly, the pH of 1 L of deionized (DI) water was first lowered to pH 2.5 by adding 2 mL of concentrated hydrochloric acid. The artificial saliva solution was then prepared by dissolving 0.68 g of potassium hydrogen phosphate anhydrous (K_2HPO_4), 0.33 g of sodium chloride (anhydrous), 0.15 g of calcium chloride dihydrate ($CaCl_2 \cdot 2H_2O$), 0.75 g potassium chloride (anhydrous), 0.53 g of potassium carbonate (anhydrous), and 0.17 g of magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$) in the acidified DI water. If needed, the pH of the solution was further adjusted to 6.8 ± 0.1 using small incremental additions of 5N sodium hydroxide.

2.4. DRT3 Chewing Apparatus Fraction Collection

The DRT3 Chewing Apparatus consists of three chewing chambers containing pistons with metallic jaws, and a gas manifold for modifying chewing frequency [16]. The temperature was regulated at 37 ± 0.5°C within each cell via water bath coupled to the outer cell walls. A steady flow of water was pumped around the exterior of the cell, simulating the *in vitro* temperature of the artificial saliva gum matrix. Forty milliliter (40 mL) of artificial saliva was added to each cell prior to mastication. Plastic netting was placed above and below each gum to prevent sticking to the jaws and to prevent the analyzed gums from breaking apart. A 10.0 mL fraction was collected manually at 2, 5, 10, 15, 20, 30, 40, 50 and 60 minutes which was then replaced with equal volume of fresh artificial after each fraction collection.

The nine fractions were used to calculate the nicotine release profiles for each of the masticated gums.

2.5. UPLC Solutions Preparation

The aqueous mobile phase (10 mM ammonium acetate) solution was prepared by mixing 10 mL of 1M acetic acid with 900 mL of DI water and 13 mL of 6N ammonium hydroxide, and the pH was adjusted to 10 ± 0.1. The needle wash solution was made by combining 950 mL of acetonitrile with 50 mL of DI water in a 1 L solvent bottle. The seal wash solution was prepared by combining 900 mL of DI water with 100 mL methanol in a 1 L solvent bottle.

2.6. Preparation of Calibration Standards

The nicotine calibration standards of 10 mL volume were prepared in six volumetric flasks. To prepare each level of the calibration curve, 1.0 mL of caffeine internal standard stock solution (0.15 mg/mL) was first added to the six volumetric flasks, followed by the addition of 0.01, 0.04, 0.2, 0.4, 1.0, and 2.0 mL of intermediate nicotine standard solution (0.5 mg/mL). Each flask was then diluted to 10 mL with an acetonitrile/water (10:90, v/v) solution, resulting in final concentrations of 0.5, 2.0, 10.0, 20.0, 50.0, and 100.0 µg/mL for each calibration standard.

2.7. Fraction Preparation for Analysis

Upon collection of all nine fractions, 0.9 mL of each fraction was added to an autosampler vial. This was followed by the addition of 0.1 mL of internal standard (0.15 mg/mL) and mixed via vortex. The resulting final concentration of caffeine internal standard in all sample fractions and calibration curve standards was 15 µg/mL.

2.8. UPLC-PDA Method for the Quantitation of Nicotine

The UPLC-PDA instrument included a Waters Acquity I-Class UPLC system coupled to a photodiode array detector. The optimized detector parameters included the sampling rate (20 points/seconds), scan range (250-410 nm), and resolution (4.8 nm). Chromatographic separation of nicotine and the caffeine internal standard was achieved using a Waters Acquity C18 column (100 mm × 2.1 mm i.d., 1.7 µm). The mobile phase eluents were 10 mM ammonium acetate buffer (pH 10) and acetonitrile, with a flow rate of 0.5 mL/minute (min) during the 8 min runtime. The elution initial composition was maintained for 4 min at 98% buffer and 2% acetonitrile, changing by linear gradient to 30% acetonitrile over the course of 1 min. The acetonitrile was then increased to 75% over a 0.2 min period and held constant for 1.3 min. The eluents were then returned to the original condition of 2% acetonitrile to allow re-equilibration of the system. The column and autosampler temperatures were maintained at 45 (±1)°C and 5 (±1)°C, respectively, and the standards and samples injection volume was 5 µL.

2.9. Nicotine Quantitation

The quantitation method was set to perform a linear calibration ($y = mx + b$) with the origin excluded and a weighting factor of 1/x, where y is the response factor (RF) relative to the internal standard and x is the concentration (µg/mL) of the standards. MassLynx V4.1 (Waters Corporation; Milford, MA) software was used to integrate the standards chromatograms and generate the corresponding calibration curve for nicotine. The concentration of nicotine in the masticated fractions (µg/mL) was determined using the calculated RF of the sample, slope, and intercept obtained from the calibration equation. The % of nicotine released was calculated by considering the theoretical and experimental weights of the gum product, fraction volume, and

concentration of nicotine labeled on the products.

2.10. Test Products and F1 and F2 Calculations

The products used in this study including, Nicorette Spearmint 4 mg, Lucy Wintergreen and Fruit Medley 4 mg, Rogue Wintergreen and Spearmint, both at 2- and 4-mg were purchased from retail stores.

The difference factor (f_1) and similarity factor (f_2) were calculated mathematically using three replicates per sample by the following equations [21, 22, 24, 25]:

$$f_2 = 50 \cdot \log\left[\frac{100}{\sqrt{1 + \frac{\sum_{t=1}^{t=n}[Rt - Tt]^2}{n}}}\right]$$

$$f_1 = \left\{\left[\sum_{t=1}^{n}|R - T|\right] / \left[\sum_{t=1}^{n} R\right]\right\} \text{ X } 100$$

R_t and T_t are the cumulative percentage dissolved at each of the selected n time points of the two products (R = reference product and T = test product). The factor f_1 is proportional to the average difference between the two profiles, whereas factor f_2 is inversely proportional to the average squared difference between the two profiles, with emphasis on the larger difference among all the time points. The dissolution measurements of the two products should also be made under identical test conditions. For curves (kinetic release profiles) to be considered equivalent, f_1 values should be close to 0 and f_2 values should be close to 100. Generally, f_1 values up to 15 (0-15) and f_2 values of 50 or greater (50-100) demonstrate equivalence of the two curves reflecting similar performance of the two products.

3. Results and Discussion

The European Pharmacopoeia specifies chewing gums as a solid with a base consisting mainly of gum, that are intended to be chewed but not swallowed [26]. Compared to other solid dosage forms, the release of nicotine from chewing gums is mainly triggered by users while chewing, and there is the opportunity to terminate delivery by removing the gum from the oral cavity. Unlike other forms of innovative, non-combustible OTDN products such as lozenges, tablets, and nicotine pouches with a spontaneous dissolution [22, 27], a mastication process is mainly needed to create new surfaces for the release of nicotine from gums and is required for continuous nicotine release from OTDN gum. Therefore, developing discriminatory mastication methods to study the release of nicotine from OTDN gum products is needed as an important tool for guiding product design, determining relative product performance, ensuring consistency during the manufacturing process, enabling regulatory reporting, and product comparisons.

Development of mastication test methods is complex because the parameters to be optimized are not just for the dissolution test procedure itself, but also for the analytical assays used to quantify the test results. Currently there is no recognized method to study the dissolution release from nicotine gum products. Herein, we discuss a systematic approach to develop a mastication test method and its applicability for evaluating the rate of nicotine release from NRT and OTDN gum products. We further discuss approaches for product-to-product comparison.

3.1. UPLC-PDA Method

We have used UPLC-PDA for the identification and quantitation of nicotine in collected fractions. We used an aqueous mobile phase containing 10 mM ammonium acetate (pH 10) to optimize the retention of nicotine on a reversed-phase LC column. Figure 1 depicts the LC chromatograms of nicotine and caffeine internal standard obtained in the presence of a Nicorette Spearmint 4 mg extract in fraction 1. Retention times of 4.51- and 3.03-min were obtained for nicotine and caffeine, respectively.

3.2. Mastication Method Development

Nicorette gum products were used for optimizing the parameters of the mastication method to reach the highest amount of nicotine that could potentially be released from the product. In this study, we used the European Pharmacopoeia (Ch. 2. 9. 25, apparatus B), DRT3 chewing apparatus [16]. The influence of various chewing stroke frequency and jaw gapping distance parameters on the nicotine release profile were systematically investigated. Figure 2 shows the release profile of nicotine when increasing the mastication stroke frequency from 40, 50, to 60 stroke per minute while maintaining the 1.4 mm jaw gapping distance, 40 mL artificial saliva volume, and 20° twisting angle. The fastest release profile was obtained with increased stroke frequency. A total of 32%, 47%, and 82% of the labeled amount of nicotine was released from the tested gum when the stroke frequency was increased from 40, 50, to 60 strokes per minute, respectively. Figure 3 compares the nicotine release profiles obtained by varying the jaw gapping distance from 2.5, 1.8, 1.6, to 1.4 mm while maintaining the 60 strokes per minute frequency, 40 mL artificial saliva volume, and 20° twisting angle. A higher release was revealed with decreased jaw gapping distance. A total of 16%, 28%, 47%, and 82% of the labeled amount of nicotine was released from the tested gum when the jaw gapping distance was decreased from 2.5, 1.8, 1.6, to 1.4 mm, respectively. Figure 4 shows an image of the gums after they have been masticated. The effect of decreasing the jaw gapping distance could be explained by the shape of the gums after mastication. Similar observations were seen in previous reports when changing these parameters to study the nicotine release profile from Nicorette NRT gums [14, 18, 19]. The optimized parameters used for the evaluation of the gum products in this study were found to be: 1.4 mm jaw gapping distance, 60 strokes per minute, 40 mL artificial saliva volume, and 20° twisting angle (the temperature was always maintained at 37 ± 0.5°C).

3.3. Product-to-Product Comparisons

To show the applicability of the method to discriminate or show similarities between gum products, we investigated the release profiles of nicotine from two OTDN gum products, Lucy and Rogue, with different flavor variants and nicotine strengths, in addition to Nicorette Spearmint 4 mg, NRT gum, under the same laboratory conditions. The mastication of these gums was performed in triplicate (n=3) using the three independent cells integrated within the DRT3 apparatus for each gum brand. All three replicates were averaged for each fraction. Figure 5 shows the cumulative percent nicotine released for Nicorette Spearmint 4 mg, Lucy Wintergreen 4 mg, and Rogue Wintergreen 4 mg over time (60 min) in each collected fraction from fractions one through nine. The gum weights for each gum product are 1.25 g, 1.35 g, and 1.8 g for Nicorette, Lucy, and Rogue products, respectively.

Distinct release profiles were obtained for the studied gums. While the fastest release of nicotine was observed for Rogue OTDN gum, the slowest release rate was seen for Nicorette NRT gum. The nicotine release profile obtained from Lucy OTDN gum was slightly faster than the one obtained from Nicorette gum but considerably slower than the release profile of nicotine from Rogue gum. The region between zero and 10 minutes shows the fastest release rate for all products with a percent release of 45%, 59%, and 73%, for Nicorette, Lucy, and Rogue gum products, respectively. The maximum amount of nicotine released from the gums was achieved within 20 min before the dissolution profiles reached a plateau. Overall, 78-82% of the labeled amount of nicotine was released from these three gums under optimized laboratory conditions and over the 60 min experiment timeframe. Lower than 5% variability was obtained from the three replicates analyzed for each gum and in each fraction time point, indicating a high degree of reproducibility from the three independent cells used in the mastication method.

To further confirm these observations, we calculated the difference factor (f_1) and similarity factor (f_2) using the equations provided in the Materials and Methods section. Our data (Table 1) demonstrated the similarity of the nicotine release profiles between Nicorette and Lucy gums. The calculated f_1 lower than 15 and f_2 higher than 50, showed equivalency. However, the f_1 and f_2 values obtained by comparing the Rogue to Nicorette gum and Lucy to Rogue gum clearly suggested that the products were different and did not present equivalency in their performance. Nicorette, Lucy, and Rogue gum products contain tobacco-derived nicotine polacrilex as the nicotine source. They are all composed of ~50 wt% gum based with elastomers. The coating is estimated to be ~20 wt% and sugar alcohol content is around 25~30 wt% [6-9]. Lucy and Nicorette gums are made with synthetic gum base and the formulation process consists of batch mixing, extrusion forming, and coating. However, Rogue gums are different as they are made with compressed gum base and the formulation process consists of powder blending, tableting, and coating. The differences when comparing Rogue to Lucy and Nicorette gums, and similarities when comparing Nicorette to Lucy gum products could be attributed to the inherent product characteristics detailed above. The data obtained indicate that the developed method can be discriminatory and used as a robust performance test to distinguish between different gums across the NRT and OTDN categories.

Furthermore, we compared the performance of the OTDN gums (Rogue and Lucy), produced at different nicotine strengths and flavor variants within the same brand category. Figure 6 compares the nicotine release profiles obtained from Rogue Wintergreen and Peppermint at 4 mg and 2 mg nicotine strengths. The nicotine release from Rogue gums with various flavors and nicotine levels were found to be the same with respect to the percent nicotine released at each collection time point as indicated by the overlapping release profiles. We have also compared these four Rogue products by calculating the f_1 and f_2 values. Our data (Table 2) show the similarity of the nicotine release profiles with calculated f_1 lower than 15 and f_2 higher than 50 demonstrating equivalency. Similarly, we have evaluated the nicotine release profiles obtained from Lucy 4 mg Wintergreen and Fruit Medley gum products (Figure 7). The release profiles were found to be equivalent, which was further confirmed by calculating the f_1 and f_2 values of 4.5 and 76.0, respectively, indicating equivalency.

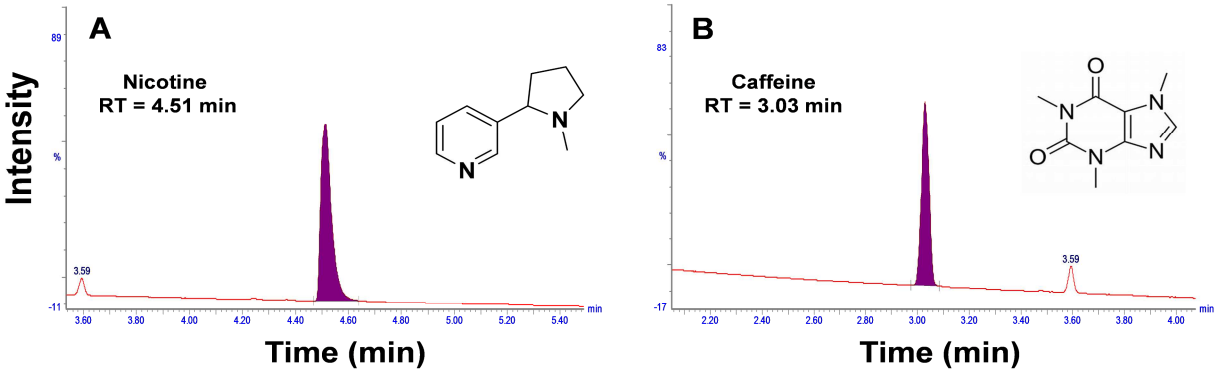

Figure 1. *UPLC-PDA chromatograms of (A) nicotine collected from Nicorette Spearmint 4 mg sample (Fraction 1) and (B) caffeine internal standard added to the same sample. The inserts show the chemical structures of nicotine (A) and caffeine (B).*

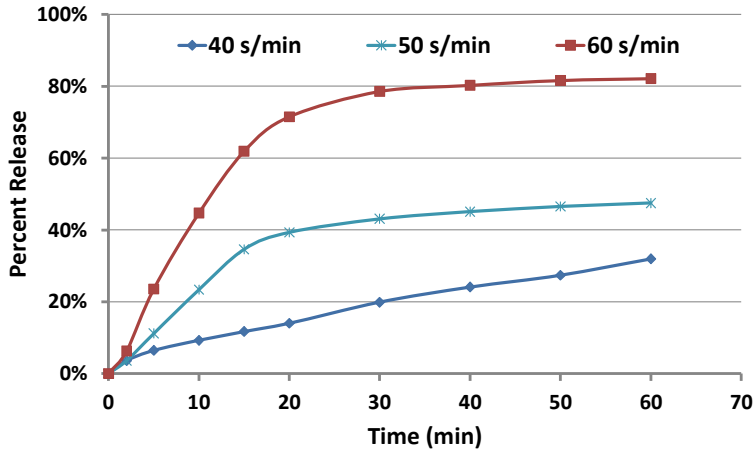

Figure 2. *Mastication cumulative percent release profiles of nicotine collected from Nicorette Spearmint 4 mg at 1.4 mm jaw gapping distance using different stroke frequencies including 40-, 50-, and 60-strokes per minute (s/min).*

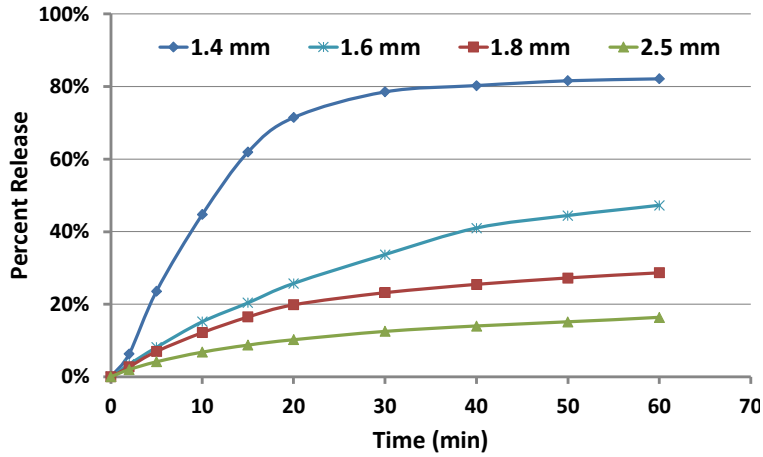

Figure 3. *Mastication cumulative percent release profiles of nicotine collected from Nicorette Spearmint 4 mg at 60 strokes per minute using different jaw gapping distances including 1.4-, 1.6-, 1.8-, and 2.5-mm.*

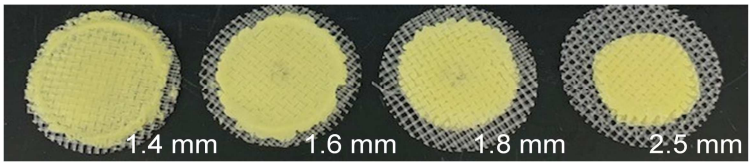

Figure 4. *Image of Nicorette Spearmint 4 mg after mastication at 60 stroke per minute using different jaw gapping distances including 1.4-, 1.6-, 1.8-, and 2.5-mm.*

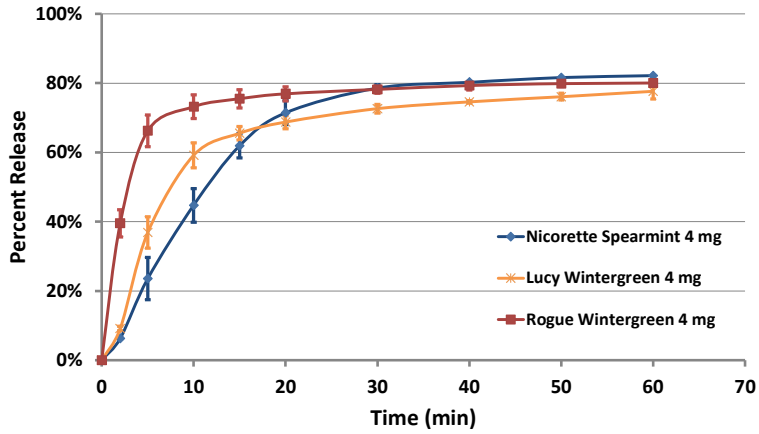

Figure 5. *Mastication cumulative percent release profiles of nicotine collected from Nicorette Spearmint 4 mg, Lucy Wintergreen 4 mg, and Rogue Wintergreen 4 mg gum products.*

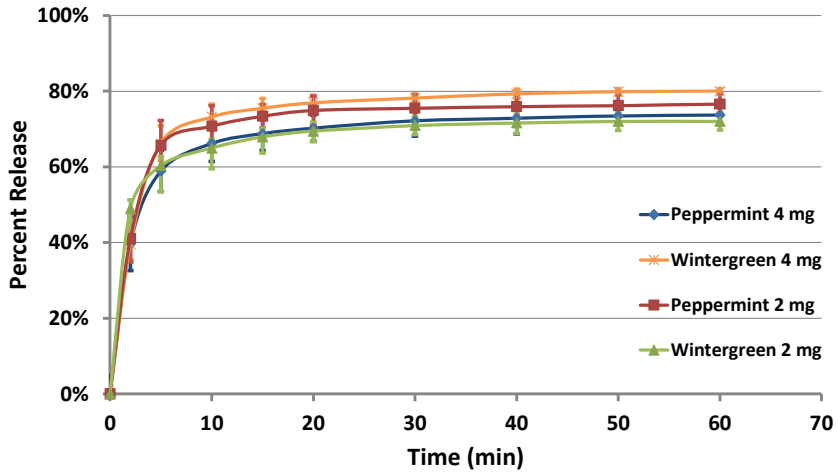

Figure 6. *Mastication cumulative percent release profiles of nicotine collected from Rogue gum products with differing flavor variants and nicotine strengths.*

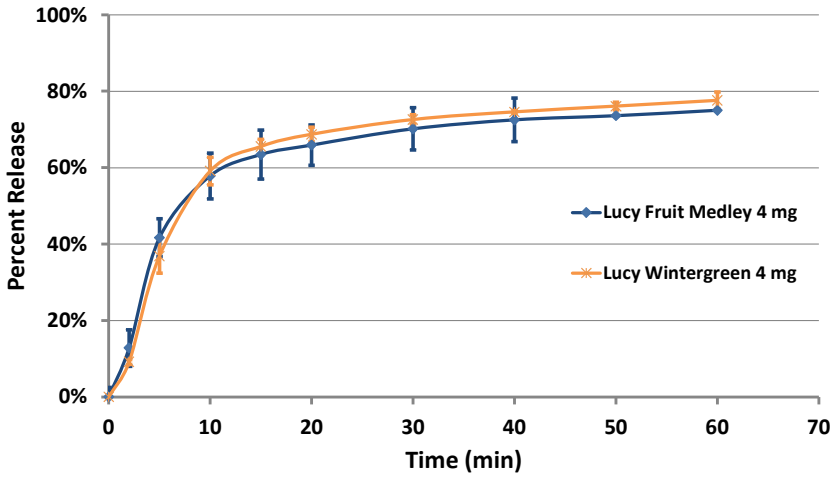

Figure 7. *Mastication cumulative percent release profiles of nicotine collected from Lucy 4 mg gum products with different flavors.*

Table 1. *Calculated f_1 and f_2 values for compared gum products including Nicorette Spearmint 4 mg, Lucy Wintergreen 4 mg, and Rogue Wintergreen 4 mg.*

Compared Products	f_1	f_2	Equivalency
Nicorette *vs* Lucy	11.0	55.5	Yes
Nicorette *vs* Rogue	24.2	33.9	No
Lucy *vs* Rogue	20	40.2	No

Table 2. *Calculated f_1 and f_2 values when comparing Rogue gum products with different flavor variants and nicotine strengths.*

Compared Products	f_1	f_2	Equivalency
Wintergreen 2 mg *vs* Wintergreen 4 mg	5.4	68.9	Yes
Peppermint 2 mg *vs* Peppermint 4 mg	5.7	68.9	Yes
Wintergreen 2 mg *vs* Peppermint 2 mg	7.6	63.0	Yes
Wintergreen 4 mg *vs* Peppermint 4 mg	5.4	68.9	Yes

4. Conclusion

We present an optimized method for mastication testing to study the nicotine release rate from a variety of nicotine gum products using the European Pharmacopoeia (Ch. 2. 9. 25, Apparatus B). The method can discern similarities and differences between the nicotine release profiles obtained from different brands of OTDN and NRT gum products. The differences between the cumulative percent release profiles obtained from gum products could be attributed to the different inherent product characteristics such as the use of compressed versus synthetic gum base in the formulations. The observed similarities in the nicotine release rate from gums of the same brand at different nicotine levels and flavor variants, suggest that the nicotine release profile is independent of the nicotine levels and flavors in these products under the experimental conditions employed. This mastication methodology can be valuable as a performance test for nicotine gum products and for product-to-product comparisons.

Notes

The authors declare no competing financial interest.

Acknowledgements

The authors thank William P. Gardner, Lyer Sucharitha, and Meghan Thompson from Altria Client Services for their assistance with this research and editorial services.

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