Dissolution Testing of White Fox Brand Modern Oral Nicotine Pouches

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Abstract

White Fox is an oral nicotine pouch product that does not contain cut, ground, powdered or leaf tobacco. The nicotine source is synthetic. Dissolution testing was performed as part of a PMTA development program in order to demonstrate that the products are appropriate for the protection of public health (APPH). The nicotine release profiles for the portfolio of White Fox brand nicotine pouches were characterized using the U.S. Pharmacopeia flow-through cell dissolution apparatus 4 (USP-4). Samples of all the study products were placed in the apparatus flow-through cells at a constant temperature of 37°C. A pump delivered a constant flow of artificial saliva for 100 minutes. The flow was sampled throughout the release period. The method followed the approach of Miller et al. 2020. 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). The tested products varied in size, flavor, and nicotine content. The excipients are the same in all of the products. About 20% of the nicotine was released over the first 30 minutes for all of the products. By 100 minutes the release was about 40%. The dissolution rate was about 0.4% per minute. All of the products were considered statistically equivalent to each other. The release rates were markedly slower than market comparators ZYN and VELO.

The Product

GN Tobacco's modern oral nicotine pouches were developed as alternatives to traditional moist smokeless tobacco products, with the intent of dramatically reducing user exposure to the TSNAs and PAHs found in MST products. GN's products are made by applying food-grade flavors, pharmaceutical-grade synthetic nicotine, salt, water, humectants, and pH modifiers to microcrystalline cellulose. The white granulate is enclosed in a fleece pouch material similar to traditional tobacco snus products (**Figure 1**).

White Fox brand products do not contain any tobacco leaf or tobacco stem material, but it does contain synthetic nicotine and is intended to emulate the organoleptic, ritualistic, and pharmacokinetic aspects of traditional MST products. The products are intended to be placed in the mouth between the cheek and gum for a period of time determined by the user (typically 30 to 60 minutes).

GN's White Fox brand pouch products are available in different pouch sizes ranging from 750 to 1000 mg/pouch and nicotine strengths (12.2 to 20.5 mg/pouch). **Table 1** shows the sizes and weights of the different pouches used in the different products. All of the products use the same pouch material and excipients. The only difference in the pouches is the size of the pouch, flavors, and nicotine strengths.

Figure 1. White Fox Nicotine Pouch

Table 1. White Fox Pouch Information

Product	Nicotine Strength (mg/pouch)	Pouch Size (mm)	Pouch Contents Weight (mg)
White Fox All White Slim Portion	12.2	14 X 32	750
White Fox Double Mint All White Slim Portion	12.3	14 X 32	750
White Fox Full Charge All White Regular Portion	17.7	18 X 32	1000
White Fox Peppered Mint All White Slim Portion	12.3	14 X 32	750
White Fox Black Edition All White Slim Portion	20.5	14 X 32	750

Methods

The products were tested using methods similar to those described for dissolution testing of controlled release pharmaceuticals. Specifically, the methods followed the Miller publication (Miller et al. 2020). Nine (9) fractions were collected and analyzed for each run. A blank and CRP 1.1 reference pouch were evaluated as controls during each collection period. The USP-4 apparatus was used with artificial saliva. Samples of all the study products were placed in the apparatus flow-through cells at a constant temperature of 37°C. A pump delivered a constant flow of artificial saliva for 100 minutes. The flow was sampled throughout the release period. 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).

Results

Table 2 shows the target nicotine concentrations in the different White Fox products. The nicotine strengths range from 12 to 20 mg/ pouch. **Figure 2** shows the cumulative nicotine released over time for each product. The recommended use time for the product is 30 minutes. Approximately 20% of the nicotine in the product is released during this time (**Table 2**). The dissolution rate for all of the products was about 0.4% per minute. The release rate of each of the White Fox products was compared to the release rates of each of the other products using the f_2 comparison test. All of the White Fox products were found to be equivalent to each other in their release rates.

The release rates from the market comparators, Zyn and Velo, were evaluated using the same methods in the same laboratory. The release rates are shown in **Table 2.** Both Velo and Zyn released at a much faster rate (0.7% and 1.19% per minute, respectively) as compared to about 0.4% for the White Fox products.

Table 2. Target Nicotine Concentrations and Nicotine Release Rates of White Fox Products and Market Comparators

	White Fox All White Slim Portion	White Fox Black Edition All White Slim Portion	White Fox Double Mint All White Slim Portion	White Fox Full Charge All White Regular Portion	White Fox Peppered Mint All White Slim Portion	Velo 7 mg Spearmint	Zyn 6 mg Cool Mint
Nicotine (mg/pouch)	12.2	20.5	12.3	17.7	12.2	7	6
Calculated release after 30 minutes (mg/pouch)	2.38	4.33	2.18	3.38	2.23	3.95	5.41
% Release after 30 minutes	19%	21%	18%	19%	18%	56%	90%
Total Released after 100 minutes (mg/pouch)	4.57	8.71	4.45	7.06	4.63	4.88	5.72
% Release after 100 minutes	37%	43%	36%	40%	38%	70%	95%
Dissolution Rate (%/Minute)	0.37%	0.43%	0.36%	0.40%	0.38%	0.70%	1.19%

Results

Figure 2. Cumulative Nicotine Release from White Fox Products

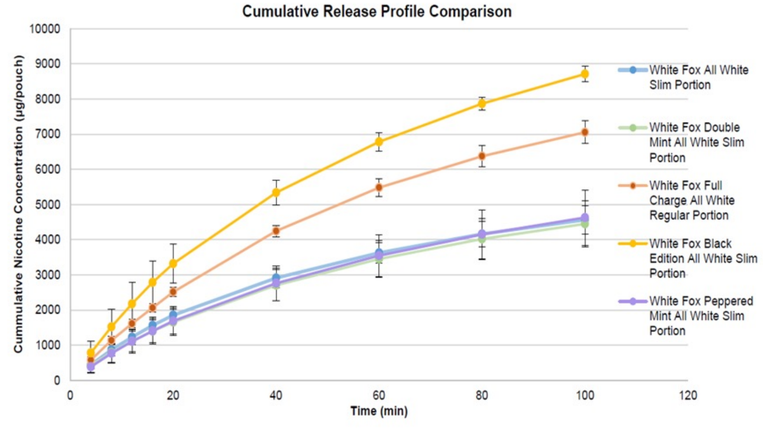
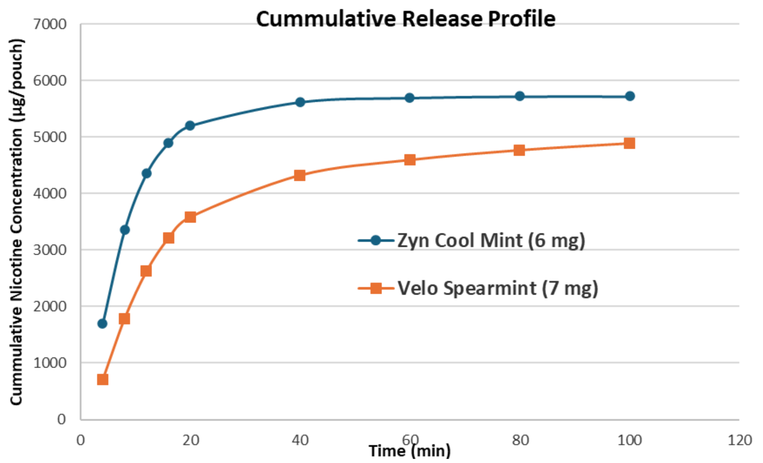


Figure 3. Cumulative Nicotine Release of Market Comparators



Conclusion

Dissolution testing of White Fox brand pouches demonstrated that the products released nicotine in an equivalent manner irrespective of the size, flavor, or amount of nicotine in the pouch. The White Fox products released nicotine slower than similar products Velo or Zyn.

References

Miller, John H., Tim Danielson, Yezdi B. Pithawalla, Anthony P. Brown, Celeste Wilkinson, Karl Wagner, and Fadi Aldeek. 2020. "Method Development and Validation of Dissolution Testing for Nicotine Release from Smokeless Tobacco Products Using Flow-through Cell Apparatus and UPLC-PDA." *Journal of Chromatography B*, February, 122012.

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