Characterization of Exposure to Methyl Salicylate in Adult Moist Smokeless Tobacco Users

Altria Client Services

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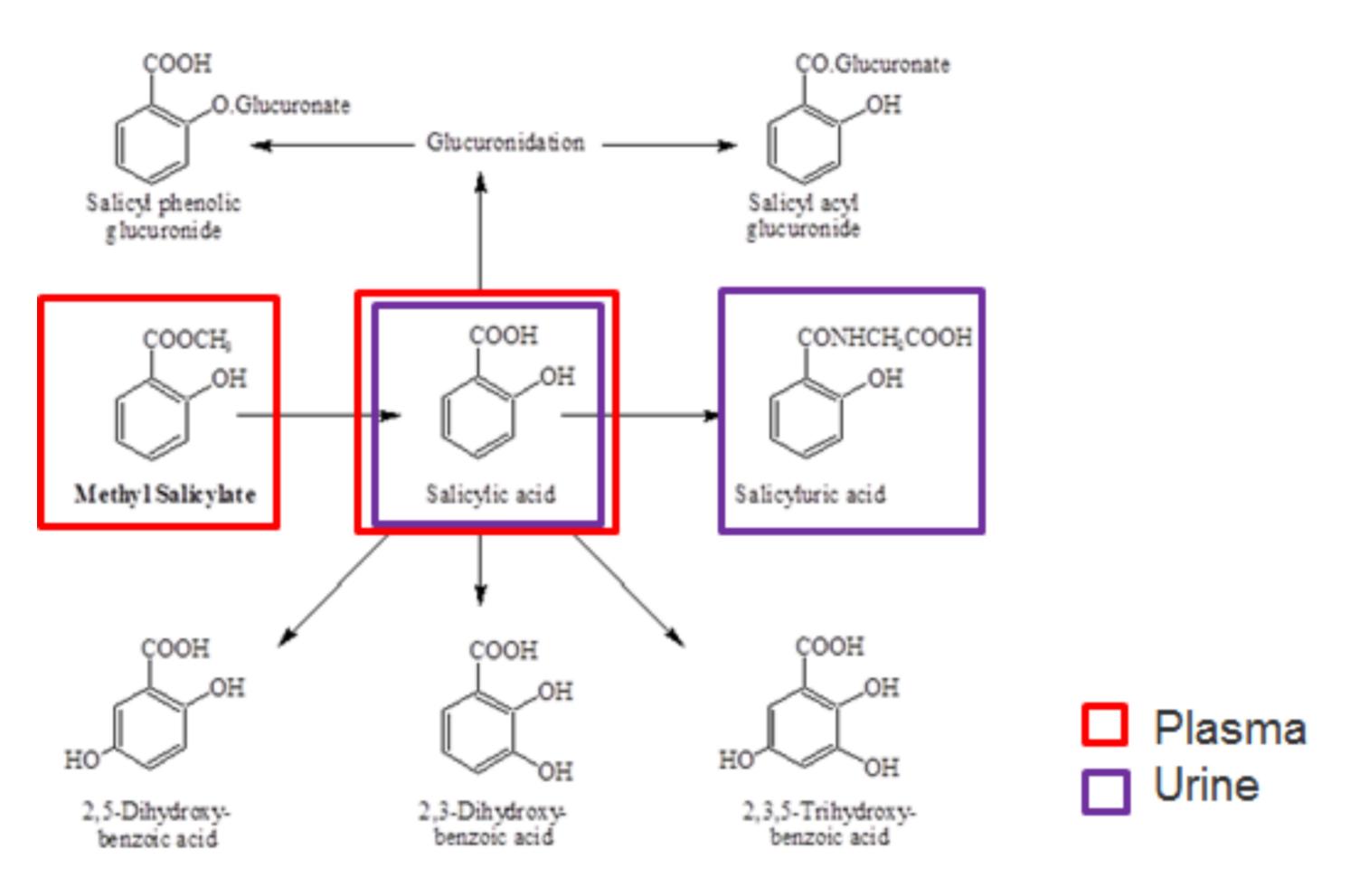
Figure 2a.

C_{max} of Plasma

Methyl Salicylate

Background

- Wintergreen is used as a flavor in many smokeless tobacco (ST) products. Methyl salicylate (MS), the chemical component of wintergreen oil, is commonly used in foods.
- The actual exposure to MS for adult ST users remains unknown
- Metabolism of Methyl Salicylate



Objectives

- To compare the rate and extent of absorption for methyl salicylate from four MST products with different wintergreen flavor levels following a single 2-g, 40 minute use in adult MST users
- To evaluate the salicylic acid (methyl salicylate metabolite) plasma pharmacokinetics (PK) from single 2-g, 40 minute use of the 4 MST products
- To evaluate the amount of total salicylates (salicylic acid and salicyluric acid) excreted in 24-hour urine collection from ad libitum use of the 4 products

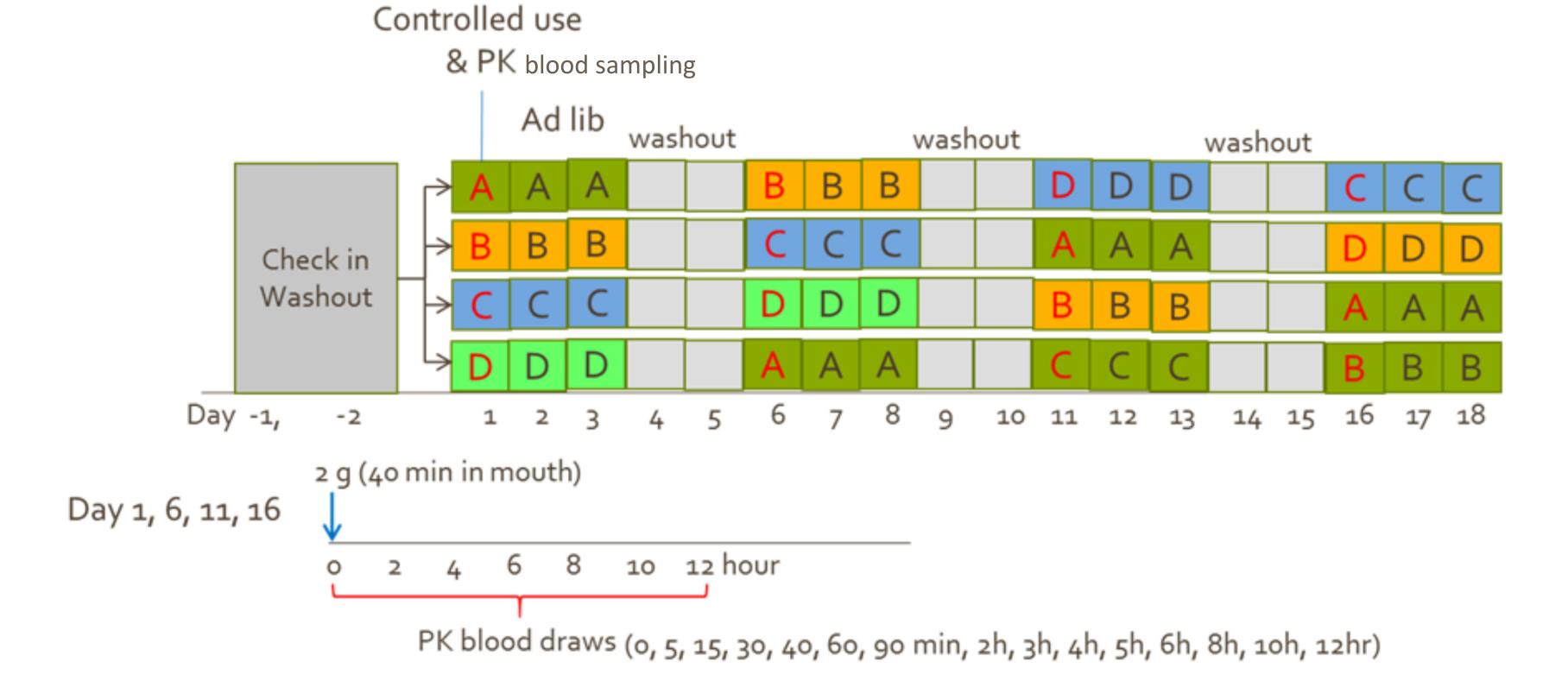
Study Products

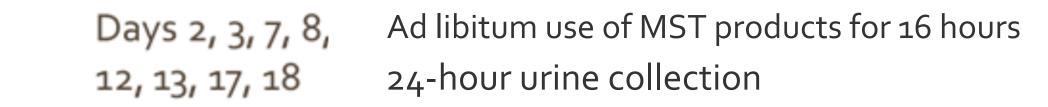
Four MST long cut wintergreen products were tested in this study.

	Table 1. Study Products	ole 1. Study Products			
Product ID	Description	Wintergreen (% weight)			
A	Prototype (Reference product)	2.38			
В	Commercial product (Test product)	2.79			
С	Commercial product (Test product)	2.99			
D	Commercial product (Reference product)	2.94			

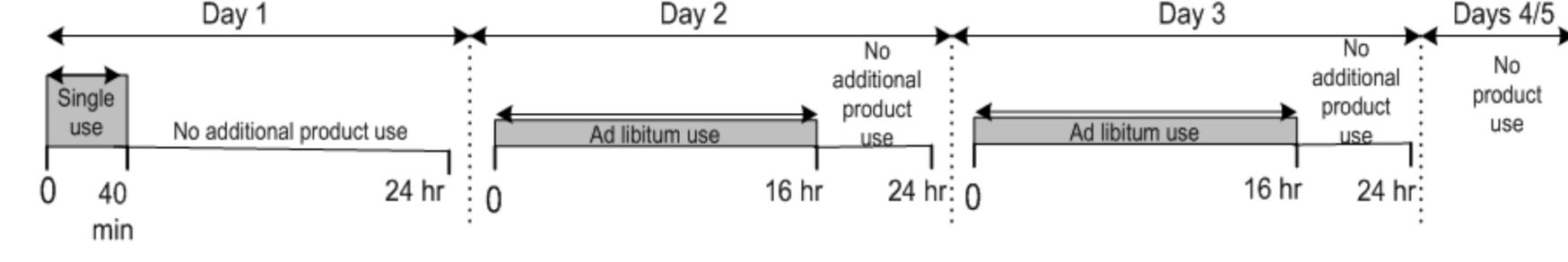
Methods

Study Design





Randomized 4-way crossover design



0= Start time of product use

Single use: - Quid size = 2 g; ~40 minute retention time in the mouth

Ad libitum use: Quid size and retention time were subject preference

Study Population

- Regular adult (21 65 years) wintergreen MST users
- Using an average of at least ½ can per day for at least 12 months

Table 2. Demographics

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	N = 73			
Age (years)	34 (8.8)			
Gender				
Male	68 (93.2%)			
Female	5 (6.8%)			
Race				
Black or African American	20 (27.4%)			
White	52 (71.2%)			
Other	1 (1.4%)			
BMI (kg/m ²)	27.30 (4.57)			

Results

Figure 1. PK Profiles (Group Mean)

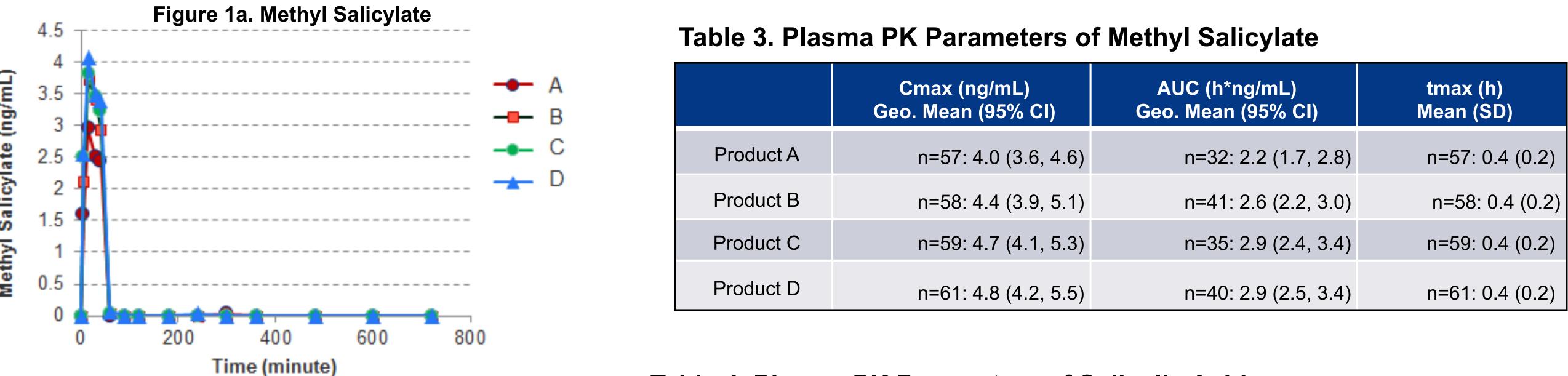


Table 4 Plasma PK Parameters of Salicylic Acid

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	Cmax (ng/mL) Geo. Mean (95% CI)	AUC (h*ng/mL) Geo. Mean (95% CI)	tmax (h) Mean (SD)	t1/2 (h) Mean (SD)		
Product A	n=69: 252.7 (234.9, 271.9)	823.5 (750.9, 903.2)	1.2 (2.2)	N=62: 2.8 (0.95)		
Product B	n=67: 277.1 (254.1, 302,3)	899.2 (812.7, 994.9)	1.3 (2.1)	N=59: 2.6 (0.6)		
Product C	n=67: 290.8 (269.4, 313.8)	952.6 (872.0, 1040.7)	1.1 (1.6)	N=60: 2.7 (0.7)		
Product D	n=71: 298.4 (272.7, 326.5)	984.7 (895.8, 1082.5)	1.2 (1.9)	N=66: 2.6 (0.6)		

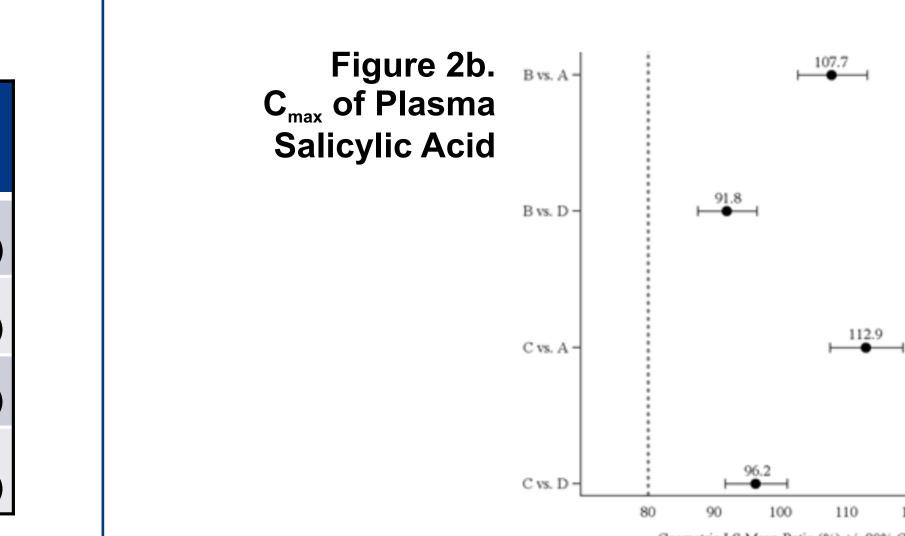


Figure 3. 24-hour Urine Methyl Salicylate Equivalents (Geometric LS Mean, 95% CI)

Figure 3a. Day 2 Figure 3b. Day 3

per use each day across the 4 products.

Figure 1b. Salicylic Acid

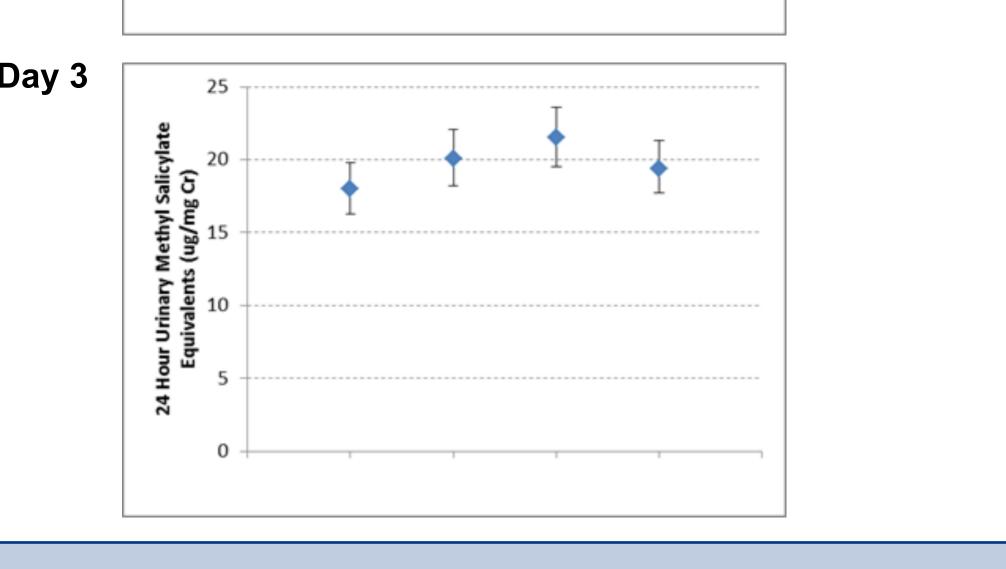


Figure 4. Product Use Topography

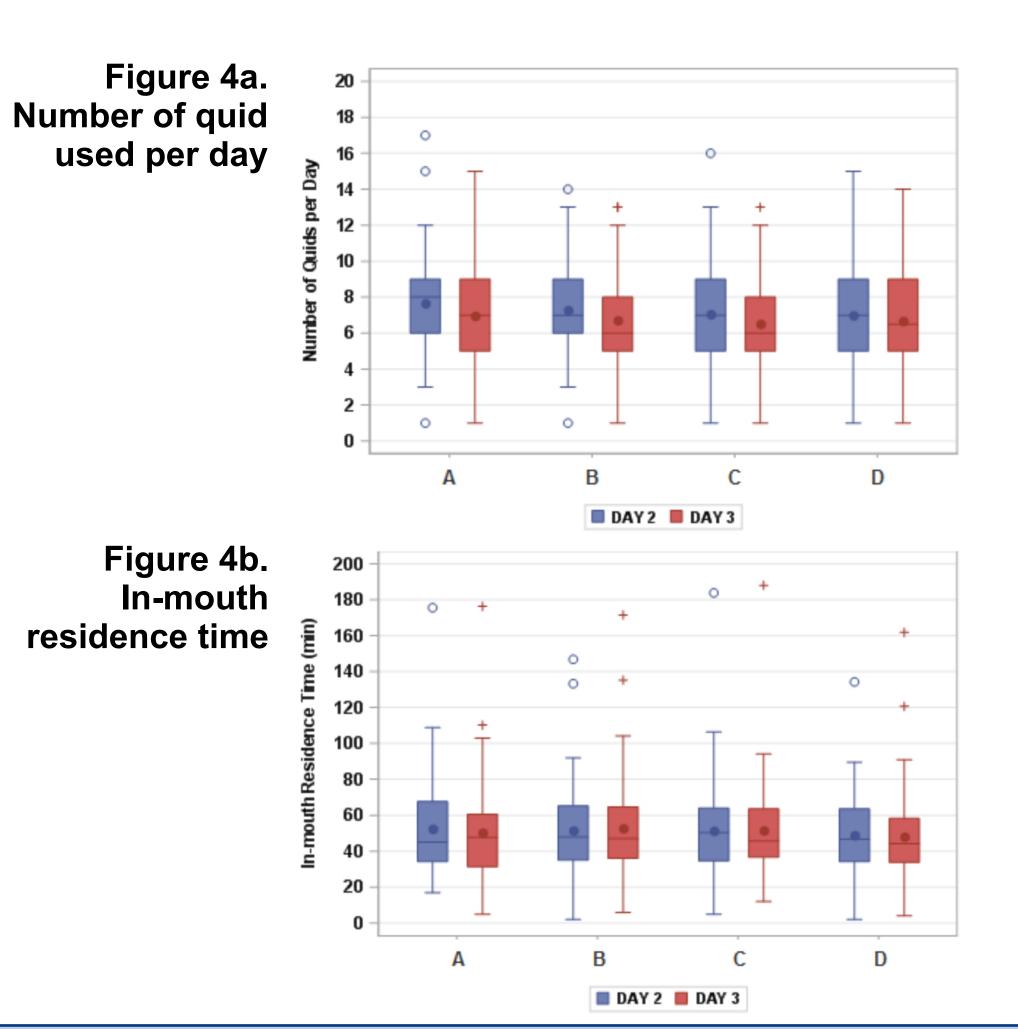


Figure 5. Daily MST Use (Mean, SD)

Geometric LS Mean Ratio

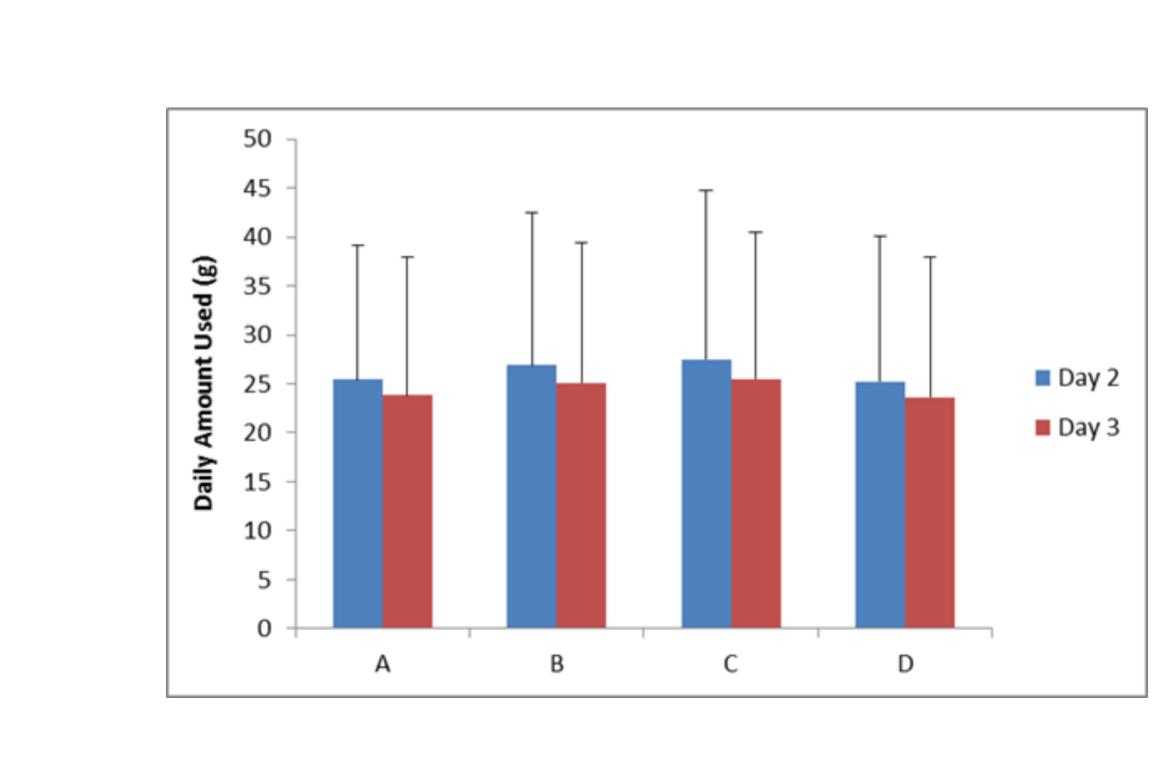
Figure 2. Bioequivalence Results

80 90 100 110 120 130 140

Geometric LS Mean Ratio (%) +/- 90% CI for each comparison

93.3

Geometric LS Mean Ratio



Summary

- Following single use, the geometric LS mean Cmax for the four products ranged from 3.94–4.76 (ng/ml) for methyl salicylate, and 254–298 (ng/mL) for salicylic acid.
- Plasma methyl salicylate levels were below the limit of quantitation (1.75 ng/mL) at all time points in n=18 subjects for at least one product and elimination half-life (t1/2) for MS could not be estimated for majority of the study participants. The average t1/2 for SA ranged from 2.6–2.8 hours.
- The creatinine adjusted geometric LS mean methyl salicylate equivalents (μg/mg creatinine) ranged from 19.4–20.8 for
- Day 2 and 18.0–21.5 for Day 3 for the 4 products. • During ad lib use period, the average consumption was 6–8 quids with 23.6–27.5 g total MST used, and 48–53 minutes

Overall Conclusions

- This is the first report characterizing methyl salicylate exposure in MST users.
- We conclude that due to the rapid elimination, methyl salicylate exposure is difficult to measure directly but can be best determined from salicylic acid plasma measurements.