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A Structured Taste Masking Process for Developing Palatable Pediatric Chewable Tablets

[1]Jeffrey Dougherty, [1]John Gawel, [2]David Tisi, and [2]Jeff Worthington
[1]Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick NJ 08903 [2]Senopsys, LLC, 800 West Cummings Park, Suite 1500, Woburn, MA 01801

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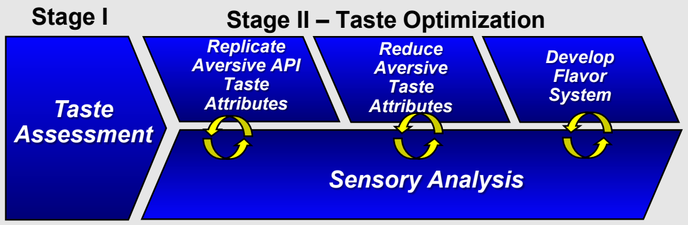
PURPOSE

Oral dosage forms are under development for two proprietary drugs indicated for children 3-11 years old who have difficulty swallowing tablets and capsules. Chewable tablets are appropriate for this patient population[1], but release their contents into saliva where the taste is detected by taste buds. Poor tasting medicines negatively impact pediatric dosing compliance, therefore the objective of this study was to evaluate the taste of the drug actives and identify pediatric chewable tablet formulations for two products.

METHOD

This was a two-stage study for the assessment of the taste properties of selected oral formulations. Stage I was an initial evaluation of unsweetened and unflavored preliminary formulations of each drug to identify negative attributes and to quantify the taste masking challenge. Stage II, taste optimization, used a three-step, sensory-directed process. Step 1: identified non-drug compounds that replicated drug taste to reduce human drug exposure. Step 2: applied taste/taste interaction principles to reduce the aversive taste characteristics. Step 3: identified appropriate flavoring aromatics. Trained adult sensory panelists evaluated samples using the Flavor Profile Method[2] of descriptive sensory analysis to provide palatability guidance while formulation scientists revised tablet formulations to assess material compatibility and impact to tablet processing. The two stages are presented below.



The study samples (Figure 1) were evaluated using the Flavor Profile Method of descriptive sensory analysis. This method is used to identify, characterize and quantify the sensory attributes of products, e.g., basic tastes, aroma, texture and mouthfeel.

Flavor Profile Definitions

Sensory Attributes: *Aromatics, basic tastes (sweet, sour, salty, bitter, umami), and feeling factors (listed in order of appearance along with a measurement of strength).*

Intensity Scale: 0 ½ 1 1½ 2 2½ 3 — *None* *Slight* *Moderate* *Strong*

Aftertaste: *Measurement of all attributes remaining at selected time intervals*

RESULTS

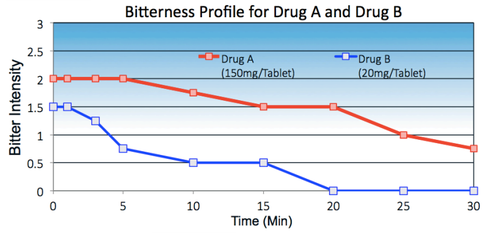
The Stage I taste assessment revealed bitterness was the primary taste masking challenge for both drugs, with secondary aromatic and mouthfeel effects. The bitterness profile of one drug active (Drug A) was significantly stronger and notably longer in duration than the other, as shown in Figure 2.

RESULTS (continued)

Figure 1

Ingredient	Drug A Composition %w/w	Drug B Composition %w/w
API (A/B)	33.33	5.00
Sugar Alcohol	35.23	40.00
Diluent	10.00	40.00
Surfactant	1.00	--
Disintegrant	2.50	5.00
Binder	8.84	5.00
Glidant	1.50	1.00
Taste Modifier	5.60	2.00
Lubricant	2.00	2.00

Figure 2



In Stage II, Step 1, model systems were developed using bitter GRAS excipients to replicate the taste of each drug (Figures 3 and 4). Denatonium benzoate (DB) represented the most bitter active, (Drug A) and sucrose octaacetate (SOA) reproduced Drug B.

Figure 3

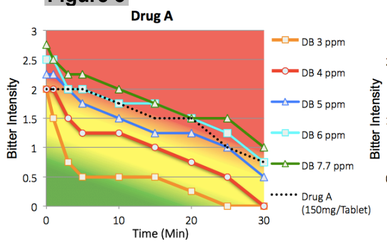
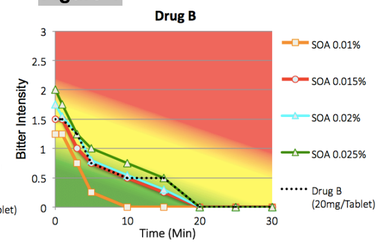


Figure 4



In Step 2, the psychophysical principle of taste-taste interaction was applied to reduce perceived bitterness by creating a neutral-tasting ("white") base. Excipients representing the complementary basic tastes of sweet, sour and salty (Figure 5) were iteratively evaluated using drug surrogate formulations.

Figure 5

Taste	Excipient	Role
Sweet	Aspartame Sucralose Acesulfame-K Sodium Saccharin	**High Intensity Sweeteners** provide sweet basic taste at low concentrations, reducing perceived bitterness of the drugs. Aside from bitterness reduction, these ingredients also contribute a sweet basic taste, which is highly desirable in pediatric formulations.
Sour	Citric Acid	**Acidulents** such as citric acid contribute a complementary sour basic taste which may further suppress bitterness. As both formulations are solids, addition of acids alone is generally acceptable, whereas aqueous forms may require a buffer system to avoid impacting target pH.
Salty	Sodium Chloride	**Salty Taste Modifiers**, classically sodium chloride, may be used to add additional balance to a formulation. Other metallic salts (e.g. potassium chloride) also have a salty basic taste but are avoided due to their metallic off notes.

The excipients above were optimized to reduce the bitterness for each formulation. High intensity sweeteners, required to reduce the lingering bitterness, were used to produce sweetened bases. For Drug A, sucralose and aspartame performed similarly but sucralose was subsequently eliminated due to compatibility issues (Figure 6). For Drug B, sucralose performed better than the other candidates – aspartame, sodium saccharin and acesulfame-potassium, as shown in Figure 7.

Figure 6

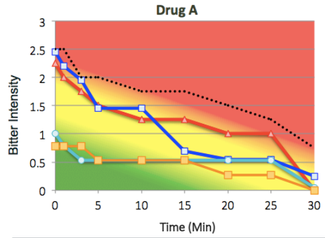
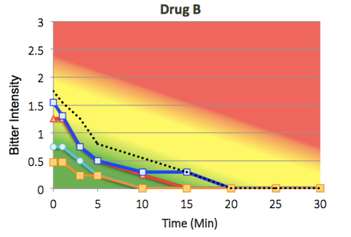


Figure 7



In Step 3, dozens of age-appropriate flavors were evaluated in the sweetened model formulations for their effectiveness in masking the aromatic effects. Usage levels of the best performing flavors were optimized for initial intensity and duration. Sensory analysis of the lead sweetened/flavored formulations with the drug actives was conducted to select lead and back-up flavors for compatibility and stability testing. The formulations developed for each drug using this approach were then used for clinical studies.

RESULTS (continued)

Figure 8

Final Flavor Candidates	
Drug A (Tier Ranking)	Drug B (Tier Ranking*)
Artificial Banana Flavor (1)	Natural and Artificial Tropical Punch (1)
Artificial Orange Flavor (1)	Artificial Cherry Flavor (1)
Artificial Tropical Flavor (1)	Natural and Artificial Orange Flavor (1)
Artificial Strawberry Flavor (2)	Artificial Mixed Berry Flavor (1)
Artificial Cherry Flavor (2)	Artificial Pineapple Flavor (1)

**All flavors for Drug B were of equal flavor quality in the mimetic system and considered tier 1 flavors.*

Leading flavor systems were confirmed with their respective APIs to ensure each provided appropriate coverage. In a palatable drug product, complete coverage occurs when the perceived intensity of positive stimuli (i.e. sweetness and flavoring aromatics) is higher than aversive stimuli (i.e. bitterness). The flavor system used for Drug A nearly covered all of the bitterness, whereas the flavor system selected for Drug B covered bitterness completely as shown in Figures 9 and 10.

Figure 9

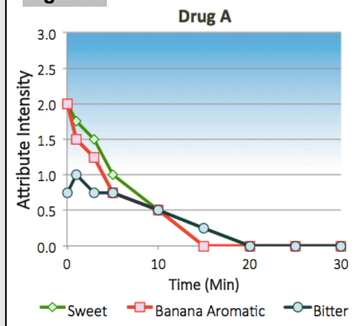
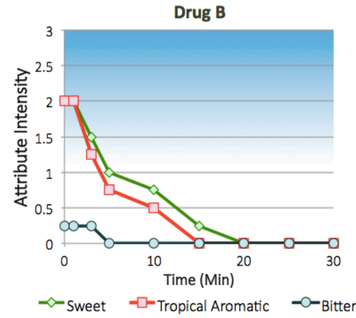


Figure 10



CONCLUSION

Palatable chewable tablet formulations for two drugs with different bitterness profiles were developed using the Flavor Profile Method. To avoid repeated drug exposure to human sensory panelists, mimetic formulations replicating drug-containing formulations could be used for white base and flavor evaluations. Formulation scientists conducting compatibility and processing studies integrated with sensory scientists taste evaluation and input provided the framework to meet development timelines.

REFERENCES

1) Committee for Medicinal Products for Human Use (CHMP), European Medicines Agency. Reflection paper: formulations of choice for the paediatric population (EMEA/CHMP/PEG/194810/2005).

2) Keane, P. The Flavor Profile Method. In C. Hootman (Ed.), Manual on Descriptive Analysis Testing for Sensory Evaluation ASTM Manual Series: MNL 13. Baltimore, MD. (1992).