W4173

Flavor Profile Method of Descriptive Sensory Analysis Guided Development of a Solithromycin Pediatric Powder for Oral Suspension Formulation

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Introduction and Purpose

Solithromycin, a new chemical entity under development by Cempra Pharmaceuticals is a fourth-generation macrolide antibiotic, and the first fluoroketolide. The chemical structure of solithromycin is shown in Figure 1 below.

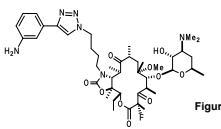


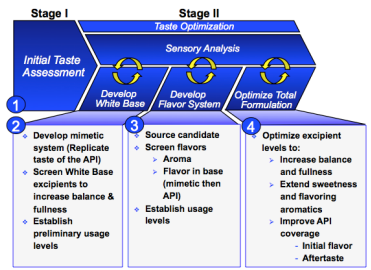
Figure 1: Chemical structure of solithromycin

Solithromycin is currently completing Phase 3 of clinical development for the treatment of community-acquired bacterial pneumonia in adult patients. As part of Cempra's Pediatric Investigation Plan, it was necessary to initiate development activities for a pediatric dosage form for the same indication. A powder for oral suspension dosage form was selected for development as it provides dosing flexibility to pediatricians and is appropriate across all pediatric developmental stages (1). All macrolides, including clarithromycin, have a bitter taste that must be masked for use in pediatric oral suspensions (2, 3). Solithromycin was found to be less bitter than clarithromycin in an initial taste evaluation. Therefore solithromycin oral suspension taste masking was included in formulation development.

Approach:

The development of a taste masked solithromycin powder for oral suspension was conducted by Senopsys LLC (Woburn, MA) following the sensory-directed approach to taste optimization illustrated in Figure 2.

Figure 2: Taste Optimization Approach



Methods

Throughout development, the flavor of samples was measured using the Flavor Profile Method of descriptive sensory analysis (4), which uses trained pharmaceutical sensory panelists to identify, characterize, and quantify the sensory attributes notes (basic tastes, aromatics, texture and mouthfeels) of formulations initially and in the aftertaste. The Flavor Profile definitions and scale are shown in Figure 3 below. As this approach involved human exposure to solithromycin, relevant portions of the taste evaluation were conducted under a Clinical Trial Protocol (CE01-124; IRB# 13-450).

Figure 3: Flavor Profile Definitions

Flavor Profile Definitions

Amplitude: Initial overall perception of the balance and fullness of a flavored product; considering the appropriateness of aromas and flavor notes present, their blend and intensity and existence of off-notes.

Amplitude Scale:

0 — ½ — 1 — 1½ — 2 — 2½ — 3

None — Low — Moderate — High

Character Notes: Aromatics, basic tastes, 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 sensation remaining at selected time intervals

Methods Continued

Panelists used the following procedure to evaluate suspension samples:

1.The panelists cleansed their palates with spring water and unsalted crackers.
2.5mL of sample was dispensed into individual 1-ounce plastic cups using a graduated oral syringe and distributed to each panelist.
3.Starting at the same time, the panelists poured the sample directly in to their mouths, swished the contents around the oral cavity for 10 seconds and expectorated. During this time the panelists independently evaluated and recorded the initial flavor characteristics.
4.The panelists then independently evaluated and recorded the aftertaste characteristics at periodic intervals out to 30 minutes as flavor persisted.
5.The panelists recited their individual results and a preliminary Flavor Profile was generated for the sample.
6.Steps 1 through 4 were repeated for a second evaluation of the sample using the preliminary Flavor Profile from Step 5 as a guide, with the panelists noting any necessary modifications.
7.The panelists recited their individual results and a final Flavor Profile was developed for the sample.

The Flavor Leadership Criteria (5) were used to interpret sensory results and guide the development of products that can be differentiated on the basis of perceived flavor quality.

1.Aromatic identity: immediate impact of the identifying flavor, e.g., orange, berry, mint
2.Amplitude: rapid development of balanced, full flavor
3.Mouthfeel: mouthfeel effects that are compatible with the flavor system, e.g., cooling (mint), oily (syrups)
4.Offnotes: minimal aversive attributes, e.g., bitterness, trigeminal irritation, aromatics
5.Aftertaste: sufficient duration of sweetness and flavoring aromatics to cover aversive attributes

Results

The initial taste assessment of an unflavored suspension of solithromycin in phosphate buffer pH 8 was used to guide the formulation development, as shown Table 1 below.

Table 1: Compositions developed for use in the taste evaluation study at Senopsys

Ingredients	Function	Unflavored Solithromycin Suspension 320 mg/5 mL
		Batch Weight (g/100mL)
Solithromycin	Drug substance	6.4
Sodium Phosphate, Tribasic Anhydrous	pH modifying agent	0.1
Purified Water	Vehicle	qs 100 mL

The results of the taste evaluation indicated that solithromycin is characterized by a strong intensity and lingering bitterness. The results are summarized in Table 2 below.

Table 2: Formulation #4 (Solithromycin control) taste evaluation

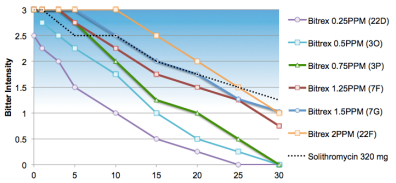
Flavor Profile Solithromycin (Lot #20140107@4) 320mg/5mL (Unsweetened/Unflavored)	Initial	1 Min	3 Min	5 Min	10 Min	15 Min	20 Min	25 Min	30 Min
Moldy / Cardboard Aromatic	2	1 ½	1	-	-	-	-	-	-
Soapy Aromatic	1½-2	1 ½	½	½	-	-	-	-	-
Bitter	3	3	2½-3	2½	2½	2	1½-2	1½	1-1½
Green Stemmy Aromatic	2	1½	1½	1½	1½	1	½	½	-
Soapy Mouthfeel	1	1	½	½	-	-	-	-	-
Tannin Mouthfeel	1½	1½	1½	1	1	½-1	-	-	-
Tongue Sting Mouthfeel	½	1	1	1	½	½	-	-	-
Drying Mouthfeel	-	-	1½	1½	1½	1½	1½	1½	1
Gritty Texture	½	½							

Flavor Leadership Interpretation				
1 - Aromatic Identity	2 - Amplitude	3 - Mouthfeel	4 – Off-Notes	5 - Aftertaste
Not applicable for unflavored formulations	Not applicable for unflavored formulations	Soapy, tongue sting, drying and tannin mouthfeels	Strong intensity bitterness and moderate intensity aromatic off-notes	Lingering bitterness, aromatic off-notes and mouthfeels

Results Continued

In order to limit exposure to human subjects, it was necessary to develop a mimetic system to match the flavor of solithromycin. As the principal taste masking challenge was a lingering bitterness, caffeine, sucrose octaacetate and denatonium benzoate (Bitrex®) were evaluated to serve as a mimetic for solithromycin. Based on the results, Bitrex at a concentration of 1.5 PPM was selected as a suitable mimetic. The bitterness profile of various concentrations of Bitrex are shown in Figure 4 below.

Figure 4: Denatonium Benzoate Mimetic Bitterness Profiles



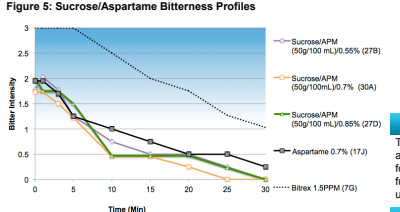
Based on the lingering bitterness profile, it was clear that high intensity sweeteners would be needed. Several options were evaluated in the functional base formulation (Table 3) including acesulfame potassium, sodium saccharin, aspartame, neotame and sucralose. Ultimately, aspartame was chosen as the leading high intensity sweetener candidate due to its beneficial bitter masking and chemical compatibility with the solithromycin functional base.

Table 3: Solithromycin Base Formulation

Ingredients	Function	Unflavored Solithromycin Suspension 320 mg/5 mL
		Batch Weight (g/100mL)
Solithromycin	Drug substance	6.4
Aerosil 200	Glident	0.5
Sodium Phosphate, Tribasic Anhydrous	pH modifying agent	0.1
Potassium sorbate	Preservative	0.2
Xanthan Gum	Viscosity modifier	0.3
Simethicone	Anti-foaming agent	0.2
Purified Water	Vehicle	qs 100 mL

Bulk sweeteners (e.g. sucrose, fructose, and sorbitol) in combination with high intensity sweeteners may increase the fullness of the flavor system. 50g/100mL sucrose was found to have the highest flavor quality in combination with aspartame as shown in Figure 5.

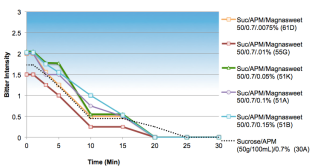
Figure 5: Sucrose/Aspartame Bitterness Profiles



Proper flavor construction is best accomplished by further introducing sourness and saltiness to the sweetened formulation. Citric acid to 0.6% (for sourness) and sodium chloride to 1.5% (for saltiness) were screened in the leading aspartame formulation. Neither provided improved flavor balance and were eliminated from further consideration.

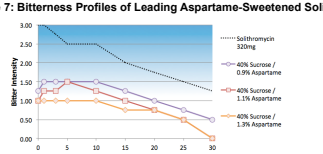
Monoammonium glycyrrhizinate (Magnasweet™) can extend and support sweetness in the aftertaste of some formulations and was evaluated in the leading aspartame mimetic system (Figure 6).

Figure 6: Sucrose/Aspartame/Magnasweet Bitterness Profile



As the mimetic system represents an approximation of the drug product, the Bitrex mimetic was replaced with 320mg solithromycin and evaluated by the sensory panelists to verify that the white base formulation performs as expected. Using the results of this confirmation round, the sweetener system was further refined (reducing sucrose and increasing aspartame), and a leading aspartame concentration (1.3%) was selected for advancement as shown in Figure 7.

Figure 7: Bitterness Profiles of Leading Aspartame-Sweetened Solithromycin Formulations



To complete the formulation, various identifying flavors were evaluated. Two flavors (cherry and bubblegum) were selected, generating the final two taste-masked formulations shown in Table 4. These compositions were then transferred to a Contract Development and Manufacturing site for formulation selection and process development studies. To date one lead formulation has been selected and the manufacture of clinical supplies for pivotal studies is ongoing.

Table 4: Final Solithromycin Formulations

Ingredients	Function	Cherry Flavored Solithromycin Suspension 320 mg/5 mL	Bubblegum Flavored Solithromycin Suspension 320 mg/5 mL
		Batch Weight (g/100mL)	Batch Weight (g/100mL)
Solithromycin	Drug substance	6.4	6.4
Aerosil 200	Glident	0.5	0.5
Sodium Phosphate, Tribasic Anhydrous	pH modifying agent	0.1	0.1
Potassium sorbate	Preservative	0.2	0.2
Simethicone	Anti-foaming agent	0.2	0.2
Aspartame NF	Sweetener	1.597	1.597
Sucrose NF	Sweetener	40.0	40.0
Magnasweet 100	Sweetener	0.023	0.023
Art Cherry Flavor NV-20,629	Flavor	0.360	
Art Bubblegum Flavor NV-10,506	Flavor		0.360
Purified Water	Vehicle	Qs100 mL	Qs100 mL

Conclusions

Taste masked formulations are used to improve pediatric compliance of bitter drug, such as macrolide antibiotics. A Flavor Profile Method of descriptive sensory was used to select a palatable suspension formulation for solithromycin to be used in Phase 1 pediatric studies. The formulations has since been further refined for pivotal clinical studies. The Flavor Profile Method of descriptive sensory analysis is a useful tool to guide the development of formulations suitable for pediatric patients.

References

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