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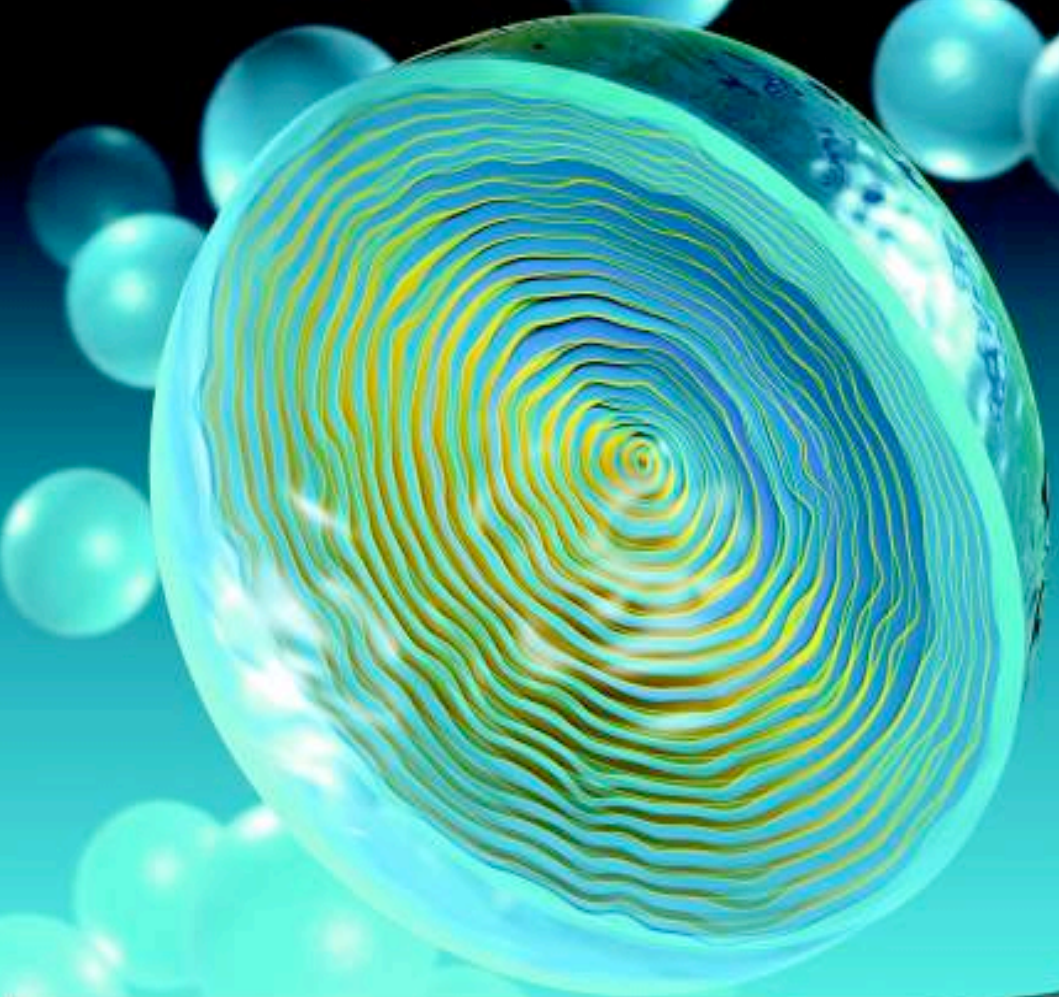

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Taste Optimization of a Model Oral Spray Drug Product

By: Jeffrey H. Worthington, MBA; David A. Tisi, MS; Frank E. Blondino, PhD; and Foyeke O. Opawale, PhD

INTRODUCTION

Technology advances are leading to the development of novel oral dosage forms that may provide faster onset of action, fewer side effects, and improved patient dosing (convenience). One such technology is oral sprays. NovaDel Pharma Inc. utilizes oral spray systems to deliver a broad range of APIs to the systemic circulation through the highly perfused lining of the oral cavity. NovaDel's core technology offers substantial benefits compared to other modalities of drug administration, including faster onset of action, increased drug bioavailability due to avoidance of first-pass effect in the liver, avoiding the need to take medication with water, and avoiding the need to swallow. Drug delivery via the oral cavity may also minimize inter- and intra-subject pharmacokinetic variability related to stomach-emptying time, food effects, and enzymatic or chemical degradation in the gastrointestinal tract. The main characteristic of the technology is the delivery of solution formulations of API to the oral cavity in the form of a spray. However, many APIs are bitter or have other undesirable taste characteristics that need to be masked in order to develop palatable, patient-acceptable drug products. The following discussion will review the approach for developing a palatable oral spray for a model API.

DEVELOPING PALATABLE DRUG PRODUCTS – A STAGED APPROACH

The development of palatable drug products can be a daunting challenge. This is exacerbated by the general misconception in the pharmaceutical industry that taste perception cannot be quantified. Nothing could be further from the truth - sensory science is a core competency of most consumer packaged goods companies that compete on the basis of product aesthetics. Pharmaceutical companies, of course, have the added complexity of managing human exposure to drug substances, which is their core competency.

It is nearly impossible to develop a palatable drug product without knowing the taste characteristics of the API. Accordingly, Senopsys LLC followed the two-stage Taste Assessment and Taste Optimization development approach described herein.

STAGE I – TASTE ASSESSMENT

The objective of this assessment was to develop the dose-response function for the model API in an unflavored, unsweetened oral spray excipient system composed principally of solubilizers. Five doses were dispensed in a fixed-dose volume of two 100 microliter actuations to deliver 1, 2, 4, 6, and 8 mg. This dose volume was set to maximize residence time in the oral cavity and minimize the swallowing reflex. At this volume, the upper end of the dose-response was bound by the solubility of the API.

Taste Profiling Procedure

The oral sprays were evaluated by trained and experienced pharmaceutical sensory panelists using the Flavor Profile method of descriptive sensory analysis.[1] Flavor Profile entails the identification and measurement of the sensory attributes of products, eg, texture, aroma, taste, and mouthfeel. Reference standards are used to define the attributes, and reference scales for intensity of different attributes ensure consistent application of the measurements across panelists and reproducibility across evaluations.

Both the initial flavor and aftertaste characteristics of drug products are important determinants of patient acceptability; therefore, it is critical that each be evaluated. Following two spray actuations directed to the tongue, the initial flavor characteristics were measured during the first 10 to 20 seconds. The aftertaste characteristics were measured at eight time intervals (1, 3, 5, 10, 15, 20, 25, and 30 minutes).

The drug product was under an Investigational New Drug application and accordingly, the study was conducted under the auspices of an external Institutional Review Board.

Dose/Response Results

The challenge for many drug products is to mask the undesirable sensory characteristics of the API and excipients in the initial flavor and throughout the aftertaste (eg, bitterness, burn, stinging, and drying). Visualizing the data as a function of time provides valuable diagnostic information (Figure 1). A series of time-intensity plots were prepared for the critical sensory attributes. In each time-intensity plot, the area above a slight intensity on the Flavor Profile scale (>1) has been shaded. Based on experience across a

wide range of drug products, undesirable characteristics above a slight intensity are clearly perceptible to most patients and are often found to be unacceptable. To increase patient acceptability, the intensity of the undesirable characteristics should remain below 1 throughout the product's flavor profile. Conversely, favorable attributes (eg, sweetness and flavor aromatics) should remain above this slight intensity throughout the product's flavor profile.

The bitterness profiles of the five doses delivered as oral sprays varied significantly over the study dose range as shown in Figure 1. As expected, the perceived bitterness increased with increasing API dose. The bitterness was found to linger at clearly perceptible levels for about 5 minutes at the lowest dose to about 20 minutes at the highest dose. The lingering bitterness of the API, represented by the relatively flat decay curves, poses a significant taste-masking challenge, particularly at the higher doses. The bitterness profiles of the 6-mg and 8-mg doses were similar, suggesting that these concentrations are approaching the upper plateau of the typical sigmoid taste-response curve.

Four other critical sensory attributes were identified and quantified - solvent aromatics and three mouthfeel factors (warming, tongue sting, and drying). The perceived intensity of these four attributes was found to be largely independent of API dose, which suggests they arise from the base excipient system. The time-intensity profiles for the critical attributes are shown in Figure 2 for the 8-mg dose.

The solvent aromatics were moderate in intensity initially but short lived, decreasing below a slight intensity by 3 minutes. The excipient system produced a warming mouthfeel, which had a profile similar to the solvent aromatics and a slightly lower tongue sting profile. The drying mouthfeel did not arise immediately as the maximum intensity did not occur until one minute - this is not uncommon for some mouthfeel perceptions, including drying, numbing, and cooling.

Based on the Flavor Profile results, it was clear that the primary taste-masking challenge for this oral spray drug product was the bitterness profile of the API itself. The base excipient system contributed other effects, but these were clearly secondary in importance from a taste-masking challenge. In order to produce a meaningful reduction in the perceived bitterness of the spray product, the concentration of the API would need to be reduced by 50% or more, ie, ≤ 2 mg per

FIGURE 1

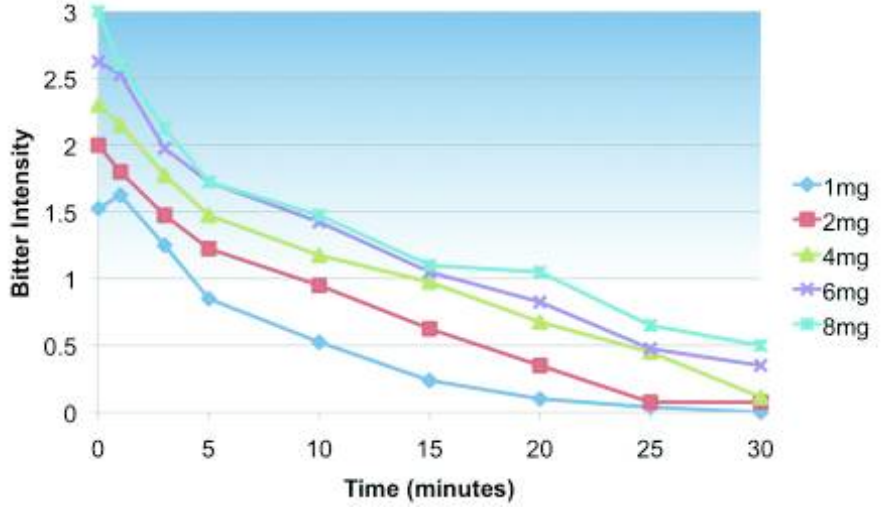
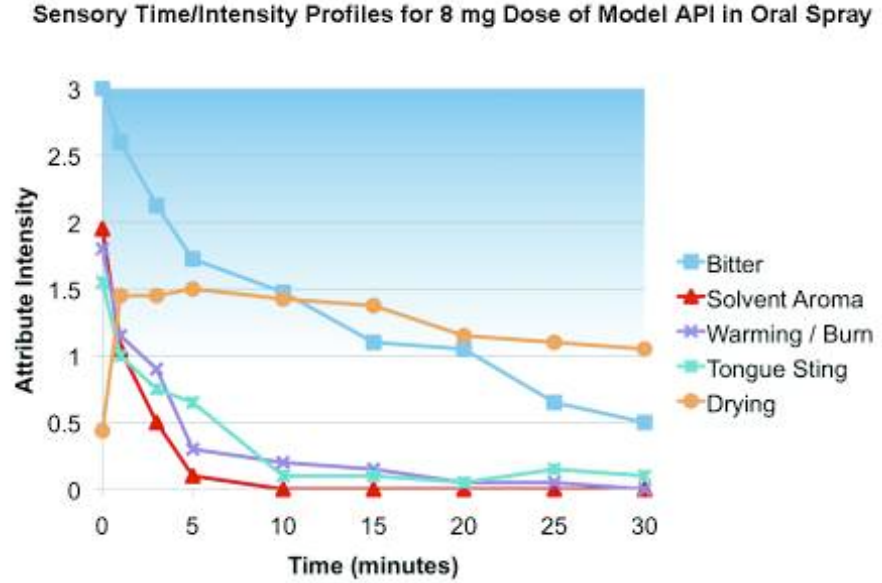


FIGURE 2



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100 microliters. However, decreasing the concentration would necessitate increasing the number of spray actuations, which was viewed as negating the convenience of the oral spray and potentially impacting dosing compliance.

STAGE II – TASTE OPTIMIZATION

The objective of this stage was to develop a series of palatable oral spray prototype formulations containing the model API at 4 mg per 100 microliters delivered in two actuations. Though the 8-mg dose poses a significant taste-masking challenge, this dose was selected based upon dose volume and solubility limitations.

FIGURE 3

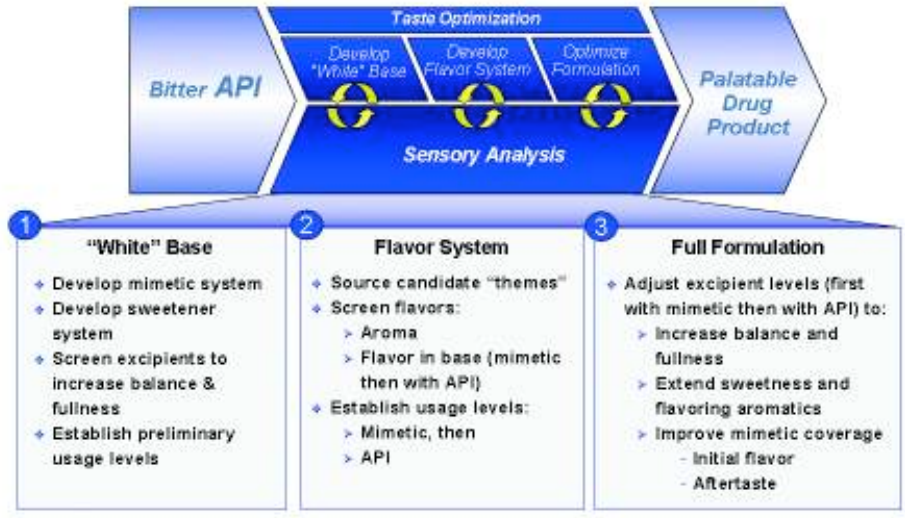
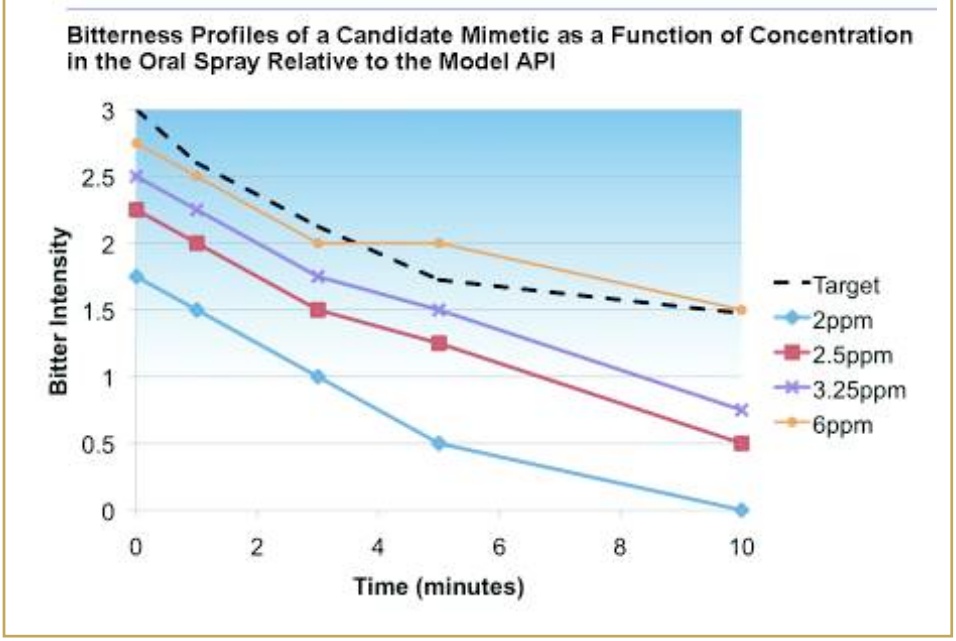


FIGURE 4



Developing a Palatable Oral Spray Drug Product

The palatability of a drug product is related to the perceived blend of the product's sensory characteristics. The model API was strongly bitter and lingered for several minutes in the aftertaste. This bitterness would be expected to "stand out" from the other basic tastes (sweet, sour, and salty). If the basic tastes can be balanced, then the bitterness of the drug substance may not be distinctly perceived, and the drug product may be more palatable. In general, this requires that the positive sensory attributes of the flavor system, specifically sweetness and flavoring aromatics, be perceived at a stronger intensity than the negative sensory attributes (eg, bitterness).

The process shown in Figure 3 was followed to develop a series of palatable oral spray formulations for the model API. This approach has been adapted from the consumer packaged goods industries where product aesthetics are critical to commercial success and has been used to develop dozens of palatable oral drug products. The first step was to develop a "white" placebo base for the oral spray. A "white" or unflavored base exhibits balanced basic tastes (sweet, sour, salty, and bitter), which, as previously mentioned, is the underpinning of taste-masking. In this case, the objective was to "blend away" the bitterness of the API and to a lesser extent the aromatics and mouthfeel effects of the excipient system.

Identify a Mimetic

To reduce human exposure to drug substances during development, the first step was to develop a mimetic system using Generally Recognized as Safe

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(GRAS) or FDA-approved excipients that closely match the critical sensory attributes of the API. For the model API, the goal was to identify a mimetic and usage level that would replicate the bitterness profile of the 8-mg dose as shown in Figure 1. There are numerous compounds that are bitter, including caffeine, sucrose octaacetate, quinine sulfate, naringin, magnesium sulfate, and denatonium benzoate. Each has a different bitterness profile. Several bitter mimetics were formulated in the base excipient system and evaluated by the sensory panelists following the same evaluation protocol used in Stage I. The resulting bitterness profiles were compared to that of the model API. The usage levels were adjusted and the bitterness profiles iteratively generated until a bitterness profile close to that of the model API was attained. The bitterness profiles for one mimetic are shown in Figure 4 as a function of concentration in the oral spray excipient system. Based on these results, the mimetic concentration of six parts per million (w/w) was selected for use in developing a series of palatable oral sprays.

Develop the Sweetener System

The next step was to develop a sweetener system with a sweetness profile that closely matches the bitterness profile of the model API in the base excipient system. There are numerous sweeteners available to formulators - nutritive, sugar alcohols, and high intensity (artificial). The concentrations required for nutritive sweeteners or sugar alcohols exceeded the usable range for the oral spray dosage form. As a result, only the high-intensity sweeteners were considered.

The candidate high-intensity sweeteners were first evaluated individually in the base excipient system to determine if they provided ample sweetness. Several could not provide the target level of sweetness without distorting the flavor profile with increased bitterness and metallic aromatic off-notes, and were subsequently eliminated. Appropriate combinations of high-intensity sweeteners were then considered to achieve the desired sweetness impact and duration. The sweetness profiles of four sweetener systems are shown in Figure 5.

The leading sweetener system was then combined with the mimetic and the usage level optimized. The results are shown in Figure 6. The sweetener system produced the intended effect of reducing

FIGURE 5

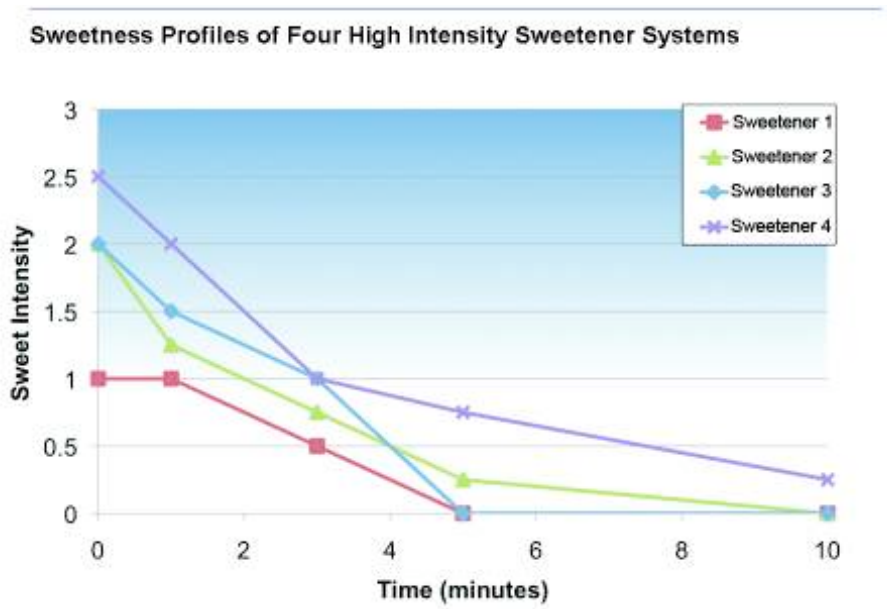
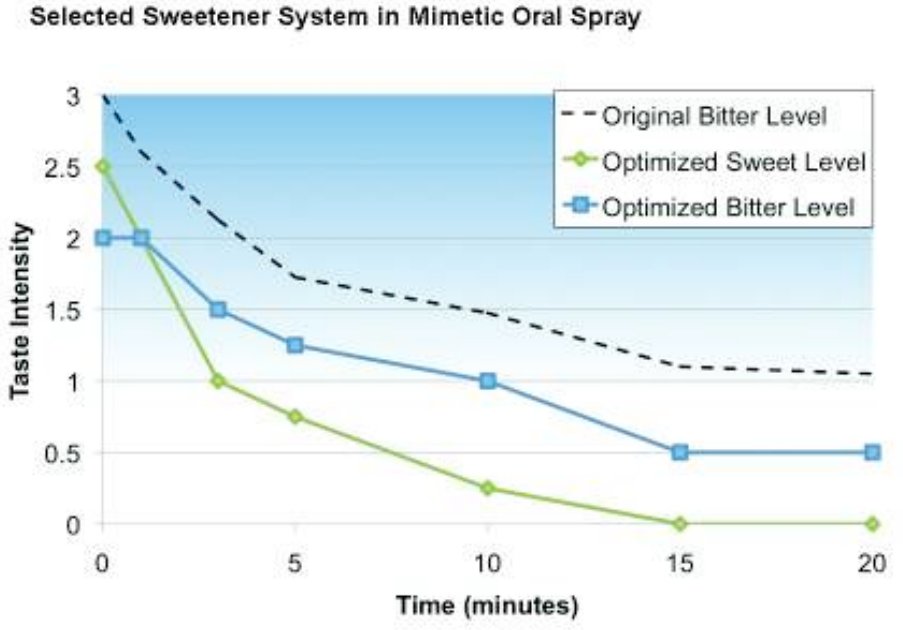


FIGURE 6



the bitterness profile of the mimetic. The sweetness profile was somewhat lower than the bitterness profile and therefore suboptimal; however, further increases in sweetness had the same deleterious distortion of the Flavor Profile previously described.

There are numerous excipients that can be used to modify specific sensory characteristics of drug products. For example, sodium chloride is used to blend or balance basic tastes. Menthol can be used at sub-odor threshold levels to provide a cooling mouthfeel that can be beneficial in certain applications. Monoammonium glycyrrhizinate is sometimes used to extend and support sweetness in the aftertaste. There are several suppliers and grades of monoammonium glycyrrhizinate, and the effects in different systems can vary significantly, sometimes adversely affecting palatability. Several flavor modifiers were explored in the mimetic placebo base; the results are shown in a series of plots in Figure 7.

Three plots are shown in Figure 7. The left chart represents the "control" with no addition of the flavor modifier (same as shown in Figure 6). The middle chart represents a low usage level of the flavor modifier, and the right represents a high-usage level. As shown, the upper usage level increased the initial bitter intensity and did not compensate with increased sweetness. The lower usage level increased the sweetness profile without increasing the bitterness, illustrating that more was not necessarily better.

It was advantageous at this point of development to verify that the results obtained using the mimetic translated well to the model API. This was accomplished by evaluating the API-containing prototypes and making any necessary adjustments to the formulations owing to perceived differences between the performance of the mimetic and API.

Develop & Optimize the Flavor System

The next step was to develop the flavor system. The objective was to improve the coverage of the undesirable critical sensory attributes in the initial flavor and aftertaste by building a well-blended and full-bodied flavor. The structured approach shown in Figure 3 was followed to select flavoring ingredients.

The first step was to select appropriate flavor "themes" based on the market image profile for the drug product. In this case, the drug product was indicated for adults; therefore, pediatric flavors, such as bubblegum, were eliminated from consideration. Additionally, the drug product was intended for worldwide marketing, which required that the flavor have widespread appeal, eliminating esoteric flavors like honey, guava, or green tea.

Candidate flavoring materials were sourced from reputable suppliers, screened in aroma, and formulated into the mimetic placebo base at appropriate initial usage levels. Flavor Profile analysis was conducted to measure key attributes, such as aromatic identity and intensity, balance (blend) and fullness (complexity), lingering flavor, and mouthfeel characteristics.

The final step was to optimize the usage levels of all excipients, using designed experiments as appropriate and sensory panels evaluating the resulting prototypes for the aforementioned attributes. The excipient levels were then adjusted to further improve the balance and fullness of the final drug product. The sensory performance of the leading

FIGURE 7

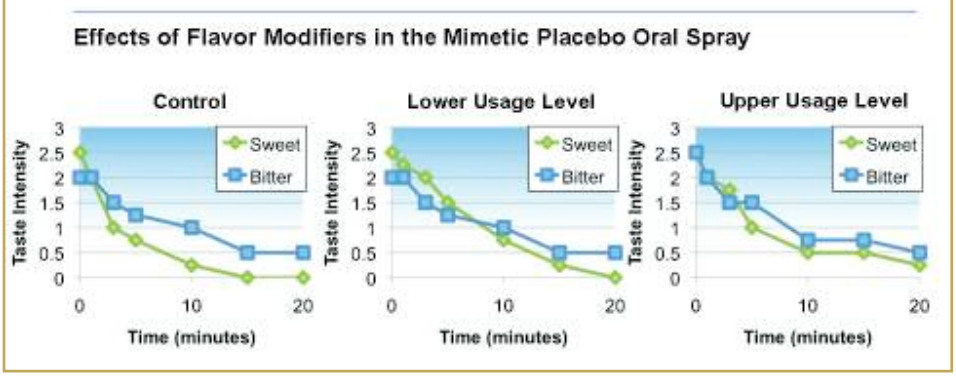
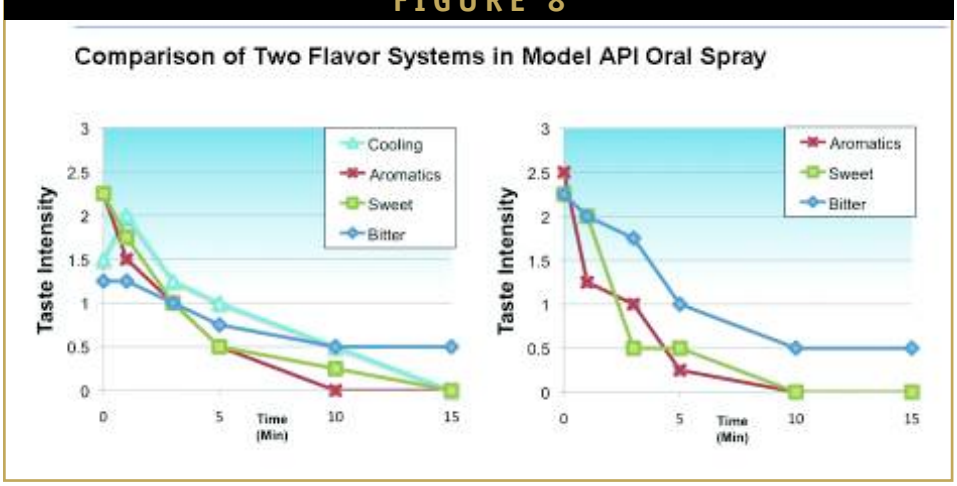


FIGURE 8



flavored formulations were verified in the API-containing drug product, and final adjustments were made to account for perceived differences between the API and mimetic.

In an effort to minimize the likelihood of chemical or physical instability, several different flavor systems were developed, each of which is expected to be patient-accepted based on overall palatability. Most importantly, the bitterness profile of each formulation was significantly reduced, and all exhibited ample initial and lingering sweetness. The flavor identity of each formulation was appropriate in impact and duration for the target patient population. The overall flavor profile was well blended such that no individual sensory characteristic "stood out" from the others. In some systems, the addition of low levels of mint produced a beneficial cooling mouthfeel and postponed the bitter breakthrough (bitter intensity rising above the sweet intensity). An example of this is shown in Figure 8. Selected formulations were placed on stability according to ICH guidelines to assess chemical and physical stability. Formulations were determined to be chemically and physically stable for up to 3 months.

SUMMARY

Oral spray drug delivery technology is capable of addressing unmet needs for a broad array of existing and future pharmaceutical products. In addition, palatable drug products improve the prospects for patient compliance and adherence. The sensory-directed formulation development approach described herein has been shown to yield a palatable oral spray product for an extremely bitter API.

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1. Keane PA. The Flavor Profile. In: Hootman RC, ed. Manual on Descriptive Analysis Testing for Sensory Evaluation. ASTM Manual Series: MNL 13. Philadelphia, PA;1992.

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BIOGRAPHIES

Jeffrey H. Worthington is President and Founder of Senopsys LLC, a specialty services firm dedicated to the development of palatable pharmaceuticals. He has more than 20 years of experience in taste assessment and optimization and has contributed to the development of numerous prescription and OTC medications. Mr. Worthington is a frequent author and speaker on the subject of developing palatable pharmaceuticals and serves on the NIH's Best Pharmaceuticals for Children Act - Pediatric Formulation Initiative. Prior to founding Senopsys, Mr. Worthington was Vice President of Pharmaceutical Technology at Arthur D. Little, Inc. He earned his BS in Chemistry from Northeastern University and his MBA from Babson College.

David A. Tisi is Technical Director at Senopsys LLC. Mr. Tisi is a trained descriptive sensory panelist and formulator with experience developing palatable foods and pharmaceuticals. Having spent his career at the intersection of food and pharmaceutical technology, he has particular expertise in applying food technology to the development of novel pharmaceutical dosage forms. Prior to joining Senopsys, he was a Scientist at TIAX LLC, where he managed and executed projects to improve the sensory quality of food and drug products. Mr. Tisi earned his MS in Food Science from Cornell University.

Dr. Frank E. Blondino is Executive Director of Formulation and Process Development at NovaDel Pharma Inc., a specialty pharmaceutical company developing oral spray formulations of a broad range of marketed therapeutics. Dr. Blondino has 13 years of experience in developing pharmaceutical products, including parenterals, inhalation aerosols, and oral sprays. Immediately prior to joining NovaDel, he was Associate Professor/Associate Director for Development Research in the Department of Pharmaceutics at Virginia Commonwealth University. He has also held positions at Magellan Laboratories, Baker Norton Pharmaceuticals, and Hoechst Marion Roussel. Dr. Blondino is co-inventor on more than a dozen patents and applications. He earned his BS in Pharmacy and his PhD in Pharmaceutics from Virginia Commonwealth University and is a licensed pharmacist.

Dr. Foyeke O. Opawale is Manager, Formulations Development at NovaDel Pharma Inc. Dr. Opawale has more than 10 years of experience in the research, development, and manufacturing of drug products and has held positions at different types of pharmaceutical companies, including OTC, biotech, generic, and specialty companies. She earned her BPharm from Obafemi Awolowo University, Ile-Ife, Nigeria, and her PhD in Pharmaceutical Sciences (Pharmaceutics) from the University of Connecticut. During her career, Dr. Opawale has gained extensive experience in the development of new liquid formulations for oral and transmucosal drug delivery, the formulation of topical drug products, development of conjugated protein formulations (liquid and solid dosage forms) for enhanced oral absorption, predicting emulsion stability from the investigation of interfacial properties of emulsifiers or surfactants, and microencapsulation via complex coacervation. She is a co-inventor on five patents and applications.