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Oral Drug Delivery Technology – Delivering on Patient Expectations

By: Jeffrey H. Worthington, MBA, and David A. Tisi, MS

INTRODUCTION

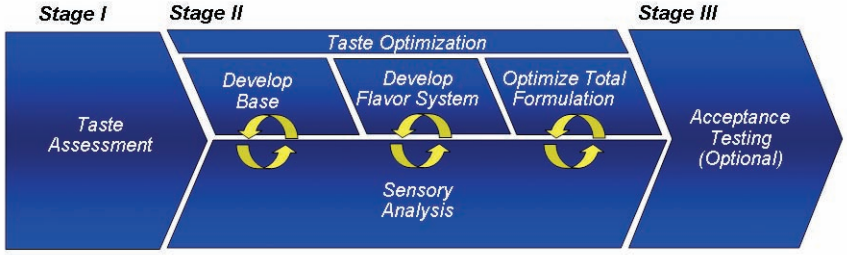
Today, most pharmaceuticals are developed and promoted exclusively on their medical benefits – superior efficacy, fewer side effects, faster on-set of action, or longer lasting (reduced dosing frequency) – many of which have been enabled by advances in drug delivery technology. While these medical benefits are of paramount importance, the product's aesthetics (appearance, aroma, flavor, texture, and mouthfeel) can have a significant effect on patient compliance. Unfortunately, drug products' aesthetic characteristics are under-considered and underutilized by many companies. This often leads to the launch of drugs that are unacceptable to many patients, despite their medical benefits. When medication compliance is compromised, health outcomes suffer and drugs fail to realize their sales potential. A properly formulated drug product that considers the aesthetic dimensions of patient acceptability will better serve the patient over the long-term and generate greater sales for the manufacturer and technology holder alike.

SENSORY ANALYSIS OF DRUG PRODUCTS

For the food and beverage industry, optimizing the sensory attributes of products is the top priority in the heated competition for "share of stomach." The mission of pharma companies on the other hand is to promote dosing compliance, not product consumption. Fortunately, patients have comparatively modest expectations of their medication. Most are looking for an "acceptable" tasting medicine – one that can be easily swallowed without gagging (odor), pain (trigeminal effects), or suffering (taste). This translates to a drug product with moderate sensory characteristics – not too bitter, not to odorous, not too irritating, not too gritty. Whether the formulation is orange, grape, bubblegum, chocolate, or mint flavored is of much lower importance to the lack of these negative sensory attributes.

FIGURE 1

Sensory-Directed Development Process



Stage I	Stage II	Stage III
• Characterize API • Quantify taste masking challenge • Establish flavor quality target	• Develop palatable formulations that meet established target • Sensory analysis of prototypes is used throughout this step to provide formulation guidance	• Conduct subject acceptance testing to: –Verify acceptability –Select preferred prototype

Regardless of whether the objective is to develop a "great-tasting" food or beverage or a "palatable" pharmaceutical, sensory analysis is required to effectively guide formulation development. There are two major classifications of sensory tests: affective and analytical. Affective tests determine customer (patient/consumer) response to products and are generally used by market research to test product concepts (eg, focus group), determine product preference, or to determine product acceptance (eg, degree of liking). Analytical tests are used to identify and quantify products' perceived sensory characteristics under controlled laboratory conditions. There are several types of analytical tests, including discrimination tests (used in quality control), grading tests (used in product quality labeling), and descriptive methods. The descriptive methods find the greatest application in formulation development and are discussed further herein. The reader is directed to the references for additional information on sensory analysis methods.

The descriptive methods provide complete characterizations of the sensory attributes of a product – appearance, aroma, flavor, texture, and mouthfeel. All descriptive methods involve the detection (discrimination) and description of both the qualitative and quantitative sensory aspects of a product by trained panels of judges (panelists or subjects). The qualitative factors are the individual perceived sensory aspects that define the product and are referred to by various terms, such as attributes, characteristics, character notes, or descriptors. The quantitative aspect of descriptive analysis expresses numerically the degree to which

each of the qualitative terms (attribute) is present, which is referred to as intensity. Use of reference standards for the qualitative terms and reference scales for intensity of different attributes ensures consistent application of the measurements across panelists and reproducibility across evaluations.

PROCESS FOR DEVELOPING PALATABLE DRUG PRODUCTS

Consumer packaged goods companies have evolved highly sophisticated processes, tools, and techniques for developing products that appeal to our sense, where product attributes, such as appearance, aroma, flavor, mouthfeel, skin-feel, and sound, are key product differentiators in these highly competitive industries. Pharma's primary focus is the safety and efficacy of its products with comparatively little resources devoted to product aesthetics, as this has not been the historic base of competition, particularly for prescription drugs. The sensory-directed process shown in Figure 1 has been adapted from the consumer packaged goods industry and provides a framework for developing palatable oral pharmaceuticals.

Stage I is sensory analysis of the API and benchmarking of competing products. This should be conducted as early in clinical development as possible (Phase II). One of the primary objectives is to characterize the API to identify and quantify its critical sensory attributes, eg, bitter basic taste, odor, and trigeminal effects, such as tongue sting or throat burn. It is particularly important that this assessment include measures of the temporal effects of the critical sensory attributes, which can significantly impact the taste-masking challenge. Additionally, if there are important competing marketed products, then it's vital to assess the sensory quality of these to ensure that the new drug product's aesthetics are as good as or better than the alternatives. The net result is the establishment of a sensory target for the drug product.

Stage II is the actual development of a series of palatable formulations that meet the sensory target established in Stage I. The development process consists of three discrete steps, beginning with the unflavored base and then the flavor system. One of greatest misconceptions in the pharma industry is the

FIGURE 2

Sensory Time/Intensity Profile of Marketed Drug Product Illustrating Complete Bitterness Coverage

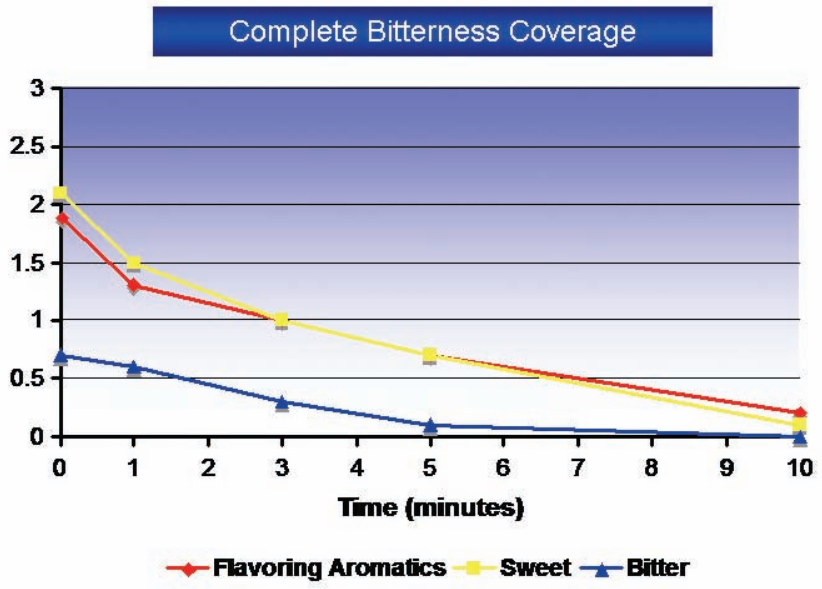


FIGURE 3

Sensory Time/Intensity Profile of Marketed Drug Product Illustrating Incomplete Bitterness Coverage

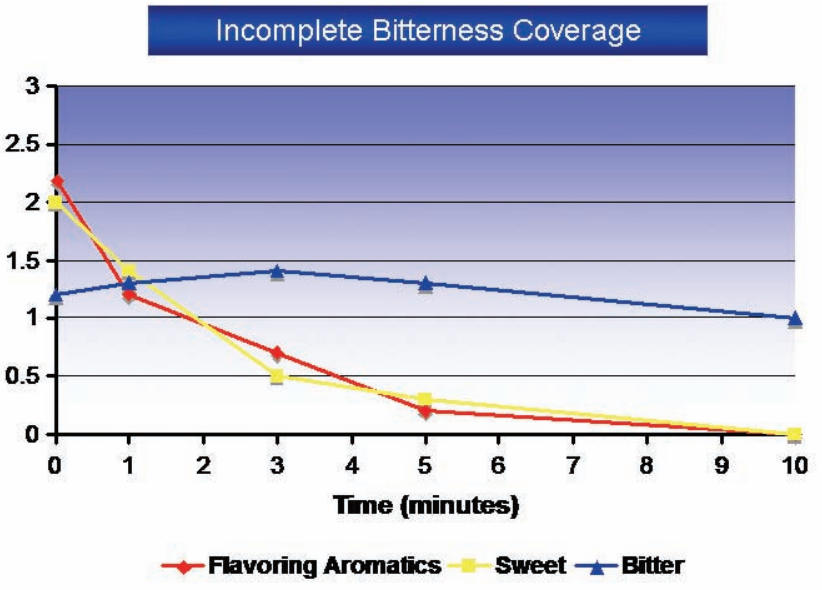


FIGURE 4

Sensory Time/Intensity Profile of Marketed Drug Product Illustrating No Bitterness Coverage

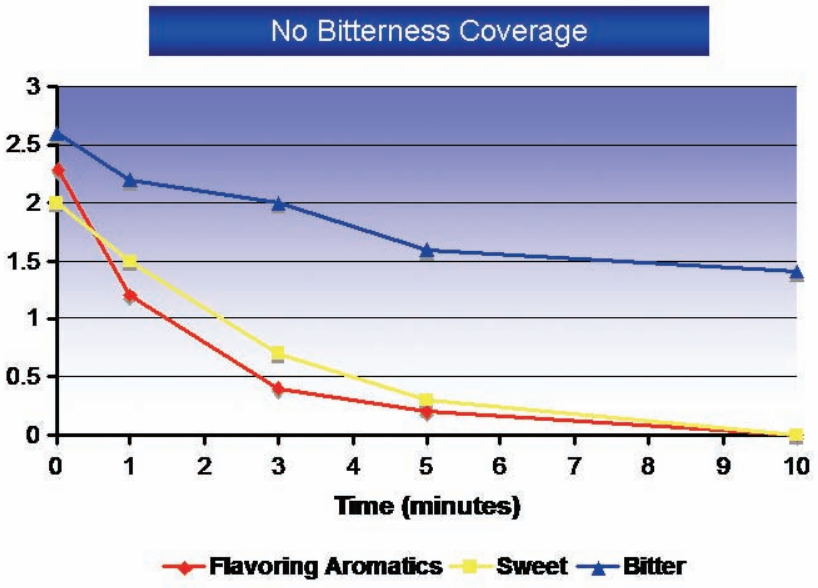
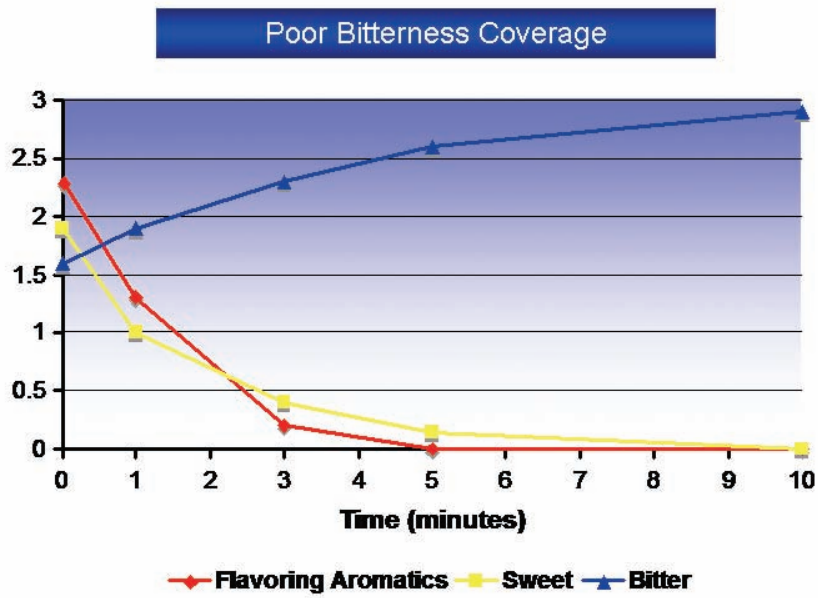


FIGURE 5

Sensory Time/Intensity Profile of Marketed Drug Product Illustrating Unique Bitterness Masking Challenge



belief that the key to bitter taste-masking is the selection of the appropriate flavoring material, eg, orange, grape, and strawberry. However, the anatomy and physiology of taste and odor perception are fundamentally different. Bitterness, like the other basic tastes (sweet, sour, and salty), is perceived through stimulation of the taste buds on the epithelium of the tongue. Flavoring materials are aromatics (odors) that are perceived through stimulation of the olfactory epithelium, which contains receptor cells and the free nerve endings of the trigeminal nerve. The olfactory receptor cells lie in the upper reaches of a small area of the nasal cavity, called the olfactory epithelium. Odors are perceived through two different routes — smelling directly through the nose (orthonasal) or during gustation when the volatile odorous molecules reach the olfactory center through the nasopharyngeal passage (retronasal). Understanding the differences in perception, one would not expect an aromatic flavoring material to mask a bitter or other basic taste. Stage II is structured in large part on an appreciation of the fundamental differences between taste and odor perception as will be discussed further.

Stage III is acceptance testing of one or more palatable prototype formulations developed in Stage II. This testing is most commonly conducted using healthy volunteers, but patients may be used as appropriate. The objective is to have the subjects select the preferred flavor type amongst a group of prototypes of similar flavor quality or to ensure that the prototypes meet the established target (eg, is liked the same or more than a competing product).

UNDERSTANDING PALATABILITY

Fundamentally, the flavor quality of a drug product is related to the perceived blend of the product's sensory characteristics. Many drug substances are bitter, and the perceived bitterness "stands out" from the other basic tastes (sweet, sour, salty). If the basic tastes are balanced through the proper selection and use of complementary excipients, then the bitterness of the drug substance will not be distinctly perceived, and consequently, the

drug product will be considered more palatable. The same concept applies to other basic tastes as well as trigeminal effects and odors; the key is to "blend away" the negative attributes. Importantly, patient acceptability of drug products is a function of both the initial flavor quality (ie, first 10 to 20 seconds following ingestion) and the aftertaste (ie, 1 to 10 or more minutes following ingestion). Get one of them wrong and palatability suffers. In general, this requires that the positive sensory attributes of the flavor system (specifically sweet basic taste and flavoring aromatics) be perceived at a stronger intensity than the negative sensory attributes (eg, bitterness) initially and throughout the aftertaste.

Time/intensity sensory profiles of four marketed prescription drug products will be used to illustrate the concept (Figures 2-5). Experienced pharmaceutical sensory panelists evaluated the four drug products using the Flavor Profile intensity scale, which ranges from none (0) to strong (3) and is defined with reference standards. For each drug product, the average intensity of the critical sensory attributes (bitter, sweet, and flavoring aromatics) is plotted as a function of time for 10 minutes. The area above a slight intensity (>1) has been shaded. In general, attributes at a slight intensity or greater can be readily perceived by most patients. Ideally, the negative attributes, in this case bitter, should be below a slight intensity, and the flavor system attributes (sweet basic taste and flavoring aromatics) should be greater than the perceived bitterness at each point in time.

The API shown in Figure 2 is not very bitter; most patients would not perceive the bitterness as it is well below a slight intensity. The flavor system (flavoring aromatics and sweet basic taste) provides complete coverage of the bitterness initially and throughout the aftertaste and will be readily perceptible to patients to about 5 minutes. This drug product is a pediatric antibiotic oral suspension and is widely considered by parents and pediatricians to be the "gold standard" of palatability based on ease-of-dose administration to children 2 years and older.

The API in the drug product illustrated in Figure 3 is more bitter than in the previous example but not extremely so. The problem is that the flavoring aromatics and sweetness decay quickly, exposing the bitterness, which remains above the "concern" intensity (>1) throughout the aftertaste. The challenge is to shift the sweetness and flavoring aromatics decay curves upward such that they are at or above the bitterness profile at each point in time. Fundamentally, this requires optimization of the flavor system to increase its initial impact and duration, a fairly straightforward exercise given the relatively low taste-masking challenge of this API.

The flavor system of the drug product shown in Figure 4 provides no coverage of the bitterness initially or at any point in the aftertaste. Unfortunately, the API is quite bitter with a relatively flat decay curve, which further exacerbates the problem. This API represents a difficult taste-masking challenge and would require complete reformulation of the excipient system in order to improve palatability. More specifically, this will require optimization of the sweetener system, necessitating the use of one or a combination of high-intensity sweeteners plus an underlying aromatic support system to extend the flavoring aromatics further into the aftertaste.

The drug product illustrated in Figure 5 represents an extremely difficult taste-making challenge. The flavoring aromatics and sweetness decay quickly, exposing the bitterness, which starts above the "concern" level (>1) and increases in intensity throughout the 10-minute aftertaste. In this case, the API is encapsulated, and the coated particles tend to get stuck between the teeth and under the gum line. As the coating dissolves, the extremely bitter API is continually released in the oral cavity where it binds strongly to the taste receptors. Food and beverages do little to ameliorate the bitterness of this drug product – a truly unpleasant dosing experience for patients of any age but particularly children. The flavor system of this product can certainly be improved; however, optimization of the coating system or another technology approach would be required to achieve a step-change improvement in palatability.

BUILDING A PALATABLE FORMULATION

Developing a palatable drug product is akin to building construction. As shown in Figure 1, the first step is to develop a solid foundation or base formulation. The base formulation consists of the API plus all of the excipients required for a commercial dosage form (buffers, preservatives, suspending agents, disintegrants, processing aids) plus the excipients added to improve palatability. The objective is to develop a "white" (unflavored) base. A "white" base exhibits balanced basic tastes (sweet, sour, salt, and bitter), which is the underpinning of taste-masking. The concept is to "blend away" the critical sensory attributes of the API, typically bitterness, through the selection and screening of appropriate excipients. It is particularly important at this stage to develop a robust sweetener system that produces a sweetness profile that closely matches the bitterness (or other critical attribute) profile of the API. Candidate excipients are selected based on knowledge of their sensory characteristics in the dosage form of interest. Screening experiments are then conducted to determine the applicability of the candidate excipients and to establish preliminary usage levels. To minimize human exposure of drug substances, it is often desirable to work with a Generally Recognized as Safe (GRAS) mimetic or surrogate for the API during the development process. In these situations, a preliminary step is required wherein an appropriate mimetic is identified and its usage level established to match as closely as possible the critical sensory attribute(s) of the API.

The next step is to develop the flavor system. The objective is to improve the coverage of the critical sensory attributes in the initial flavor and aftertaste by building a well-blended and full-bodied flavor. A structured approach is followed to select flavoring ingredients. To begin, reputable flavor suppliers that serve the pharmaceutical industry are asked to submit samples based on a description of the projects technical requirements. Experienced sensory panelists screen the

aroma of candidate flavorings to eliminate those with a low or inappropriate aromatic identity or the presence of off-notes, eg, solventy, soapy, aldehydic characteristics.

Flavoring materials that pass the initial aroma screening are then formulated into the pre-optimized (mimetic) base from the previous step. The flavor quality of the resulting prototypes is evaluated by the sensory panelists for key attributes, such as aromatic identity and intensity, balance (blend) and fullness (complexity), lingering flavor aromatics and sweetness, bitterness masking, mouthfeel characteristics, and off-notes. Often, multiple flavoring materials are required to provide the required degree of coverage.

The final step is to combine the most promising excipients from the previous two steps and optimize the usage levels of all excipients. No new excipients are introduced during this step; however, individual excipients may be dropped if their contribution to the overall palatability of the formulation is determined to be limited. Designed experiments may be employed to efficiently optimize the formulations, with the sensory panels evaluating the resulting prototypes for the aforementioned attributes.

BEYOND THE BENCHTOP

When a series of palatable flavored formulations have been developed, acceptance testing may be conducted to down-select to the subject-preferred (patient or healthy volunteer) prototype (Stage III). Most companies elect to advance a primary and back-up flavored formulation in the unlikely event of a compatibility issue with one of the flavor system excipients. In addition, manufacturers are advised to measure and monitor the sensory quality of the prototypes during manufacturing process development and scale-up to ensure that the flavor quality does not deviate from the original specification. Finally, sensory evaluation of stability samples is often conducted to ensure the flavor quality of the drug product is acceptable not just upon manufacture but also at its expiry date.

OPPORTUNITY

Advances in oral drug delivery technology continue to yield important medical benefits ranging from faster onset of action and improved side-effect profiles to more convenient dosage forms. However, many of these technologies have their own sensory challenges that will need to be addressed in order to fulfill their promise. While in vitro techniques, such as the "electronic tongue" are available, these techniques are of limited value to developers, particularly in the absence of correlations between human taste panel and instrumental responses for the specific API of interest. Additionally, advances in our understanding of the biochemistry of taste and odor perception may one day result in the discovery of new chemical entities that ameliorate the negative sensory attributes of many drug substances. In the meantime, drug developers would be well served by mining the food science and technology literature for information on quantitative sensory analysis, flavor construction, and the sensory characteristics of ingredients (excipients) in various formulation systems, all which are critical to developing palatable drug formulations. Palatable drug formulations improve the prospects for patient dosing compliance, which translates to improved health outcomes and increased product sales.

REFERENCES

1. Meilgarrd MC, Civille GV, Carr BT. Thomas. Sensory Evaluation Technique. 3rd ed. Boca Roton, FL: CRC Press;1999.

2. Neilson AJ, Ferguson VB, Kendall DA. Profile methods: Flavor profile and profile attribute analysis. In: Moskowitz H, ed. Applied Sensory Analysis of Foods. Vol. 1. Boca Raton, FL: CRC Pre3ss;1988.

BIOGRAPHIES

Mr. Jeffrey H. Worthington is Founder and President 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 over-the-counter medications. Mr. Worthington is a frequent author and speaker on the subject of developing palatable pharmaceuticals and serves on the National Institutes of Health'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.

Mr. 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, Mr. Tisi was a Scientist at TIAX LLC, where he managed and executed projects to improve the sensory quality of food and drug products. He earned his MS in Food Science from Cornell University.