DEVELOPING PALATABLE DRUG PRODUCTS

Top 10 Myths of Taste Masking

Many Active Pharmaceutical Ingredients (APIs) are extremely bitter or have other aversive attributes, which can make developing palatable drug products a daunting challenge. In addition, sensory science and the formulation principles associated with flavor construction are not well established within the pharmaceutical industry. In the absence of this knowledge, mythology tends to fill the void, which unfortunately can impede development of palatable drug products. The result can be suboptimal drug products that patients have difficulty taking or reject altogether. Yet when compliance suffers, so do health outcomes.

Our goal in writing this paper is to provide an overview of the science and formulation principles of taste masking to dispel the ten most common myths.

Taste and aroma are the same

One of the great myths of taste masking is that taste and smell are the same. We are routinely asked: "Which flavor – orange, grape, chocolate, or mint – is most effective in masking a bitter taste?" The answer is none. And the reason why stems from human physiology.

Tastes (or "basic tastes") are perceived through stimulation of receptor cells located in the taste buds on the epithelium of the tongue. There are five basic tastes – sweet, sour, salty, bitter and umami (savory) – each with distinct receptor pathways. Sour and salty tastes are perceived through ion channel receptors, detecting H^+ and Na^+ ions respectively. Sweet, bitter and umami are mediated by G-protein complexes, which upon detection of target molecules, initiate signal transduction cascades leading to taste perception. Sweet, bitter and umami are also similar in that each may be triggered by a large number of target molecules.

Odors (aromas), on the other hand, are perceived through stimulation of G-protein mediated receptor cells in the olfactory epithelium located in the upper reaches of the nasal cavity. These volatile aromatics reach the olfactory epithelium via the nose during inhalation (orthonasal olfaction) or via the nasopharangeal passage during mastication (retronasal olfaction). Odorant molecules bind to the receptor of an olfactory neuron, activating a G-protein-mediated reaction cascade that triggers the olfactory nerve, signaling the brain. Though each olfactory neuron only expresses a single receptor, that receptor can bind to multiple odorant molecules. Different combinations of activated receptors are perceived by the brain as a distinct odor.

The critical point in explaining the physiology of taste and aroma is to highlight their fundamentally different receptor/transduction pathways and loci of perception in the brain. Taste and aroma represent completely different modalities, just like the sense of sight is different than touch, and have no impact on one another. In this way, commercial flavoring aromatics – such as orange, grape, chocolate, or mint – cannot mask bitterness.

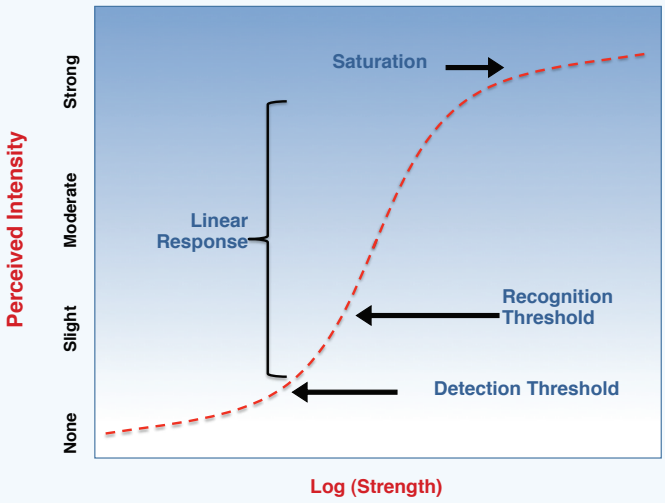
Taste is subjective and cannot be measured

Pharmaceutical products are developed, approved and marketed based on efficacy and safety. Tablets and capsules typically, but not always, offer good protection from aversive characteristics, and represent the majority of orally administered drug products. As the majority of oral medications are in tablet and capsule form, the need for developing palatable formulations represents a small fraction of all drug product formulation challenges. In contrast, the food industry is focused on developing great tasting products and has evolved highly sophisticated approaches, tools and methodologies for measuring and optimizing the sensory attributes (taste,

aroma, texture, mouthfeel) of products. Due to differences in their regulatory framework, there is little overlap between these two industries. As such, pharmaceutical professionals are generally unaware of the sensory analysis methods and formulation techniques available for use in guiding taste optimization.

Psychophysics is the scientific study of the relation between stimulus and perception. Nearly all stimuli (sound, sight, taste, smell, and taste) are shown to follow a log-linear signal response profile[1], idealized in **Figure 1**.

Figure 1. Illustrative Stimulus Response Curve



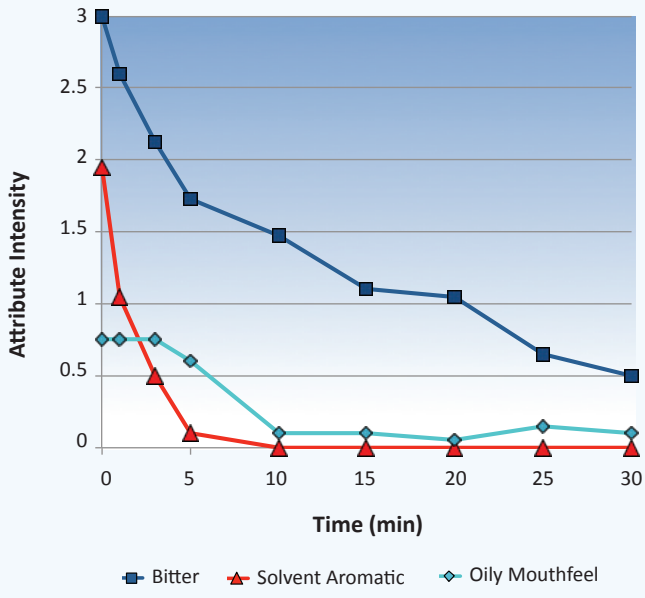
Below the detection threshold, stimuli cannot be perceived. At the detection threshold, stimuli can be perceived but not described. In the case of taste, the detection threshold is the point at which a subject would indicate a tasted solution as different than water, but could not describe the difference.

The recognition threshold is the strength at which stimuli elicit a qualitative response from the subject, e.g., "sweet," "cherry," or "cooling." As the stimuli strength increases, the signal enters a linear portion of the response curve whereby an increase in perceived intensity is proportional to the log strength. Finally, as stimuli strength continues to increase, a point of saturation is reached, beyond which large changes in strength are not perceived as stronger.

At low and high strengths, perceived changes in stimulus intensity become asymptotic to the change in strength. Therefore, in the field of sensory science, human taste panels are generally used to measure intensity changes in the linear portion of the stimulus response curve. These measurements are made using a variety of sensory analysis methods, such as the Flavor Profile Method, which was used to generate the data presented herein. Fundamentally these methods are used to 1) identify the perceived attributes (taste, aroma, mouthfeel, or texture) of a product, and 2) rate the intensity of each, although a more detailed discussion of sensory analysis methods is beyond the scope of this paper. The intensity rating scale is established using chemical reference standards and ranges from 0 (none) to 3 (strong).

The importance of this function cannot be overstated. Stimuli below the recognition threshold have no impact on flavor quality, and those above the threshold become clearly perceptible to subjects (patients). Therefore, to create a palatable drug product, aversive stimuli – bitterness, trigeminal irritation, malodor – must be kept below the recognition threshold (≤ 1). Correspondingly, the strength of positive (desirable) stimuli – sweetness and flavoring aromatics – needs to be above the recognition threshold (> 1). **Figure 2** is a graphical representation of intensity results as a function of time for an unsweetened/unflavored drug product. In this example, bitter basic taste and solvent aromatics would all be patient-perceptible, with bitterness perceptible for 20 minutes. On the other hand, oily mouthfeel can be measured by trained panelists but is not likely to be perceived by patients.

Figure 2. Example Time-Intensity Profiles



MYTH #3

A positive taste can be used to obscure a negative one

The art and science of taste masking is built upon the concept of proper flavor construction, where multiple ingredients contribute complementary characteristics that are well blended and not separately identified. For example, Coca-Cola® comprises hundreds of individual flavoring components that are hard to single out individually since the components are very well blended. Unlike most foods and beverages, the challenge for drug products is to "blend away" the negative sensory attributes of the API, e.g., bitterness. This is accomplished by blending with excipients that produce complementary and supporting basic tastes, aromatics and taste modifiers so that the bitterness is no longer separately perceived by the patient. Once this balance is achieved, identifying flavors such as orange, grape and bubblegum can be selected based on the patient demographics, dosing frequency and quality-of-life factors.

This important concept of neutral base creation can be illustrated with a simple demonstration. Four aqueous solutions representing the basic tastes – bitter, sweet, sour and salty – are shown in **Figure 3** along with the perceived intensity of each stimulus (column labeled "Intensity – Individual Solution"). By combining the excipients at the listed concentrations into a single aqueous solution, the perceived intensity of each basic taste is reduced substantially when properly blended (column labeled "Intensity – Combined Solution"). This simple experiment demonstrates how an aversive attribute like bitterness can be reduced with proper balancing of the complementary basic tastes – sweet, sour and salty. Since many APIs are significantly more bitter than caffeine, complex blends of excipients may be required to produce the effects described herein.

Figure 3. Intensity of Aqueous Basic Taste Solutions

			INTENSITY	
Basic Taste	Excipient	Concentration	Individual Solution	Combined Solution
Bitter	Caffeine	0.2%	3	½
Sweet	Sucrose	12%	2½	1
Sour	Citric Acid	0.15%	2½	1
Salty	Sodium Chloride	0.2%	½	½

MYTH #4

Only APIs require taste masking

Excipients serve many functions, including improving drug solubility (e.g., solvents, co-solvents, surfactants); maintaining physical, chemical and microbial stability (e.g., buffers, preservatives, antioxidants, suspending agents); enhancing disintegration; controlling release; and improving manufacturability, to name a few. It is often assumed that all excipients are bland-tasting relative to APIs; however nothing could be further from the truth.

Many excipients are known to impact the sensory attributes of drug products as illustrated in **Figure 4**. For example, excipients used to increase API solubility can contribute trigeminal irritation or malodors that are the principal source of aversive sensory attributes in a formulation. Chemical preservative systems may also impart aversive sensory attributes. For example, parabens can be challenging due to their aroma and trigeminal effects. Buffer systems can impart basic tastes (e.g., sour, salty) and trigeminal irritation (e.g., astringency, tongue sting). Other excipients may have their own set of aversive sensory attributes, each with different onset, duration and decay profiles.

All drug products contain excipients and formulators need to be cognizant not only of the function of each excipient, but of their sensory characteristics.

Figure 4. Sensory Attributes of Selected Excipients

Excipient	SENSORY ATTRIBUTES		
	Basic Tastes	Aromatics	Trigeminal Sensations/ Mouthfeels
Methyl Paraben	--	Phenolic	Numbing, tongue sting
Polysorbate -80	Bitter	Oxidized oil, soapy	--
POLOXAMER 188	Bitter	Oxidized oil, soapy	--
Polyethylene Glycol	Bitter	Oxidized oil	Oily
Acesulfame Potassium	Sweet, bitter	--	--
Propylene Glycol	Sweet, bitter	--	Oily, warming
Glycerin	Sweet	--	Oily, soapy
Sodium Bicarbonate	Salty, bitter	"Fishy" amine	Saline
Silicon Dioxide	--	Musty	Chalky, drying
Magnesium Stearate	Bitter	"Fishy "amine	Waxy

MYTH #5

The most intense sweetener is the best sweetener

There are numerous nutritive sweeteners (e.g., sucrose, fructose and glucose) and non-nutritive sweeteners (e.g., sugar alcohols and high intensity sweeteners). Each has a different relative sweetness, onset and duration, which must be considered to select the most appropriate candidate(s).

Nutritive sweeteners and sugar alcohols generally have linear dose-response curves, while high intensity sweetener curves are generally nonlinear[2], as illustrated in **Figure 5**. As such, several high intensity sweeteners cannot provide the equivalent sweetness of sucrose at moderate (2) or strong (3) intensity, even at extremely high concentrations, as their sweetness response curves asymptote before reaching a strong intensity (See Acesulfame-Potassium in figure 5). This effect is evidenced by the frequent use of acesulfame-potassium in combination with other sweeteners in highly sweetened products such as soda.

The nonlinearity of high intensity sweetener dose-response data makes it impossible to express sweetness as a single value. Yet sweetener intensities are widely reported as a single multiple in the literature (**Figure 6**), without reference to the corresponding sucrose concentration. This is an over simplification that often leads to inappropriate sweetener choices.

Figure 5. Concentration Response Curves for Selected Sweeteners

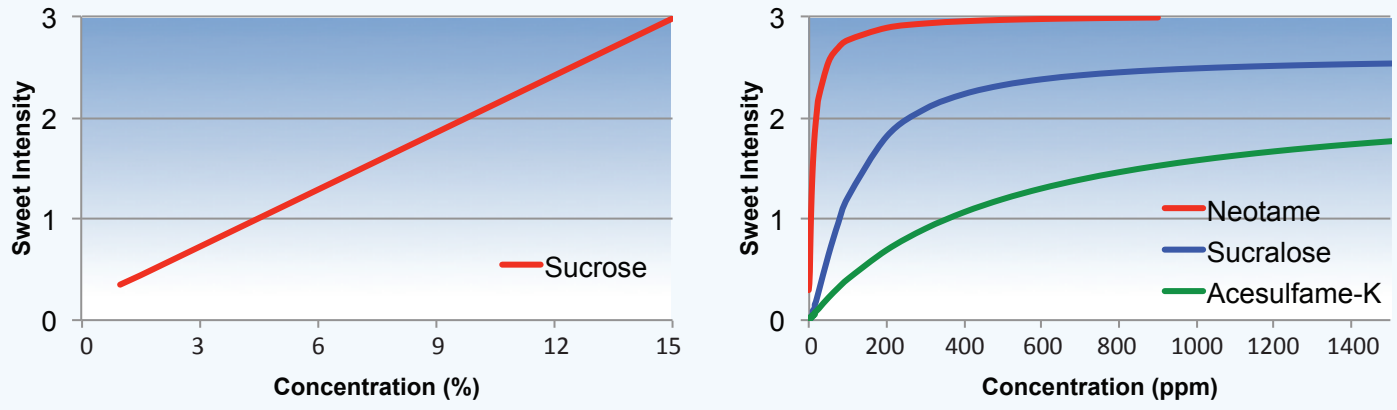


Figure 6. Relative Sweetness Intensities

Sweetener	Commonly Reported Sweetness (Sucrose =1)
Neotame	8000
Sucralose	600
Acesulfame-Potassium	200
Sodium Saccharin	300
Stevioside	250
Fructose	1.3
Glucose	0.6

Even at the same intensity, sweetness onset, duration and decay profiles differ between sweeteners as illustrated in **Figure 7**[3]. The sweetness profile of sucrose is the "gold standard" in the food and beverage industries where a short aftertaste is desired. For APIs with lingering bitterness, a longer sweet aftertaste may be appropriate, requiring use of high intensity sweeteners. Additionally, many formulations require combinations of bulk and high intensity sweeteners to provide the requisite sweetness profile to blend effectively with the other basic tastes in the initial flavor and aftertaste.

Finally, there is a tendency to overuse sweeteners in the belief that more is better; however this can have a deleterious effect on palatability. Several high intensity sweeteners become bitter at concentrations above their functional levels, most notably saccharin and acesulfame-potassium.

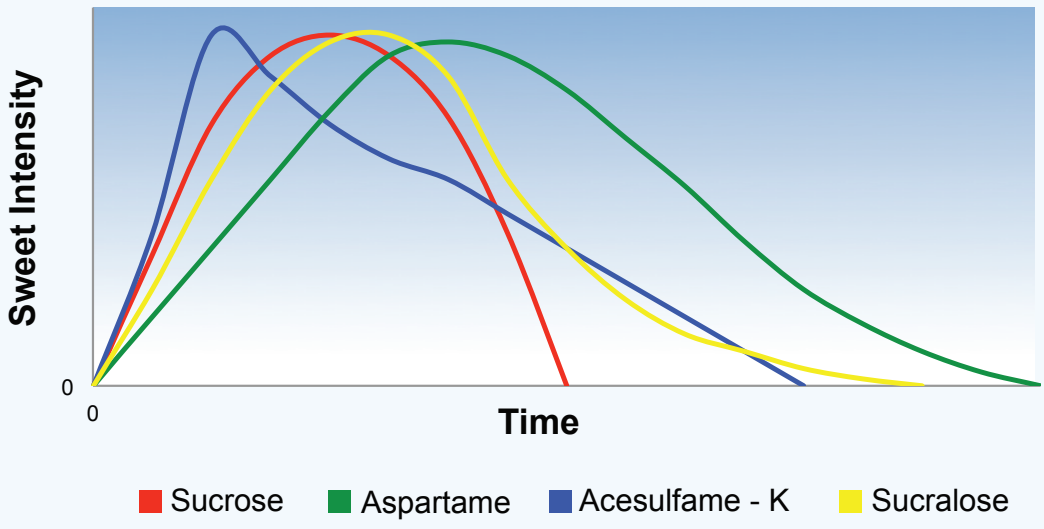
Sweetener system performance cannot be predicted a priori, and must be assessed within the specific base formulation through appropriate experimental design. As described herein, the process is far more complicated than simply choosing the most potent sweetener.

Flavor preference determines acceptability

Much has been written about the need to develop palatable pediatric drug products but the word "palatable" is open to interpretation. Common definitions include "agreeable to the palate or taste" (Merriam-Webster); and "acceptable to the taste; sufficiently agreeable in flavor to be eaten" (The Free Dictionary). The food industry strives to create products that "delight the palate" as flavor quality drives sales. Medicines, on the other hand, are developed primarily for efficacy and safety. Palatability is necessary to ensure dosing compliance, rather than to promote consumption, and is therefore of secondary importance.

Palatable drug products are those in which the aversive sensory attributes have been minimized or eliminated. They are not overly bitter, produce little trigeminal irritation, are

Figure 7. Sweetener Time-Intensity Curves



smooth not gritty and have no perceptible malodors. The degree to which the negative attributes have been eliminated, on balance, is the true measure of palatability.

A common myth is that incorporation of "desirable" (positive) flavoring aromatics – orange, grape, chocolate, or mint – is the primary determinant of palatability, when in actuality, the presence of positive attributes is much less important than the absence of negatives. Time and energy are often wasted in a futile attempt to find a "silver bullet" flavor or sweetener rather than pursuing the more productive task of reducing aversive attributes.

Adult panelists cannot be used to guide the development of palatable pediatric drug products

To dispel this myth we must look at how flavor preferences are formed during child development and apply this knowledge to the underlying driver of palatability: the absence of aversive attributes.

Children are born with a mostly complete ability to detect the chemical stimuli around them. Though their cognitive faculties lack the ability to recognize and integrate odors and tastes, the biochemical means to detect these stimuli is present at birth. Taste buds begin to form in utero, first appearing around the 7th or 8th week of gestation, and fully formed by 13 to 15 weeks[4]. At birth, children have an inherent aversion to bitter taste and fondness for sweetness. From an evolutionary standpoint, this instinctual behavior makes sense – compounds that have a sweet taste are generally sources of energy, and many of those that are bitter can be poisonous. This preference/aversion is inherent in all cultures and is well conserved even between species. After birth, the sensitivity of taste detection holds relatively constant until old age. Over time adults may learn to accept and appreciate the bitterness of individual foods, such as beer, coffee, and chocolate, but this tolerance is product-specific. For the most part, adult humans retain their infantile preference for sweets, and dislike of bitter foods.

The body's aroma-detecting olfactory bulbs and receptor cells are also developed in utero, and have attained adult-like morphology by the 11th week of gestation. However unlike their instinctual taste preferences, a child's liking of certain aromas is a learned response. Children develop preferences based on aromatics that have been provided to them, preferably those that have been experienced in a calm, nurturing environment. It has been shown that this familiarization process begins prenatally, as the baby is exposed to amniotic aromas reflecting foods consumed by the mother[5]. This makes aroma preference more culturally specific, as infants from different parts of the globe are exposed to varied foods. Humans are constantly expanding their library of familiar aromas as they age, however, as with taste, sensitivity to aromas is generally constant throughout adult life, decreasing slightly in the elderly.

As discussed previously, palatability is most associated with the lack of aversive attributes. Since children and adults have similar sensitivities, negative attributes that are not perceptible to adult panelists will not be perceptible to pediatric patients. This similarity allows trained adult panels to effectively be used to measure the sensory attributes and guide development of palatable pediatric drug products.

In formulating drug products, once the aversive attributes have been ameliorated, child specific adjustments can be made. For example, children tend to prefer more intense sour and sweet tasting formulations than do adults, and are familiar with fewer aromas[6]. Accordingly, general preference differences by age should be taken into account when selecting sweetener levels and flavors.

Patient studies are effective in guiding formulation development

The term "acceptance" is widely used in the context of dosing compliance. Regulatory agencies increasingly require sponsors to conduct palatability studies to ensure "acceptability" of pediatric drug products as part of a Pediatric Investigation Plan (PIP). However, as will be described, there are no direct measurements of product acceptance, so what is the alternative?

Affective tests measure human response to products, and are extensively used in the consumer products industries. This type of testing is performed using untrained respondents, ideally the target consumer. Affective tests can be conducted on either an absolute or relative basis. An absolute test would

use language similar to: "On the following 7-point scale, how much do you like this product?". Preference tests measure one product relative to another e.g., "Which product do you prefer: A or B?" Both types of tests may be modified for pre-verbal children and infants by including caregiver interview questionnaires, facial expression interpretation or, for slightly older children, Likert-type pictorial hedonic scales.

Comparator products are often used in the consumer products industries to measure preference. For pharmaceuticals, however, appropriate comparator products of known palatability are generally not available. In addition, there are significant ethical and regulatory challenges associated with conducting palatability studies of multiple drug products.

In the absence of direct measures of product acceptance, inferences are made based on liking scores, preference ratings, use tests, purchase intent and other measurements that are subsequently correlated with post-market sales. Over time, companies build experience-based databases to support commercial decision-making. In the case of drug products, post-market data is generally not available to establish such relationships.

The execution of pediatric (or adult) palatability studies poses numerous challenges: subject recruitment, ethical considerations (informed consent/assent), methodological concerns (test instrument, scales) and outcome assessment. Industry is equipped to handle challenges associated with recruitment, ethics and measurement of patient response to products. However, since there is no direct measure of product acceptance, industry is left without guidance for interpreting the outcome of the palatability studies. Thus while pediatric palatability studies may fulfill regulatory requirements, they are insufficient to guide development of palatable drug products.

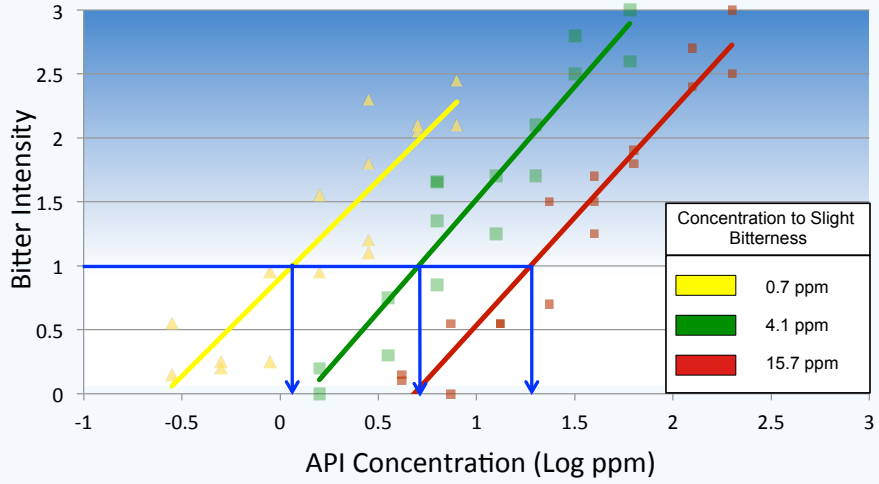
MYTH #9

Solids and suspensions don't require taste masking

It is commonly thought that a moiety must be in solution in order to be perceived by the taste receptors located on the tongue (sweet, sour, salty, bitter). This principle often and quite naturally leads one to presume that solids cannot be perceived. However, this overlooks the fact the many compounds can produce sensory effects at extremely low concentrations – parts-per-million, parts-per-billion and perhaps lower. Even some of the most intractable, poorly soluble drugs will have enough solubility in saliva to be perceived, particularly at the mucosal interface, where localized pH, osmotic force and molecular geometry may enhance dissolution. Even particle coated APIs can be perceived due to variable processing or incomplete coating. There are many examples of bitter oral suspensions, including OTCs such as ibuprofen and pseudoephedrine, and antibiotics such as clarithromycin and others.

Figure 8 represents the dose response curve for three aqueous antibiotic suspensions. Though sparingly soluble in water, these aqueous suspensions show bitterness response at low concentrations. For a numerical comparison, the API concentration necessary to reach the perception threshold of a slight intensity bitterness of 1 was calculated at 0.7, 4.1 and 15.7 ppm for the compounds below. Imagine the bitterness at clinically relevant concentrations!

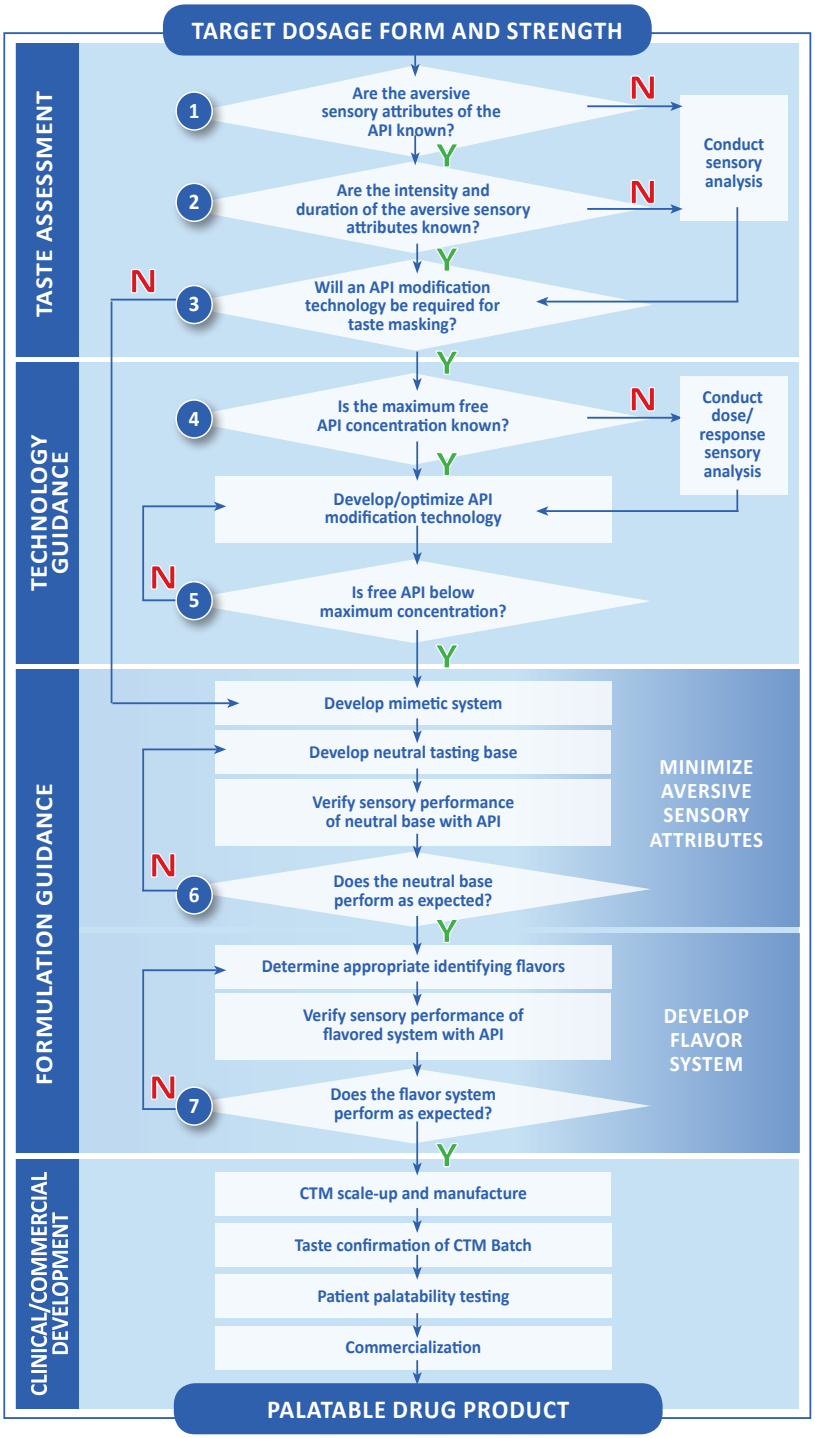
Figure 8. Dose Response Curves of Aqueous Suspensions



MYTH #10

There is not a well-defined process for developing palatable drug products

Figure 9. Palatable Drug Product Development Process



Development of palatable formulations is necessary for only a small fraction of all drug product dosage forms. Not surprisingly therefore, sensory analysis and flavor optimization are not core competencies of the pharmaceutical industry. Yet well-defined processes for developing palatable products are nevertheless available to the industry.

Figure 9 outlines a structured, sensory-directed system for developing palatable drug products. This approach was devised during Senopsys' decades of experience in the highly competitive food industry, where taste is the key market success factor. It integrates rapid formulation prototyping and taste assessment by trained, GCP-complaint human panelists to efficiently optimize drug product aesthetics, including aroma, taste, texture and mouthfeel.

The flowchart is divided into 4 sections. The top section labeled "Taste Assessment" contains the key questions that need to be answered to support the development of age-appropriate clinical trial materials. It is specifically related to the sensory attributes of the API at the target dosage strength, e.g., bitter, sour, trigeminal irritation, odor and the magnitude of these effects.

If the initial taste assessment indicates a requirement for a taste-masking technology, such as encapsulation or adsorption (i.e., a difficult challenge), additional questions need to be answered to guide development. These are highlighted in the "Technology Guidance" section of the flow chart. Here the goal is to establish the maximum free-API concentration that can be accommodated in the drug product formulation and still be palatable.

The "Formulation Guidance" section outlines a strategy for developing palatable drug products and is separated into two distinct parts. The first part is intended to minimize or eliminate the aversive

(negative) attributes of the API by creating a "neutral" tasting base. Once the aversive attributes have been successfully ameliorated in the neutral base, the second part of formulation guidance begins by adding the "desirable" (positive) attributes of the flavor system, specifically the age-appropriate sweetness, flavoring aromatics and feeling factors.

Following taste optimization of the drug product, the formulations are scaled up to Clinical Trial Material (CTM) batch size with requisite compatibility and stability testing. Selected steps are shown in the last section of the flowchart, labeled "Clinical/Commercial Development." Since the target shelf life for most drug products is two years, the goal is to ensure the drug product remains palatable over the full expiry period. To ensure consistent flavor quality, it is common practice to assess the sensory attributes of stability samples at 6-month intervals within the target expiry period.

Myths Busted

The concepts of flavor and good taste, though ancient, are incredibly complex, and lay at the intersection of biochemistry and psychology. Though we all have experienced flavor, our perceptions many times belie what is happening chemically, giving rise to some common myths surrounding taste.

How to Learn More

The authors hope to have dispelled many common myths about taste masking. To learn more about the process for developing palatable drug products depicted in **Figure 9**, contact Senopsys to arrange a private "lunch & learn" seminar for your team. These seminars build on the information described herein and explore through case examples a proven sensory-directed process for optimizing the palatability of drug products.

Senopsys – Dedicated to the Development of Palatable Drug Products

Whether your goal is to develop a new product, manage a product's lifecycle, or comply with regulatory requirements such as the U.S. Pediatric Research Equity Act (PREA) or EU Pediatric Investigation Plans (PIPs), Senopsys can help you develop formulations that will enhance patient compliance, increase product sales and improve health outcomes.

Senopsys provides a range of development services to improve the palatability of drug products:

Taste Assessment - Senopsys uses proprietary, GCP-compliant taste assessment tools to identify the taste attributes of APIs and drug products, measure the flavor quality of drug product prototypes and guide taste optimization.

Taste Optimization - Senopsys' formulation scientists are experienced in the art and science of taste masking, flavor construction, excipient functionality and processing technology. We develop palatable liquid, powder and solid dosage forms of investigational and approved drugs.

To learn more about our services or to schedule a seminar on taste optimization of drug products, please contact:

Jeff Worthington, President & Founder
jeff.worthington@senopsys.com
781-935-7450

David Tisi, Technical Director
david.tisi@senopsys.com
781-935-7451

1 Meilgaard M, Civille GV, Carr BT (1999) Sensory Evaluation Techniques. CRC Press: Boca Raton, FL. 45-51.
2 "Sweeteners: Discovery, Molecular Design, and Chemoreception," D.E. Walters et al., Eds., American Chemical Society, 1991.
3 Adapted from: Kelelsen SM, Keay SG, Wiet SG. "Time-Intensity Parameters of Selected Carbohydrate and High Potency Sweeteners. Journal of Food Science. 6.58 (1993), 1418–1421
4 Witt M, Reutter K. "Embryonic and early fetal development of human taste buds: a transmission electron microscopical study". The Anatomical Record. (1996) 246(4):507-23.
5 Marlier L, Schaal B, Soussignan R. "Neonatal responsiveness to the odor of amniotic and lacteal fluids: a test of perinatal chemosensory continuity". Child Development. (1998); 69:611– 623
6 Liem DG "Sweet and Sour Taste Preferences of Children". Thesis Wageningen University 2004.