

# Helping the Medicine Go Down

All aspects of the sensory experience need to be considered when it comes to developing patient-acceptable drug products.

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Jeffrey H. Worthington, BS, MBA is the founder of Senopsys LLC, a specialty services company that partners with pharmaceutical, biotechnology and drug delivery companies to develop palatable drug products. He has over twenty years' experience in the field and has contributed to the clinical and commercial development of numerous prescription drugs – including paediatric formulations – for diverse indications and a wide variety of over-the-counter medications. Mr Worthington is a frequent speaker on the subject of developing palatable pharmaceuticals, and serves on the US National Institutes of Health's Pediatric Formulation Initiative.



**The market for paediatric medicines is large and growing, spurred in part by regulatory requirements and economic incentives in the United States and soon in Europe. Developing palatable oral pharmaceuticals can be a daunting challenge – a challenge that parents everywhere feel the industry has not adequately overcome. But it's not just children that are affected by unpalatable drug products. Difficulty in swallowing (dysphagia) is common among all age groups, especially the elderly and those afflicted with certain progressive neurological disorders; these patients require easy-to-swallow dosage forms that unfortunately cannot bypass the sensory receptors of the oral cavity.**

Technology advances are leading to the development of novel oral dosage forms that provide a faster onset of action with fewer side effects. However, many of these technologies have their own sensory challenges that will need to be addressed in order to fulfill their promise. All of these factors portend an increase in demand for palatable drug products. On the other side, advances in our understanding of the biochemistry of taste and odour 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, demand for palatable drug products is likely to continue to rise. In this article we discuss the issue of palatability, review the anatomy and physiology of flavour perception, and introduce methods of sensory analysis that can be used to guide the development of palatable drug formulations.

## THE DEFINITION OF PALATABLE

The Merriam-Webster online dictionary defines palatable as "something agreeable or pleasant especially to the sense of taste." The American Heritage Dictionary definition is somewhat broader: "acceptable to the taste; sufficiently agreeable in flavour to be eaten." The terms

taste and flavour are often used interchangeably; however they are not the same, as will be discussed later.

The food industry provides consumers with vast product choices, representing a myriad of aromas, flavours, colours, textures and 'mouth-feels' to promote consumption at seemingly all times of day, occasion and location. Patients, unlike consumers, do not look forward to taking their medication – and pharma's mission is to promote dosing compliance, not product consumption.

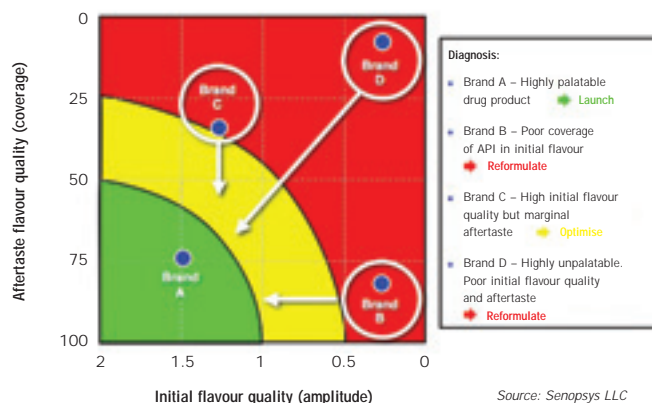
Most patients expect an 'acceptable' tasting medicine, one that is not so disagreeable that it requires great determination to swallow. This translates into drug products with moderate sensory characteristics – not too bitter, not too hard, not too gritty, not too chalky, not too irritating. Whether the formulation is orange, chocolate or mint-flavoured is of much lower importance to the lack of these negative attributes. In other words, it's the product's overall sensory quality that determines its palatability, not the flavour type.

## THE ANATOMY AND PHYSIOLOGY OF FLAVOUR PERCEPTION

Flavour is a combination of taste (gustation), smell (olfaction) and trigeminal sensations. Taste is perceived through stimulation of receptor cells clustered in the taste buds on the epithelium of the tongue. There are five basic tastes – sweet, sour, salty, bitter and umami (savory). Many drug substances are known to be bitter – some extremely so.

Odours 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 the nasal cavity, called the olfactory epithelium. Odours are perceived through two different routes – smelling directly through the nose, or during gustation when the

Figure 1: Drug palatability profile



volatile odorous molecules reach the olfactory centre through the nasopharyngeal passage. Thus, when someone describes his or her favourite flavour, they are more properly referring to the product's odour or aroma.

In addition, compounds found in ginger, horseradish and mint stimulate the endings of the trigeminal nerve producing sensations of warmth, burning, stinging, cooling and pungency in the mucosa of the nose and mouth. These trigeminal sensations are anatomically independent from the senses of taste and smell, but are important characteristics of many products, including drugs.

The distinction between taste and odour has important implications for drug developers. Many drug substances are bitter, yet developers often focus on the addition of flavouring materials (for example, orange, cherry, mint) to the formulation to improve its palatability. Understanding the physiology of taste and smell, one would not expect an aromatic flavouring material to mask a basic taste – bitter or otherwise.

A product's appearance and physical characteristics while it is masticated are also important to the overall sensory experience. Take colour for example. Is the colour natural in appearance? Is it consistent with patient flavour expectations, for example, a red colour for strawberry? The textural attributes of the dosage form can have a dramatic affect on patient acceptability. Is the chewable tablet too hard? Does it disintegrate into imperceptibly small particles or is it gritty? Does the soft chew stick to the teeth and palate making mastication difficult? Does the liquid provide an oily or waxy mouth-feel?

In order to develop patient-acceptable drug products, all aspects of the sensory experience need to be considered. Get any one of them wrong and palatability suffers – along with patient dosing compliance, health outcomes and product sales.

## SENSORY ANALYSIS METHODS

Numerous articles and reviews of taste-masking technology can be found in the pharmaceutical literature. However, comparatively little is available on pharmaceutical sensory analysis, which is critical to developing palatable drug formulations.

There are two major classifications of sensory tests: affective and analytical. Affective tests determine patient/consumer response to products, and analytical tests measure the perceived sensory attributes of products. Affective tests include preference and hedonic (liking) tests to compare products; these tests are often used to support product launch decisions and product positioning, including advertising claims. Humans have little difficulty telling whether they like or dislike a product, or which product they prefer. However, their ability to reliably describe the reason for their likes, dislikes and preferences and – more importantly – to offer meaningful suggestions for improvement is notoriously poor. Thus the affective tests are of limited value to developers.

Analytical tests are used to identify and quantify products' perceived sensory characteristics under controlled laboratory conditions. Analytical tests include discrimination tests, grading tests, ratings by expert tasters and descriptive methods.

Discrimination testing is used for detecting differences between products and test methods include the Paired-Comparison, Duo-Trio and Triangle (1). Because these methods provide little information about the nature of the differences, they are of limited value to developers.

Grading tests are used mainly in the meat and dairy industries to rate products on specific attributes such as physical appearance (colour, shape, size) and flavour and texture characteristics. The product score depends on the extent or severity of any defects noted in these areas. These methods are used to support commercial labeling and are of limited value to developers.

Expert tasters are employed in certain 'craft' industries such as wine, beer and tea, where production largely remains an art form. Extensive training, often involving apprenticeship, is required to become an expert taster. Expert tasters are generally not employed in the science-driven pharmaceutical industry.

Descriptive methods provide complete characterisations of the sensory attributes of a product – aroma, flavour, texture and mouth-feel; methods include Flavour Profile, Profile

Attribute Analysis and Quantitative Descriptive Analysis, and are used in product development and quality control (1,2). The descriptive methods were developed in the food industry where taste is paramount and, more recently, have been applied to create palatable drug formulations.

Sensory analysis of pharmaceuticals naturally involves human exposure to drug substances, and therefore proper precautions must be taken to ensure the safety and well-being of the evaluators, including Good Clinical Practices for Investigational New Drugs. So called 'sip and spit' tasting protocols are recommended to minimise human exposure to drug substances, as is the use of Generally Recognized as Safe (GRAS) surrogates for the Active Pharmaceutical Ingredient (API) during the development process. Additionally, instrumental taste and odour measurement is finding application in quality control to detect lot-to-lot differences and reduce the sample burden on human taste panels. There are comparatively few applications of these instrumental techniques in formulation development, owing to the general lack of API-specific data correlating the human taste panel with instrumental response.

#### CREATING A PALATABLE DRUG FORMULATION

At the most fundamental level, the palatability of a drug product is determined by the perceived blend of its sensory characteristics initially (that is, the first 10-20 seconds following ingestion) and throughout the aftertaste (that is, 1-10 or more minutes following ingestion). Many drug substances are bitter and this perceived bitterness 'stands out' from the other basic tastes. 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. This lack of a perceived negative results in a more palatable drug product. The same concept applies to other basic tastes, as well as trigeminal effects and odours – the key is to 'blend away' the perceived negative attributes.

Palatable pharmaceuticals have a flavour that develops rapidly, and is full-bodied and well-balanced. This requires several compatible elements in the proper proportions, perceived in the proper order, and supported by a complex body of underlying sensory impressions not separately identified. Unlike foods and beverages, the flavour systems of many drug products are very simple and thin providing poor coverage of the API. Amplitude – an integrative measure of balance (degree of blend) and fullness (degree of complexity) used in several descriptive methods – has been shown to correlate with patients' immediate acceptance of drug products.

The degree of coverage of the 'negative' sensory attributes remaining a minute and longer following ingestion is the key measure of the acceptability of the after-taste. For many APIs, the after-taste is most critical as many flavour systems provide adequate coverage in the early aftertaste but these beneficial effects quickly decrease, exposing the API. As a general rule, it is easier to mask a strongly bitter API that 'fades' quickly (steep decay curve) versus a moderately bitter API initially that lingers well into the aftertaste (flat decay curve) – or worse, an API with bitterness that builds. The challenge for the formulator is to mask the taste of the active throughout the duration of the after-taste – be it 30 seconds or 30 minutes!

As mentioned earlier, patient acceptability of drug products is a function of both the initial impression and the after-taste. This concept is illustrated in Figure 1, where initial flavour quality (Amplitude) and after-taste flavour quality (API Coverage) are plotted together. Empirically-derived decision boundaries have been overlaid to translate descriptive analysis results into palatability. This type of empirical model can be used to guide formulation decision-making during clinical and commercial development.

#### THE OPPORTUNITY FOR DRUG MANUFACTURERS

The food industry focuses on providing consumers with great-tasting products that provide both sustenance and enjoyment – so it's no surprise that quantitative sensory analysis has been employed for over a century. However, because palatability has not been the primary concern of drug manufacturers, knowledge of sensory science, the principles of flavour construction and the sensory characteristics of excipients are not well imbued within the pharma industry. The opportunity for drug manufacturers is to translate relevant 'best practices' from the food industry to guide the development of palatable drug formulations. Such a strategy would improve the prospects for patient dosing compliance – translating into improved health outcomes and increased product sales.

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