Using an Electronic Tongue to Optimize Taste-Masking

in a Lyophilized Orally Disintegrating Tablet Formulation

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Formulators must consider a wide range of factors in producing an acceptable lyophilized orally disintegrating tablet product. The electronic tongue technology provides a technically suitable and cost-effective method for screening and directing taste formulation, while eliminating both safety concerns and subjective bias.

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Making orally disintegrating tablets (ODTs) and their active pharmaceutical ingredients (APIs) palatable is one of the most significant technical obstacles to "patient friendly" formulations.

This is particularly important for lyophilized tablets, which disintegrate nearly instantaneously when placed on the tongue. The formulation's organoleptic properties—taste, mouth-feel and appearance—are of considerable importance in differentiating products in the market and can ultimately determine the success, or otherwise, of a product.

Pharmaceutical taste-assessment typically requires a large, trained taste panel, and sophisticated interpretation. The tests may require the same health safeguards as a clinical trial. All told, a properly conducted taste test adds time and money to the development process.

Here, we describe an objective, quantitative approach to ODT taste analysis and taste masking, using an electronic sensor array, the "e-tongue."

Background

Some of the characteristics that make ODTs valuable for drug delivery also pose special challenges to palatability. The tablets are very porous, which allows water to penetrate instantly, dissolving the matrix and releasing the active pharmaceutical ingredient. Thus, patients may take ODTs without water, and without the compliance issues often associated with swallowing solid

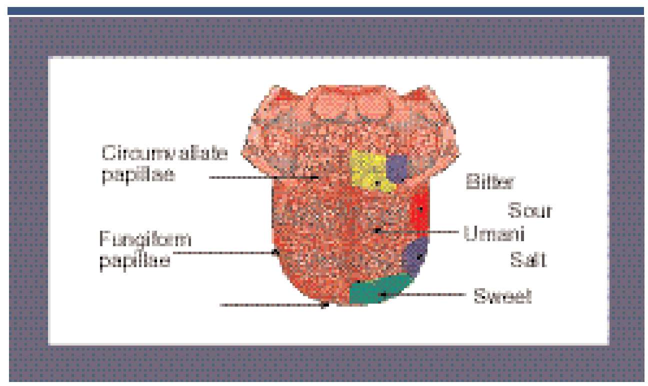

Figure 1: Diagram of the tongue surface showing localized taste buds.

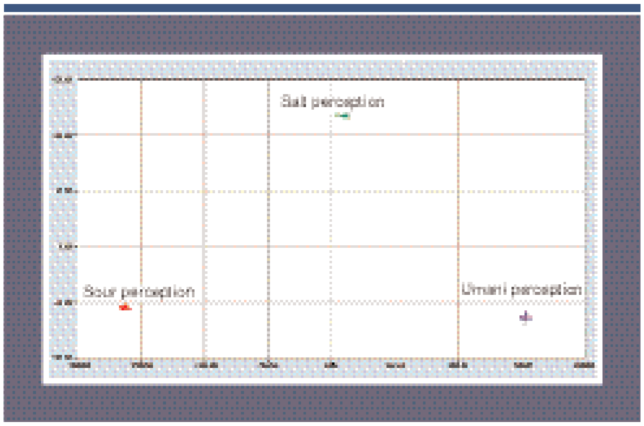

Figure 2: Principal component analysis (PCA) map showing discrimination of salt (NaCl), umani (monosodium glutamate) and sour (HCl) taste perception.

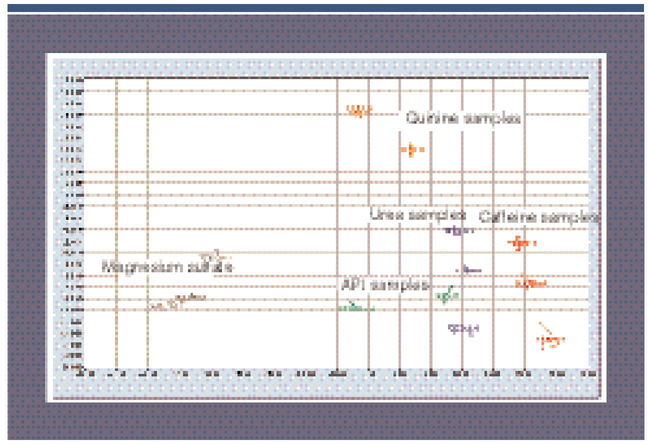

Figure 3: Discriminate factorial analysis of an active pharmaceutical ingredient against known bitter compounds.

tablets whole (especially when the patients are very young or very old). As a variety of ODT approaches—lightly compressed tablets, compression-molded tablets, and films—join more-traditional liquid and chewable preparations, effective taste-optimization becomes more crucial to product success.

Taste is a survival mechanism, alerting us to potentially harmful or potentially nutritious substances. We process taste at three levels: the receptor level, the circuit level, and the perceptual level.

At the receptor level are approximately 10,000 chemoreceptors or taste buds, residing primarily on the tongue, with some delocalized receptors at the back of the throat. These receptors fall into five primary categories: bitter, sour, umani, salt, and sweet, with grouped receptors dissipated over the surface of the tongue for each stimulus (see Figure 1 and Table I).

Sweet signals carbohydrates or certain amino acids. Sour characterizes vitamins. Salt detects needed minerals. Umani indicates protein and amino acids. In general, we experience these tastes as pleasant. Bitter sensation, however, is often unpleasant, suggesting alkaline water, alkaloid poisons, and spoiled foods. APIs, of course, usually fit into the bitter category.

Chemoreceptors for taste and olfaction (smell) respond to chemicals in an aqueous environment. Chemicals dissolved in saliva excite the taste receptors of the mouth, and airborne chemicals dissolved in epithelial mucus excite the olfactory receptors of the nose. The senses are complementary, with smell and taste working together to respond to, and more narrowly define, the same stimuli.

Taste depends on physiological and psychological factors. Physiological properties such as temperature and texture, clearly affect the perception of taste (consider the limited appeal of a cold cup of coffee). Human taste also appears to change with age. Many children dislike fresh vegetables, yet grow to enjoy them in adult life. Psychological factors can also influence taste perception: a childhood memory of badly formulated cough medicine can significantly modify taste perception of a modern formulation. Such factors underscore the role of taste in manufacturing a product that achieves patient compliance.

Culture influences perceived palatability. Market research has revealed standard combinations of specific sweeteners with relevant flavors and colors, which may vary by country and target market. National favorites include "green tea" in Japan, "bubblegum" in the United States, "citrus" notes in Europe, and "licorice" in Scandinavia. A bubblegum or cherry flavor married with a red color and high intensity sweetener may suit a US pediatric market, while a less intense sweetener may be more appropriate for Japan. Similarly, a mint flavor coupled to a white unit may be a more traditional approach for an adult market.

Table I: Compound categorization for taste perception.

Taste perception	Compounds
Sweet	Sugars, saccharin, alcohols, some amino acids
Sour	Acids (dissociation of H+ in solution)
Salt	Metal ions (inorganic salts)
Umani	Amino acids (glutamate)
Bitter	Alkaloids (quinine, nicotine, caffeine, morphine) and non alkaloids (aspirin)

Regardless of the flavor system used, the challenge is how to deliver unpleasant compounds (APIs) while maintaining patient acceptability, efficacy, and compliance.

Several formulation approaches may mask an unpleasant-tasting API. In tests of our proprietary lyophilized orally disintegrating tablet (the Zydis formulation from Cardinal Health, Somerset, NJ), we have successfully used coating of the drug substance, complexation (as with ion-exchange resins) to remove the API from solution, lecithins or cyclodextrins, and pH modification (to a value that renders the API insoluble), along with more traditional sweeteners, colors, and flavors.

Clearly, any complexation or insolubilization technique that inhibits interaction between the drug and the taste buds may also affect API dissolution and absorption profiles. It is thus critical to develop ODT performance and taste formulation together.

Because pharmaceutical taste-assessment can demand large panels and elaborate analysis and raise safety and scheduling concerns, a full taste program can be time-consuming and expensive. Alternatively, the "taste study" may be reduced to an informal gathering of executives, who reach consensus on the best formulation without considering statistical significance or protocol. Data derived by such a method is highly subjective, limited, and potentially biased.

E-tongue

An electronic tasting apparatus such as the e-tongue (Alpha M.O.S., Toulouse, France) offers one solution to these challenges. This technique compresses timelines and lets researchers gather taste and dissolution data simultaneously. Telescoping these steps reduces development time, development costs, subjectivity, bias, and safety concerns.

Key benefits of e-tongue taste evaluation include:

- helping quantify bitterness of drug actives when limited basic taste information is available, especially if the drug supply is limited
- developing suitable matching bitter placebos for blinded clinical testing
- developing optimized taste-masked formulations

Table II. Perceptual recognition and its application in product development.

Statistical analysis	Broad use	Application
Principal component analysis (PCA)	Qualification, exploration and discrimination	Initial formulation studies
Discriminate factorial analysis (DFA)	Discrimination and identification	Recognition of unknown sample
Soft independent modeling of class analogy (SIMCA)	Good/bad modeling	Quality control against reference good product
Partial least square (PLS)	Quantification	Quantification of bitterness against sensory panel

- measuring efficiency of complexation/coating within formulation
- conduction comparator studies (benchmark analysis)
- serving a quality control function for flavored product and excipient.

The e-tongue mirrors the three levels of biological taste recognition: the receptor level (taste buds in humans, probe membranes in the e-tongue); the circuit level (neural transmission in humans, transducer in the e-tongue) and the perceptual level (cognition in the thalamus in humans, computer and statistical analysis in the e-tongue).

At the receptor level, the e-tongue uses a seven-sensor probe assembly to detect dissolved organic and inorganic compounds. The probes consist of a silicon transistor with proprietary organic coatings, which govern the probe's sensitivity and selectivity. Measurement is potentiometric, with readings taken against an Ag/AgCl reference electrode. Each probe is cross-selective to allow coverage of full taste profile.

At the circuit level, the system samples, quantifies, digitizes, and records potentiometer readings.

At the perceptual level, taste cognition happens not in the probe, but in the computer, where the e-tongue's statistical software interprets the sensor data into taste patterns. Depending on the study design, data analysis can produce a variety of information. Table II summarizes some broad perceptual recognition options.

Initial taste optimization studies explore the formulation properties with principle component analysis (PCA), discriminating among subtle differences in the formulation to display a large "distance" between samples (see Figure 2).

For a new chemical entity for which no data are available regarding the taste of the compound, other than perhaps some in-

Table III: Reduction in bitterness as a function of sodium chloride concentration.

Sodium chloride concentration (M)	Reduction in bitterness (%) Urea	Quinine HCl	Magnesium sulfate
0.00	0.00	0.00	0.00
0.10	82.04	25.85	4.82
0.30	66.70	57.33	16.23
0.50	76.83	54.37	24.34
Sensor RSD %	0.17	0.18	0.30

formation solicited from the synthetic chemist, it is often insightful to quantify bitterness as a function of known bitter agents. This approach can be taken using discriminate factorial analysis (DFA, see Figure 3).

In this case, the API bitterness is comparable to that of a known concentration of urea. Knowing this gives the formulator a reference for comparison and a starting point for taste optimization. Moreover, this activity can provide a bitter matching placebo formulation for blinded clinical trials.

E-tongue analysis can reveal the "distance" between formulation tastes. This data can suggest and quantify simple bitterness-reducing strategies such as adding low levels of sodium salts. Table III shows how varying concentrations of sodium chloride can reduce the bitterness of known bitter compounds.

With this data, formulators can add optimal levels of appropriate sodium salts to the formulation to suppress the bitter taste of the product (see Figure 4). Comparison of such data to that of a trained taste panels provides confidence in the data set and furthermore demonstrates a reduction in the variability for e-tongue generated data over that of data derived from the human taste panel. Variance in human testing generally ranges from 6 to 26%; by use of the e-tongue this variance is reduced to $<$0.5% (see Table IV).

Applying PCA analysis to taste optimization studies can yield relevant information, allowing selection of an appropriate system to achieve a product with a desired taste profile.

Summary

Formulators must consider a wide range of factors in producing an acceptable lyophilized orally disintegrating tablet product. Processing conditions and formulation choices can optimize physical properties such as disintegration time and mouth feel. A number of formulation approaches can modify absorption characteristics to produce desired bioequivalence.

At the same time, however, formulators should consider the finished product's organoleptic properties, which could profoundly influence the product's success. Developers should consider taste, and taste-optimization strategies, along with

Table IV: Comparison of taste panel data to e-tongue data for suppression of bitterness.

Bitter Compound	Suppression of bitterness (%): Published data	Suppression of bitterness (%): Cardinal Health experimental data
Urea	76% (±6%)	76% (±0.17%)
Magnesium sulfate	4% (±26%)	24.34% (±0.30%)
Quinine hydrochloride	41% (±11%)	57.33% (±0.18%)

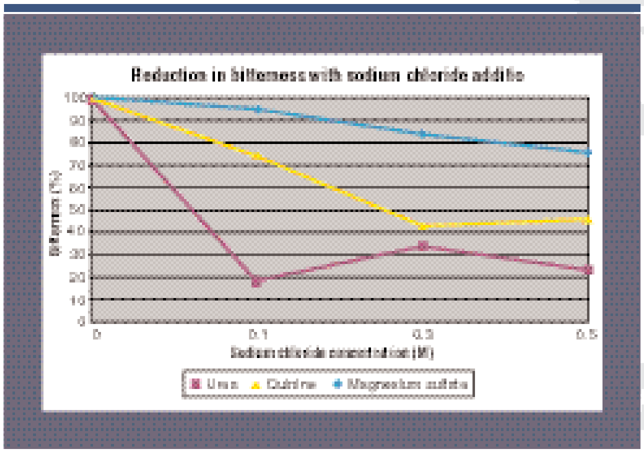

Figure 4: Reduction in bitterness as a function of sodium chloride concentration.

the absorption and physical properties with which they are intimately linked. When selecting taste profiles, the formulator should also remember that taste is just one sensory component and consider factors like dispersion, color and mouth-feel.

The time required to coordinate, execute and interpret a human taste study can have significant effect on overall project time and cost. These concerns sometime limit taste evaluation in the early stages of product development, where it truly should occur. The e-tongue provides a technically suitable and cost-effective method for screening and directing early formulation activities, while eliminating both safety concerns and subjective bias. **PT**

FYI

PDA opens new European headquarters in Brussels

PDA has opened a new European headquarters office in Brussels, Belgium, increasing the association's ability to serve its active European membership and the European pharmaceutical and biopharmaceutical communities. The Brussels office will be dedicated to developing learning initiatives, member services, event management, and promoting PDA science and technology. The European headquarters will handle all day-to-day business for PDA and its members in Europe, including queries and requests. The Brussels staff also will provide exhibition, sponsorship, and publications management, as well as process registration forms, membership applications, and renewals. Contact the new PDA European headquarters at: PDA European Headquarters, 287 Avenue Louise, BE-1050 Brussels, Belgium; tel +32 2 643 20 45; fax +32 2 645 26 71; Info-europe@pda.org.