International Journal of Pharmaceutics 367 (2009) 65–72

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Evaluation of a taste sensor instrument (electronic tongue) for use in formulation development

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ARTICLE INFO

Article history:
Received 7 July 2008
Received in revised form
15 September 2008
Accepted 16 September 2008
Available online 4 October 2008

Keywords:
Taste sensor
Taste masking
Human taste panel
Pharmaceutical bitterness intensity
Electronic tongue

ABSTRACT

A taste sensor instrument (electronic tongue) was evaluated to determine its utility in developing a taste-enhanced liquid formulation. To train the electronic tongue, human sensory panel data were collected for two prototype formulations, a solution of the drug in water and several marketed products. Studies using the electronic tongue were conducted to determine taste-masking effectiveness of formulations compared to a matching placebo, to establish correlation with human sensory data, and to evaluate unknown formulations and predict their bitterness scores.

In the first experiment, the effectiveness of a proposed taste-masking strategy was determined by comparing formulation prototypes containing a bitter active pharmaceutical ingredient (API) against corresponding placebos (i.e. formulations without an active ingredient) using electronic tongue data. The analysis of the electronic tongue data was based on the assumption that the drug was well taste masked if the placebo matched the formulation with API. In a second set of experiments, electronic tongue data were compared to existing data from a human taste panel for several marketed products and prototype formulations. A good correlation ($r^2 = 0.99$) was achieved from this comparison, and the relative taste of prototype formulations not tasted by humans was predicted.

1. Introduction

Oral pharmaceutical products residing in the mouth long enough to be tasted should be palatable. Palatable attributes include appearance, taste, smell, and texture/mouthfeel. Palatability could significantly affect compliance and therefore, dictate whether a successful or unsuccessful therapeutic outcome is attained. Palatability of the drug product should be given careful consideration to achieve optimal efficacy, since the drug cannot work if the patient does not or cannot take the medication.

Palatability may also affect the commercial success of a given drug product. In a crowded marketplace like oral liquid antibiotics, palatability may be a driver of commercial success. When a pediatrician considers an oral antibiotic for a child, having a choice of several products with similar efficacy and safety profiles, palatability could become the deciding factor for drug product selection (Steele et al., 1997, 2001; Kardas and Muras, 2005). Inferior palatability could potentially lead to decreased commercial success.

Besides its importance to commercial success of drug products, palatability may be a critical success factor during the development of a drug substance being tested in pediatric or geriatric age-groups. For drug products targeted for the pediatric age-groups or geriatric age-group, age groups that generally have difficulty swallowing tablets and capsules, palatability must be built into the target product profile. Therefore, palatability testing becomes part of the development process. Pediatric testing may occur even though the drug substance's target patient population is the adult age-group. As part of the drug development process, recent legislation in the United States (Pediatric Research Equity Act of 2003 and Best Pharmaceuticals for Children Act, both amendments to the Food, Drug and Cosmetic Act) may require clinical testing in children to support pediatric labeling for the drug product. The clinical testing could be mandatory and/or extend the patent life of a drug substance as an economic incentive. Whether the drug firm decides to commercialize a pediatric form or not, clinical trials may need to be completed to satisfy requirements for the pediatric labeling and would be part of the regulatory dossier. A palatable pediatric formulation would be vital to completing the clinical trial in a timely

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doi:10.1016/j.ijpharm.2008.09.042

fashion, with fewer drop-outs due to non-compliance. The mandate for pediatric labeling could be waived by the Food and Drug Administration if difficulties arise in formulating a pleasant-tasting pediatric formulation for the purposes of conducting clinical trials for pediatric labeling. However, enabling the taste-enhancement of pediatric formulations by streamlining the process for formulating an acceptable tasting formulation would avoid the time-consuming process to obtain a pediatric waiver from the FDA. In summary, palatability could be a critical and necessary product attribute to achieve therapeutic and commercial success, not only for drug products targeted for pediatric and geriatric patient populations, but also for the adult population.

How can the formulation scientist streamline the development paradigm for achieving palatability? A tool that has recently become available is the "electronic tongue" (Roy, 1997; Legin et al., 2002; Toko, 2000a,b; Vlasov et al., 2002; Winquist et al., 2004). The electronic tongue is an instrument that can be trained for screening the taste attributes of formulations in a rapid timeframe, when used in conjunction with human taste assessment data. Sufficient aqueous solubility of test compounds is necessary for successful application of the electronic tongue. However, co-solvents (e.g. ethanol) may be used to increase solubility of the test compound and widen the utility of the instrument. A decision-tree for how the electronic tongue could fit into the development paradigm is depicted in Fig. 1.

Examples of how the electronic tongue has been used for pharmaceutical applications have appeared in the literature. The examples demonstrate the electronic tongue's utility in characterizing bitterness and taste masking of the bitterness (Takagi et al., 1998, 2001; Legin et al., 2004; Miyanaga et al., 2002, 2003; Tanigake et al., 2003; Stier, 2004; Sadrieh et al., 2005; Zheng and Keeney, 2006; Kayumba et al., 2007; Li et al., 2007). Articles appearing in the literature that correlate electronic tongue to human taste panel data are described below.

Using quinine sulfate (QS) as a model bitter substance, Zheng and Keeney (IJP 2006) showed how increasing concentrations of acesulfame potassium (AceK), a high intensity artificial sweetener, reduced bitterness of a 0.2-mM QS solution. Using electronic tongue data, the authors reported better taste masking as the concentration of AceK increased. They also evaluated selection of a taste-masking vehicle for first in human or Phase I clinical trials. Bitterness of active pharmaceutical ingredients (APIs) was ranked using electronic tongue data.

Kayumba et al. (2007) studied the effect of taste-masking coatings on quinine sulfate beads, a flexible way to titrate dosing in pediatric patients. The authors measured the release of the drug for different types and levels of coating and correlated the drug release within 5 min with the Bitterness Index (BI). BI is a value generated by the Bitterness Prediction Module of the Astree Electronic Tongue (Alpha MOS, Toulouse, France). Using this technique, the researchers were able to optimize the coating composition for bitterness reduction.

Legin et al. (2004) studied the capability of an electronic tongue developed at St. Petersburg University. The unit sufficiently discriminated basic tastes (sweet, bitter and salty); discriminated different sweet, salty and bitter substances; and rank-ordered masking of bitter substances (e.g. caffeine, quinine, proprietary drug substances) similar to a trained tasted panel.

A group from the United States Food and Drug Administration (Sadrieh et al., 2005) reported on taste masking drugs with foodstuffs, using a correlation of human data to electronic tongue data. Often times, solid formulations need to be mixed with liquids or foodstuffs for ease of administration to pediatric or geriatric patients. Three counterterrorism drugs, doxycycline, potassium iodide and ciprofloxacin, were mixed with liquids including water, low-fat chocolate milk, low-fat milk, apple juice with table sugar (100 ml apple juice with 183 g of sugar), orange juice, raspberry syrup, chocolate syrup, and maple syrup. Results from a human adult taste panel and an electronic tongue were compared. Comparison was made based on ranking which matrix provided the highest level of taste masking. This study supports how the electronic tongue can be used as a screening tool to limit the number of samples to be tested in humans.

Li et al. (2007) utilized the electronic tongue to determine the most effective ratio of Amberlite IRP 64 resin, Carbopol 971P and pH of the test dispersion to optimize the taste masking for a bitter drug. The objective data from the electronic tongue enabled a modified special-cubic mixture design to be used. A total of 14 different formulations in addition to controls were evaluated. These results were confirmed by a human sensory panel. The data obtained from these electronic tongue studies were used to develop a taste-masked orally disintegrating tablet containing the bitter drug.

To further evaluate the potential utility of the electronic tongue in drug product development, we compared various drug-containing samples using human taste panel and electronic tongue data. Multiple formulas of the same bitter drug were evaluated and compared to commercial products.

2. Objectives

A liquid oral dosage form was desired for a drug with a slightly to moderately bitter taste; therefore, taste-masking efforts were pursued using various sweeteners, flavors and sweetness enhancers. To train the electronic tongue, human sensory panel data were collected for two prototype formulations, a solution of the drug in water and several marketed products. Studies using the electronic tongue were conducted to determine taste-masking effectiveness of formulations compared to a matching placebo, to establish correlation with human sensory data, and to evaluate unknown formulations and predict their bitterness scores.

3. Materials and methods

3.1. Formulations

All tested formulations consisted of drug in an aqueous-based solution, containing 0.2 mg/ml drug, sorbitol solution, citric acid, sodium citrate, artificial cherry flavor (except the unflavored prototype), and sodium benzoate. Descriptors for differentiating the formulations are provided in Table 1. The study used two controls: an aqueous solution of drug (0.2 mg/ml) and an unflavored prototype. The drug used in this study is slightly to moderately bitter as described from human taste panel evaluation and is characterized as objectionable and/or noticeable to a naïve taster. The marketed products were purchased and used as provided by the manufacturer. These marketed products include a cherry flavor suspension containing acetaminophen dextromethorphan HBr and phenylephrine HCL, a cherry flavor liquid containing diphenhydramine, and raspberry and cherry flavor syrups containing oxybutynin chloride. These products are also listed in Table 1.

3.2. Human taste panel

The aqueous solution of drug (0.2 mg/ml), flavored prototype, unflavored prototype, and commercial products (Table 1) were evaluated by a human trained pharmaceutical sensory panel at TIAX LLC. The trained pharmaceutical sensory panelists used two sensory analysis methods—Flavor Profile and Profile Attribute Analysis (Neilson et al., 1988). The aqueous solution of drug (0.2 mg/ml),

FIGURES

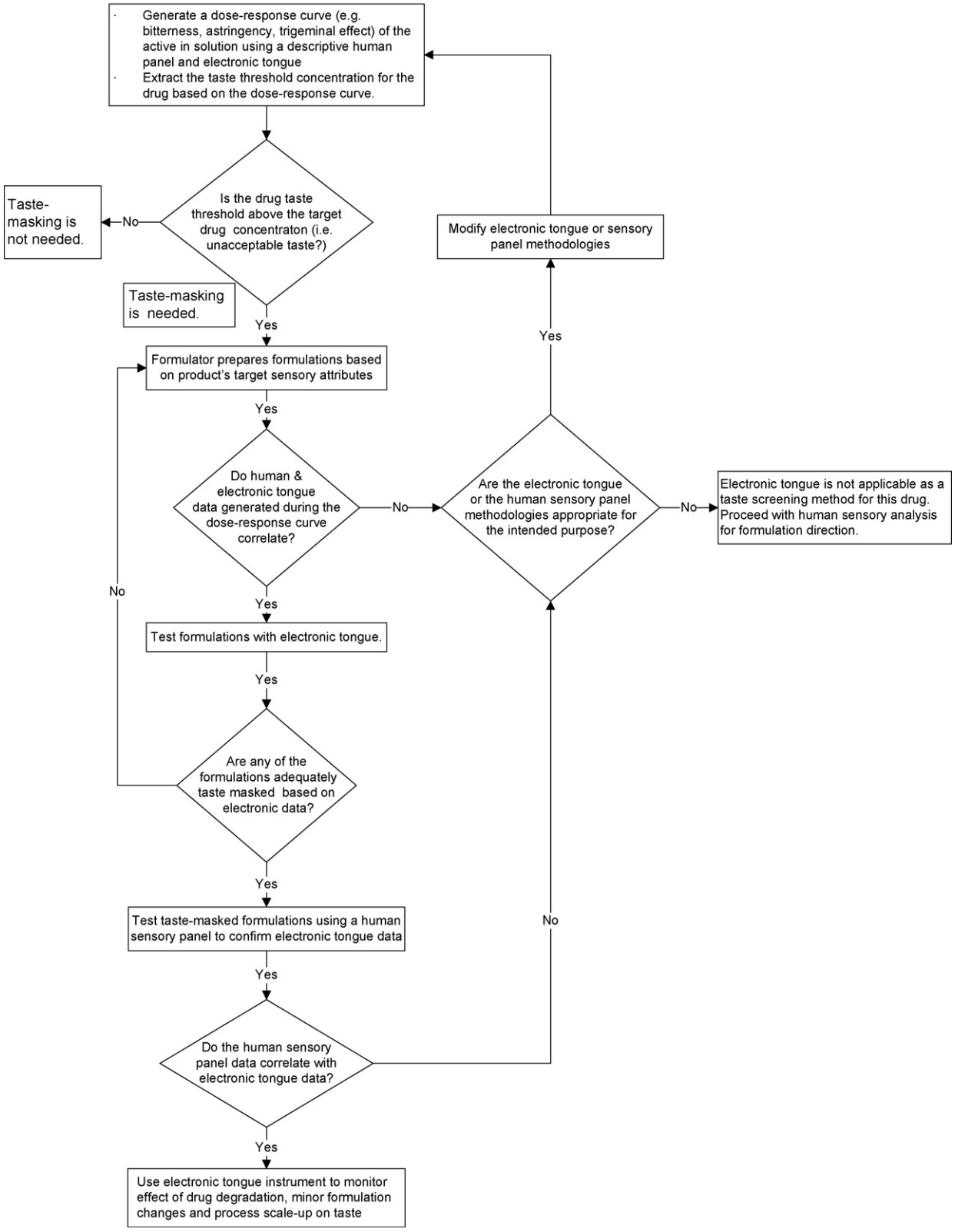

Fig. 1. Application of the electronic tongue and sensory panel in formulation development.

Table 1
Qualitative compositions of control, prototype formulations and commercial drug products used in the study. All formulations contain 0.2 mg/ml of drug in aqueous solution and the flavored samples contain the same type and level of flavor. The four marketed products were used as purchased.

Sample name	Descriptor
Control: aqueous solution of drug	0.2 mg/ml
Flavored prototype (Formulation 2)	HFCS*, 0.5 mg/ml Sweetness Enhancer A, cherry flavor
Unflavored prototype (Formulation 3)	HFCS*, 0.5 mg/ml Sweetness Enhancer A, no flavor
Formulation 4	HFCS*, cherry flavor
Formulation 5	HFCS*, 15.0 mg/ml Sweetness Enhancer A, cherry flavor
Formulation 6	HFCS*, 15.0 mg/ml Sweetness Enhancer B, cherry flavor
Formulation 7	2.5 mg/ml Sweetness Enhancer A, 2.5 mg/ml Aspartame, 2.5 mg/ml Acesulfame K, cherry flavor
Formulation 8	2.5 mg/ml Sweetness Enhancer A, 7.5 mg/ml Aspartame, 7.5 mg/ml Acesulfame K, cherry flavor
Formulation 9	2.5 mg/ml Sweetness Enhancer A, 0.5 mg/ml Na Saccharin, cherry flavor
Formulation 10	2.5 mg/ml Sweetness Enhancer A, 2.5 mg/ml Na Saccharin, cherry flavor
Acetaminophen suspension**	Cherry flavor oral suspension
Diphenhydramine HCL liquid	Cherry flavor liquid
Oxybutynin chloride syrup 1	Cherry flavor syrup
Oxybutynin chloride syrup 2	Raspberry flavor syrup

* HFCS = high fructose corn syrup.
** Also contains dextromethorphan HBr and phenylephrine HCL

an unflavored prototype, and a flavored prototype (prototypes contain drug in aqueous solution, 0.2 mg/ml) were first evaluated by the sensory panel using the Flavor Profile method to identify the relevant sensory attributes of these samples. The Flavor Profile is a standard method for the measurement and analysis of the sensory attributes of products, e.g., aroma, flavor, texture, and mouthfeel. It employs perceptual judgments of both the elements and structure of flavor impressions, made by carefully selected and extensively trained panelists. The characteristics of a product (sample) that are evaluated in a Flavor Profile evaluation are (1) amplitude, which is a rating of the degree of blend and the amount of fullness present in the flavor as a whole; (2) an identification of the individual components of aroma and flavor; (3) the strength, or intensity, at which these components appear; (4) the order in which they appear and (5) a description of the aftertaste after swishing and expectorating the sample. Objective reference materials are used to establish the amplitude and intensity scales.

The human taste panel evaluations were conducted in accordance with Good Clinical Practices. The Study Protocol, Informed Consent Form and Case Report Form were reviewed and approved by TIAX's Review Board. The samples were evaluated by a panel of four to six trained pharmaceutical sensory analysts. Two samples were tasted during a 1-hour session and the panelists participated in no more than two panels per day as specified in the Study Protocol. Each panelist was provided a 2-ml sample. The sample was swished in the mouth for 10 s then expectorated. The initial flavor was evaluated during the swishing and the aftertaste at 1, 3, 5 and 10 min after expectoration. The panelists used spring water and unsalted crackers to cleanse their palettes between samples. A 20-min washout period was provided between samples.

Research reveals that the perennial sales leaders in many categories (foods, beverages and pharmaceuticals) have a set of sensory characteristics in common. This was true 45 years ago when the concept of Flavor Leadership was first introduced and remains true today. Sales leaders possess the following characteristics:

- Have a quickly recognizable identifying flavor.
- Develop full flavor that rapidly blends with and covers the active and base characteristics.
- Have no unpleasant mouth sensations (e.g. tongue sting).
- Have no off-notes in the early impression or in the aftertaste.
- Have a short aftertaste.

These are known as the Flavor Leadership Criteria (Sjostrom and Cairncross, 1953) which are used to interpret the Flavor Profile results and to guide formulation development.

The flavored prototype and the marketed products were then evaluated by the sensory panels using the Profile Attribute Analysis method. Profile Attribute Analysis is an extension of the Flavor Profile method, which generates highly reproducible data which is amenable to statistical analysis. Based on the Flavor Profile results, the following attributes were defined for product evaluation using Profile Attribute Analysis.

- Initial flavor—balance; fullness; aromatic intensity; sweet, sour and bitter basic tastes; mouth irritation; other mouthfeels and aromatic off-notes.
- Aftertaste (1, 3, 5, and 10 min)—aromatic intensity; sweet and bitter basic tastes; mouth irritation; other mouthfeels and aromatic off-notes.

Each product was evaluated in triplicate and the order of presentation of samples to the panel was randomized. All samples were coded for blind evaluation by the panelists. The tasting protocol was the same as described for the Flavor Profile evaluations.

The initial flavor attribute data and the combined aftertaste attribute data were separately summarized into an Initial Flavor Index and an Aftertaste Index using Principal Components Analysis–PCA (a general description of PCA is covered in Section 3.3). Flavor maps were constructed by plotting the two flavor indices against each other and using Analysis of Variance to quantify and summarize significant differences between products. For the purposes of the current study, the panel's consensus of the initial bitterness was used for comparison to the results obtained from the electronic tongue. Initial bitterness was rated using a 7-point scale (1 = no bitterness, 2 = very slight bitterness, 3 = slight bitterness, 4 = slight to moderate bitterness, 5 = moderate bitterness, 6 = moderate to strong bitterness, and 7 = strong bitterness). A untrained taster would perceive an objectionable and/or noticeable bitterness if the bitterness score is greater than or equal to 3.

3.3. Electronic tongue

The electronic tongue used to analyze samples described in Table 1 was an Alpha MOS Astree II with 7 sensors designated by Alpha MOS as the pharmaceutical sensor set (sensors ZZ, AB, BA, BB, CA, DA, and JE). The sensors are chemically modified field effect transistors (ChemFET), similar to an ion selective FET but are coated with a proprietary coating/membrane. Specific chemical compounds are embedded in the co-polymer coating to impart cross-selectivity/cross-sensitivity. The manufacturer, Alpha MOS, does not disclose the detailed composition of the sensors but indicated that they are made with a matrix of polymer, plasticizer and various sensitive materials (e.g. alcoholic or hydrophobic ionophores).

The measurements are collected using a Ag/AgCl reference electrode. The raw data is expressed as voltage versus time. For these experiments, only the last 90 s of the 120 s data were used in the analysis. Samples were replicated six times, with only the last three replicates used in the data analysis. The sensors were rinsed in two beakers of water following each analysis.

Due to the high dimensionality of the data produced by the electronic tongue, multivariate analysis commonly referred to as chemometrics, is a frequently used tool to interpret the data. Principal components analysis (PCA) discriminant function analysis (DFA), and partial least squares regression (PLS) were employed as data analysis tools in this study.

PCA is a method that computes a new system of axes so that a high variance of data (typically, 80% or greater) can be conveyed within two or three axes. PCA involves a mathematical procedure that transforms a number of (possibly) correlated variables into a (smaller) number of uncorrelated variables called *principal components* (Smith, 2002; Pratt, 2003; Jackson, 2003). The first principal component accounts for as much of the variability in the data as possible, and each succeeding component accounts for as much of the remaining variability as possible. In the case of the electronic tongue, this method allows the data attained by all seven sensors to be used to differentiate between samples on a two-dimensional graph representing the first two principal components. The axis that contains the most amount of variance is referred to as the first principal component (shortened as PC1), the second is the second principal component, etc. It is therefore important to recognize what value of variance relates to each axis—this value is typically listed next to the axis and, in the Alpha MOS software, is computed as a percentage for convenience.

Using PCA, data points for one sample or set of samples are compared by measuring the distance between them. The distance is the Euclidean distance between the calculated center of the cluster of one sample set to the center of the cluster of another sample set. A discrimination index (DI), ranging from negative values to 100, is reported on a PCA map. The higher index number represents better discrimination (or less similarity) between samples or groups.

Discriminant functional analysis is similar to principal components analysis in that the dimensionality of the data is reduced but a slightly different algorithm is used in this computation. The DFA model assumes like samples are clustered. One of the main features of a DFA calculation is its usefulness as a predictive model. The DFA is used to explain correlations in data and has the ability to project an unknown data set onto the predictive or training set. This is often used to determine how a set of unknown samples relates to a group of references. The DFA assumes replicate samples are clustered; the PCA treats each replicate samples as individual data. It is this predictive ability that separates the DFA from the PCA model.

Correlation of electronic tongue to human taste data was achieved using an inverse calibration model based on partial least squares analysis (PLS). In its simplest form, this model specifies the relationship between a single independent variable (bitterness score from human taste panel data) with a combination of the multiple components of the electronic tongue sensor data (Danzer et al., 2004).

4. Results and discussion

4.1. Taste masking—placebo compared with active

In the first set of experiments, several different active formulations were tested against their matching placebo. The data were interpreted by assuming that an active formulation is well taste masked if the active formulation is recognized by the electronic tongue to be similar to the placebo formulation. This analysis does not predict whether the placebo tastes good or is palatable, only that the active formulation tastes like the placebo. In order to use this information in formulation development, one must assume that the placebo does indeed taste good or have a taste panel measure the taste of the placebo.

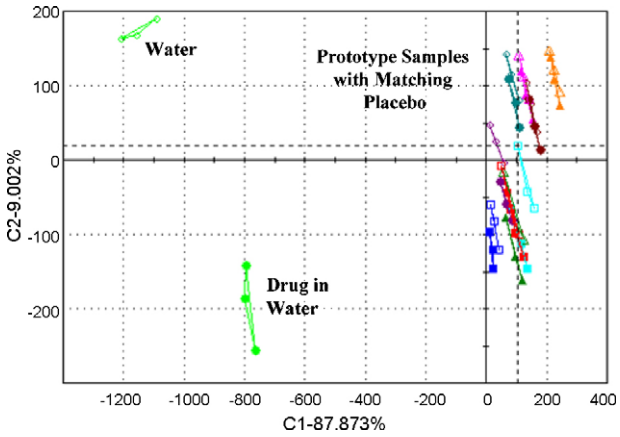

Fig. 2. Principal Components Analysis (PCA) of placebo vs. active formulations (closed symbols = formulations containing active; open symbols = matching placebo formulations). C1 and C2 are the percentages of data differentiation along the *x*-axis and *y*-axis axes calculated for PC1 and PC2, respectively. For this PCA, almost 88% of the data is represented on the *x*-axis, suggesting that the distance along the *x*-axis is most important in differentiating the samples. An expanded view of the Prototype Samples shown in the right of this PCA is shown in Fig. 3.

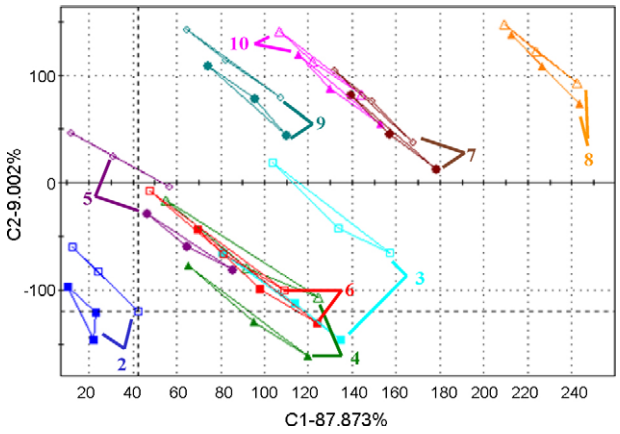

Fig. 3. Expanded view of the prototype formulations shown in Fig. 2. The open symbols represent the placebo formulations (no bitter active present) and the closed symbols represent the active formulations. The numbers adjacent to the data points correspond to the formulations provided in Table 1.

The data were evaluated using PCA by computing a group distance which is the distance between the replicate placebo and active samples. Larger group distances are interpreted to predict less taste masking of active compound. As can been seen in Figs. 2 and 3 and Table 2, the largest group distance is calcu-

Table 2
Group distances as calculated from PCA data. The group distances are calculated from the seven-dimensional PCA data; it is the distance between the center points of two sample clusters. The PCA plots in Figs. 2 and 3 represent two of these seven dimensions.

Active–placebo pair	Group distance
Control: aqueous solution of drug (0.2 mg/ml)	557
Flavored prototype (Formulation 2)	64
Unflavored prototype (Formulation 3)	99
Formulation 4	70
Formulation 5	92
Formulation 6	48
Formulation 7	39
Formulation 8	27
Formulation 9	38
Formulation 10	29

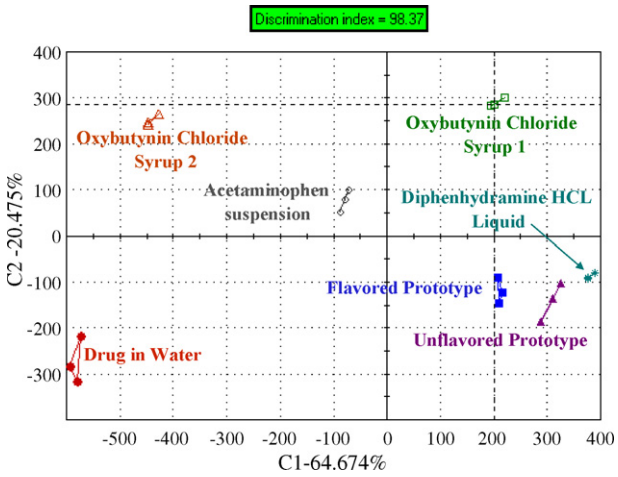

Fig. 4. PCA of prototype formulations, a solution of drug in water, and marketed products.

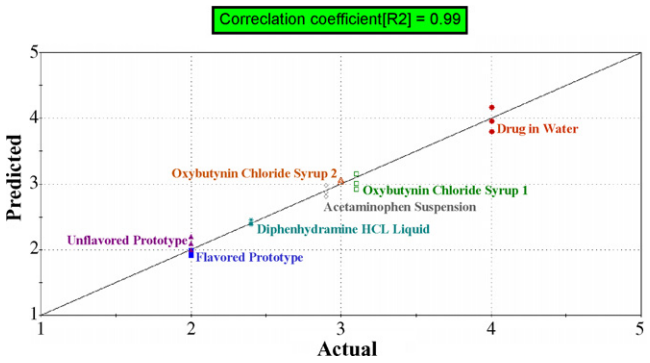

Fig. 5. Partial least squares (PLS) regression of human taste panel data vs. electronic tongue data. The *x*-axis is the bitterness score from the human taste panel data; the *y*-axis is bitterness score predicted from the electronic tongue data assuming a correlation exists. Note that the variation in data along the *y*-axis represents differences in replicate analyses of the samples measured by the electronic tongue.

lated for an aqueous solution of drug (0.2 mg/ml) versus water. This result is expected since there are no taste-masking ingredients present. The other samples can be clustered into formulations made with high fructose corn syrup (HFCS) and formulations made with artificial sweetener. The artificial sweeteners appear to taste mask better than high fructose corn syrup. Higher levels of artificial sweetener appear to only slightly improve taste masking compared to the original level. Both types of formulations contained a sweetness enhancer (labeled A or B). Within sweetener types (high fructose corn syrup as the example), sweetness enhancer B appears to taste mask this drug slightly better than sweetness enhancer A.

4.2. Comparison to marketed products

Prototype samples were analyzed together with marketed product samples in order to determine the relative position on the PCA (Fig. 4). This PCA was developed to show how the electronic tongue data can be used to determine which samples taste similar assuming no human taste data are available. The PCA does not represent the human taste data. Without human data the electronic tongue cannot provide a hedonic taste characteristic. The flavored and unflavored prototypes used in this study were clustered close together compared to the marketed products and the drug in water. The diphenhydramine HCL liquid sample most closely matched the flavored and unflavored prototypes. This claim was verified by the human taste panel data collected for the experiment described in the next section.

Table 3
Initial bitter intensity data from the human sensory panel (consensus scores). Bitter intensity was rated on a seven-point scale (1 = no bitterness, 2 = very slight bitterness, 3 = slight bitterness, 4 = slight to moderate bitterness, 5 = moderate bitterness, 6 = moderate to strong bitterness, and 7 = strong bitterness).

Sample	Initial bitter intensity
Control: aqueous solution of drug (0.2 mg/ml)	4.0
Flavored prototype (Formulation 2)	2.0
Unflavored prototype (Formulation 3)	2.0
Diphenhydramine HCL liquid	2.4
Oxybutynin chloride syrup 1	3.0
Oxybutynin chloride syrup 2	3.0
Acetaminophen suspension*	2.9

* Also contains dextromethorphan HBr and phenylephrine HCL.

4.3. Correlation of bitterness intensity to human taste data

Human taste panel data were collected for the aqueous solution of drug (0.2 mg/ml), the unflavored prototype, the flavored prototype, acetaminophen plus dextromethorphan HBr and phenylephrine HCL cherry flavor suspension, diphenhydramine HCL cherry flavor liquid, and the two oxybutynin chloride syrups. Data are shown in Table 3. Initial bitterness scores ranged from 2 to 4 on a scale of 1–7 as described in the Section 3.2 (1 = no bitterness, 2 = very slight, 3 = slight, 4 = slight to moderate, 5 = moderate, 6 = moderate to strong, and 7 = strong bitterness). An objectionable and/or noticeable bitterness score is greater than or equal to 3.

Identical samples were analyzed using the electronic tongue. Electronic tongue data were compared to the initial bitterness intensity as determined by the human taste panel and a correlation plot was constructed. The electronic tongue data fit the human taste panel data according to the PLS analysis with $r^2 = 0.99$ (Fig. 5). When comparing the PLS plot (Fig. 5) to the PCA plot (Fig. 4), it is important to note that the PLS regression represents all seven principal components. The two dimensions of the PCA plot shown represent 2 of the 7 principal components (~85% of the data set). More work is needed to understand how the relative positions of samples on the PCA correspond to the PLS bitterness scores when the human data are considered.

Electronic tongue bitterness scores were calculated based on the fit of the data. The calculated bitterness scores are shown in Table 4. The electronic tongue and human bitterness scores varied by 0.1 units or less suggesting that the electronic tongue is able to predict the initial bitterness score of the formulations.

Table 4
Initial bitterness intensity from human taste panel (consensus scores) and predicted corresponding electronic tongue data based on PLS shown in Fig. 5 (1 = no bitterness, 2 = very slight bitterness, 3 = slight bitterness, 4 = slight to moderate bitterness, 5 = moderate bitterness, 6 = moderate to strong bitterness, and 7 = strong bitterness). The electronic tongue prediction is based on an average of the three data points collected for each sample shown in Fig. 5.

Sample	Initial bitter intensity	Electronic tongue bitterness score
Control: aqueous solution of drug (2 mg/ml)	4.0	4.0
Flavored prototype (Formulation 2)	2.0	1.9
Unflavored prototype (Formulation 3)	2.0	2.1
Diphenhydramine HCL liquid	2.4	2.4
Oxybutynin chloride syrup 1	3.0	3.0
Oxybutynin chloride syrup 2	3.0	3.1
Acetaminophen suspension*	2.9	2.9

* Also contains dextromethorphan HBr and phenylephrine HCL.

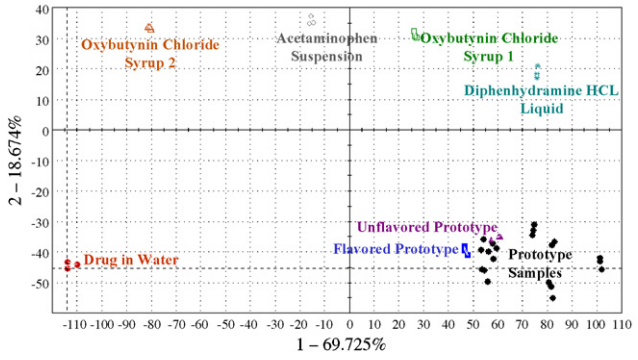

Fig. 6. Discriminant Functional Analysis (DFA) of prototype formulations and marketed products. The relative taste of the prototype formulations not tested by the human taste panel can be predicted using this plot; prototype samples are shown in the lower right corner of the DFA and are represented as closed circles. Their positions in the lower right corner of the DFA plot are expected given the positions of the flavored and unflavored prototype formulations tested by the human taste panel.

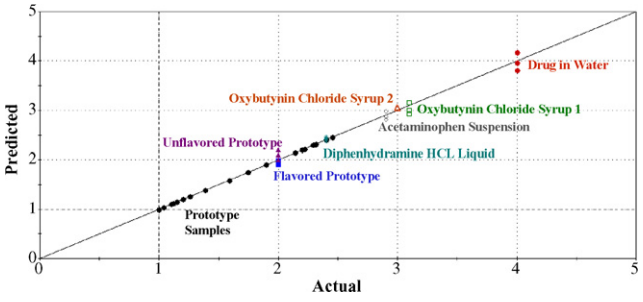

Fig. 7. PLS regression of a solution of drug in water, prototype formulations, and marketed products showing prediction of prototype formulations not tested by the human taste panel. Predicted bitterness scores are shown in Table 5. Prototype samples not tested by the human taste panel are represented as closed circles located on the left half of the line.

4.4. Prediction of samples not tasted by humans

Several samples that had not been tasted by humans were evaluated using the electronic tongue and plotted using DFA (Fig. 6). These data were also projected onto the PLS correlation developed previously and their taste was predicted as compared to the other prototype samples (Fig. 7 and Table 5). These data indicate that the electronic tongue recognizes these unknown samples as tasting similar to the other prototype formulations as compared to the marketed products; however, this was not verified in a human taste trial. These data suggest that the formulations containing artificial sweeteners are slightly less bitter than the samples containing HFCS consistent with the placebo experiment discussed in Section 4.1.

Table 5
Bitterness scores for formulations not tasted in humans as predicted by the PLS in Fig. 7 (1 = no bitterness, 2 = very slight bitterness, 3 = slight bitterness, 4 = slight to moderate bitterness, 5 = moderate bitterness, 6 = moderate to strong bitterness, and 7 = strong bitterness). These data lead to similar conclusions as the taste masking data—the formulations with artificial sweeteners appear to better mask the bitterness of the drug and consequently have a lower predicted bitterness index.

Sample	Electronic tongue predicted bitterness score
Formulation 4	2.3
Formulation 5	2.3
Formulation 6	2.3
Formulation 7	1.7
Formulation 8	1.3
Formulation 9	1.1
Formulation 10	1.1

5. Conclusion

By comparing active formulations to their matching placebo, the electronic tongue data provided differentiation of samples. The smaller group distance between active and placebo formulations for samples containing artificial sweetener compared to high fructose corn syrup suggests that the artificial sweetener better masks the bitter taste of the drug. The electronic tongue data provided a good correlation to the human taste panel data. Prediction of formulations not previously tasted by humans was achieved by projecting the electronic tongue data onto the PLS regression curve. These predictions indicate that the artificial sweetener samples were slightly less bitter than the high fructose corn syrup samples consistent with the electronic tongue taste-masking data, comparing placebo versus active formulations.

Acknowledgements

The authors gratefully acknowledge assistance from Sandrine Isz and Marielle Bronn at Alpha MOS, and Joseph Esquibel, Ken Yamamoto, and Steven Overholt who helped with sample preparation while at Pfizer Inc.

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