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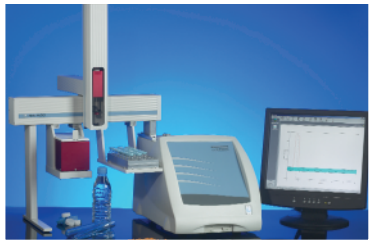


TOP: Gemini Electronic Nose
BOTTOM: Astree Electronic Tongue

ELECTRONIC SENSING TECHNOLOGIES

E-Nose and E-Tongue Put a Face on Flavor

Electronic sensing technologies optimize formulation process development

BY MARIELLE GARNIER

Most pharmaceutical drugs or nutraceutical products have an unpleasant odor or taste. However, organoleptic properties are very important in differentiating products and determining product success. Taste evaluation of pharmaceutical formulations requires human safety precautions. Electronic sensing instruments can be efficiently used to perform larger taste screening of formulation candidates to speed up and optimize the formulation process. Formulation departments need safe and objective evaluation methods to reduce development time, costs and safety issues.

Electronic nose and tongue instruments have been developed by Alpha M.O.S. (Toulouse, France and Hillsborough, N.J.) to perform fingerprint analysis of a product's complex chemistry. These electronic sensing technologies are sensor-based analyzers.

These instruments mimic the human nose and tongue. Chemical compounds responsible for odor or taste are perceived by human odor or taste receptors, and the sensors of electronic instruments react to those same compounds.

The odor or taste signals are transducted by nerves in the brain into electric signals. A similar process is done by the sensors that generate electric signals. In the case of the electronic nose sensor, it is resistance variation and for electronic tongue sensor, it is potentio-metric variation.

Odor or taste quality perception and recognition is based on building or recognition of activated sensory nerves pattern by the brain and on the chemical fingerprint of the product. This is accomplished with the aide of a multivariate statistical analysis of the electronic nose and tongue.

Electronic nose and tongue sensors, like human receptors, are partial and cross-selective and can react to many substances responsible for various odors or tastes. Each sensor has a spectrum of reaction that is different from the other. The information given by each sensor is complementary and the combination of all sensor results generates a unique fingerprint.

Most of the detection threshold sensors are similar or better than those of human receptor (see Table 1). These instruments are then able to detect some chemical variations before they can be detected by human receptors.

Bitterness Masking and Benchmarking Analysis

An electronic nose and tongue can quantify, qualify and compare chemical properties of oral formulations such as gels, syrups, solutions, emulsions, tablets, lozenges, capsules and films. These sensors can compare raw materials (flavors, excipients or APIs) and various formulations according to their origins, qualities, shelf life or stability, reactions during aging under various storage conditions or packaging.

TABLE 1. **DETECTION THRESHOLD OF SENSORS COMPARED TO THOSE OF HUMAN RECEPTORS**

Taste	Basic Taste Substance	Taste Threshold (M)	
		Human Tongue	Electronic Tongue
Sweetness	Sucrose	1×10^{-2}	2×10^{-6}
Bitterness	Caffeine	0.7×10^{-3}	1×10^{-6}
Sourness	HCl	9×10^{-4}	5×10^{-6}

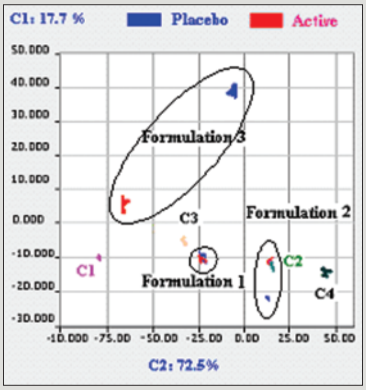
THRESHOLD: The lowest intensity of a stimulus that can be registered on a sensory channel by the receptor. Absolute threshold refers to the minimum amount of stimulation that can be detected on a sensory channel.

DETECTION THRESHOLD: When the background is a neutral stimulus (e.g., a dilutent or distilled water) the minimum level that can be discriminated is called the detection threshold.

Detection threshold given in this table is the concentration of a compound (sucrose, caffeine or HCl) that can be distinguished from water either by the human tongue or by the e-Tongue.

FIGURE 1.

PRINCIPAL COMPONENT ANALYSIS (PCA)



In the PCA Map, 72.5 percent of the information given by the seven sensors of the ASTREE Electronic Tongue lies on the C1 axis, 17.7 percent of the information lies on the C2 axis and the remaining information lies in the other axis. Thus, most of the information is on the C1 axis.

The two Formulations 1 (active and placebo) have similar C1 and C2 axis scores on the map and so they are very close.

The two Formulations 2 (active and placebo) have a close C1 axis score but the difference is greater than Formulation 1. They also have a different C2 axis score. This means they are close but less so than Formulation 1.

The two Formulations 3 (active and placebo) have axis scores very far from each other, meaning they are far from each other.

TABLE 2.

A BITTERNESS MASKING ANALYSIS OF THREE FORMULATIONS

Formulation 1	19
Formulation 2	51
Formulation 3	415

To compare the differences between the drug and placebo formulations, Euclidean distances are used between each active (in red in Fig.1) and placebo (in blue in Fig.1) formulations.

Euclidean distances represent the distance between two points in the tri-dimensional map of the PCA and are automatically calculated by the software.

The optimal bitterness-masking formulation will be the one with the smallest distance between the drug and placebo formulations. Thus, 19 is the distance between active formulation 1 and placebo formulation 1.

51 is the distance between active formulation 2 and placebo formulation 2.

415 is the distance between active formulation 3 and placebo formulation 3.

TABLE 3.

BENCHMARKING STUDY BETWEEN FORMULATIONS F1, F2 AND F3 AND COMPETITIVE PRODUCTS C1, C2, C3 AND C4

Formulations	C1	C2	C3	C4
Active F1	227	255	55	251
Placebo F1	231	267	69	261
Active F2	291	140	144	144
Placebo F2	314	167	163	140
Active F3	72	235	182	300
Placebo F3	475	365	535	431

In the benchmarking study, active or placebo formulations are compared to active competitive products. The distances between formulations and competitive products are calculated. In this example, active Formulation 1 is very close to competitive product C3. In Fig.1, active formulation 1 (red point) and placebo formulation 1 (blue point) are very close to competitive product C3.

The active formulation 2 (red point) appears to be very close to the competitive product C2, but it is not. C1 and C2 together represent only 90.2 percent (72.5 + 17.7) of the information, and so, we lose nearly 10 percent of the information given by the sensors. This information brings the difference between active formulation 2 and competitive product C2.

Active formulation 3 appears to be different than competitive product C1, but in fact the distance is only 72.

This is why it is more reliable to calculate distances than merely rely on visual approximation of the two-dimensional map!

The sensors are also capable of quantifying formulation ingredient in a specific formulation, measuring taste-masking efficiency of formulations, designing taste-matching placebo and characterizing odor or taste formulation profiles to compare them with each other, competitor products or reference target quality.

The methodology used with the electronic taste analyzer when performing a masking study is based on a comparison of various candidate formulations. Pharmaceutical formulations often vary according to the type and level of sweeteners, flavors, additives and/or masking agents. Each candidate formulation will be compared with its corresponding placebo formulation.

In order to choose the best combination or the best level of ingredients, the differences between the drug and placebo formulations are calculated. The differences are represented by distances calculated by the software (Euclidean distances used traditionally in mathematical calculations). The optimal bitterness-masking formulation will be the one with the smallest distance between the drug and placebo formulations (see Table 2, Formulation 1).

In the benchmarking study, formulations (actives or placebos) will be compared to various competitive products. The distances between formulations and competitive products are calculated (see Table 3). In this example, active Formulation 1 is very close from the competitive product C3.

Electronic noses and tongues, which require minimal sample preparation, can objectively and safely characterize many chemical properties of ingredients and formulations including their global taste and odor profiles. They make possible a larger screening of ingredients, additives or taste agents during formulation development.

While reducing the sensory panel tests, electronic sensing instruments can be efficiently used to speed up and optimize the formulation process, especially for pharmaceutical formulations that cannot be safely tasted by a human panel. ■

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