Taste analysis of oral formulations using an electronic tongue

MARION BONNEFILLE

Alpha M.O.S. France
20, avenue Didier Daurat
31400 Toulouse, France
Tel +33 (0) 5 62 47 64 55
bonnefille@alpha-mos.com

TASTE: A KEY PARAMETER DURING FORMULATION

If the taste of medicines has long been considered as a minor concern, nowadays patients are no longer willing to swallow bad-tasting remedies. Therefore, pharmaceutical companies must now count taste as a new priority during formulation development, especially for pediatric and geriatric medicines. Moreover, the increasing interest for oral forms such as disintegrating tablets, dissolvable films, chewable tablets, syrups, etc has led to the development of numerous taste-masking strategies using sweeteners, flavorings, vehicles, and coatings.

To monitor taste features during formulation, it is important to dispose of a solid base of excipients, fully screened taste masking agents and reliable testing methods to control the process. Commonly, pharmaceutical laboratories have recourse to trained sensory panels in order to assess taste of formulations. In addition of being time- and money-consuming, these human tests yet require a strict supervision of health risks. These drawbacks can explain why the Electronic Tongue, a taste analyzer, is considered as a solution that meets the formulation department's needs for safety, rapidity and cost-effectiveness.

THE ELECTRONIC TONGUE: AN INSTRUMENT THAT MEASURES AND COMPARES TASTES

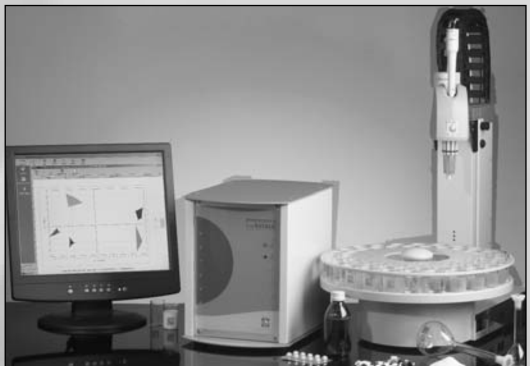
The specificity of the Electronic Tongue analyzer is that its working principle is similar to human taste perception. Instead of measuring and identifying the various compounds responsible for taste in a liquid solution, as many analytical techniques can do, the E-tongue captures the global profile of a taste.

In the mechanism of human taste perception, chemical compounds responsible for taste are perceived by taste receptors. With the Electronic Tongue, sensors detect the same dissolved organic and inorganic compounds. Like human receptors, each sensor has a spectrum of reactions different from the other. The information given by each sensor is complementary and the combination of all sensors results generates a unique fingerprint. Most of the detection thresholds of sensors are similar or better than those of human receptors.

In the biological mechanism, taste signals are transmitted by nerves up to the brain as electric signals. In the same way, E-tongue sensors generate electric signals (potentiometric variations) in the presence of dissolved compounds.

In human smell, the brain compares the patterns of activated sensory nerves to its library of known tastes and consequently identifies or builds a taste perception. With the E-Tongue, this step is achieved by a statistical software which interprets sensor data as taste patterns.

Running an analysis is fast and easy. Liquids are directly analyzed without any preparation. Solids require a preliminary



The Alpha M.O.S. Astree electronic tongue

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Via Cesare da Sesto, 10
20123 Milano - Italy
Tel. 0039 02 83241119
Fax 0039 02 8376457
www.b5srl.com

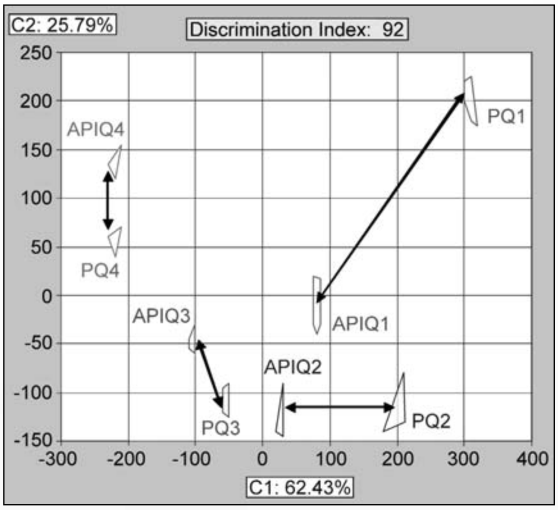

Figure 1 – PCA (Principle Component Analysis) map of e-tongue taste results

dissolution before measurement. Reference electrode and sensors are dipped in a beaker containing a test solution for 120 seconds. A potentiometric difference between each sensor and the Ag/AgCl reference electrode is measured and recorded by the E-Tongue software. The set of sensors and reference electrode are rinsed with distilled water between two analyses. Results are displayed within minutes as decision tools.

WHY AN E-TONGUE CAN HELP FORMULATION DEVELOPMENT?

The E-Tongue significantly reduces development time and costs, subjectivity, bias, and safety concerns.
The various applications in the pharmaceutical industry include:

- quantification of bitterness of APIs or NCEs (New Chemical Entities);
- support to developing suitable matching bitter placebos for blinded clinical testing;
- monitoring of optimized taste-masked formulations;
- efficiency measurement of coating within formulations;
- comparative studies between test medicine and competitive products.

Three applications developed by pharmaceutical companies will present typical uses of an Electronic Tongue at formulation stages, to optimize product composition or assess the efficiency taste-masking strategies.

OPTIMIZATION OF SWEETENER CONCENTRATION IN FORMULATIONS

In order to mask bitter taste in medicines, sweeteners are commonly used in the pharmaceutical industry. To determine rapidly the amount of sweetener that is the most effective at masking bitterness efficiently, the E-tongue can provide useful and reliable tools to visualize results at a glance. By comparing distances between samples, formulators can check the difference between the active formulation and the corresponding placebo containing the same amount of sweetener. Figure 1 shows the results of an experiment conducted with several active formulations of quinine (API) and related placebo consisting of water (P). The samples contain various levels of sweetener (from 1 to 4 for increasing sweetener amounts) to mask quinine bitterness. The distances between the clusters for each quinine-containing sample and its matching placebo were calculated.
Reduction of distance in the presence of sweetener suggests that the bitterness of quinine was inhibited. Figure 2 (distance as a function of sweetener concentration) indicates that at the level of 5.0 mM AceK, reduction of the group distance begins to stagnate, suggesting that the masking efficiency of sweetener has reached a maximum. Therefore, the E-Tongue was used to rapidly determine the most appropriate amount of sweetener in order to mask active formulation bitterness and optimize raw material costs.

COATED PELLETS OF QUININE: BITTERNESS REDUCTION TESTING WITH AN E-TONGUE

Quinine, which is an important drug in treatment of malaria, has a very bitter taste that reduces compliance in patients, especially children.

In order to reduce this bitter sensation in mouth, quinine pellets with a variable amount of coating were developed and their taste assessed over time. An Electronic Tongue further equipped with a Bitterness Prediction Module (BPM), was used to measure the bitterness masking efficiency of coating in quinine sulfate pellets in comparison with usual quinine tablets.

Five samples of pellets containing the equivalent of 100 mg of quinine sulfate (uncoated and coated with 10, 20 and 30% w/w) were dipped in 100 ml water during 1, 2, 3, 4 and 5 minutes. A measurement was performed at each time, after filtration of the mixture.

The bitterness score of the different solutions was projected on the BPM

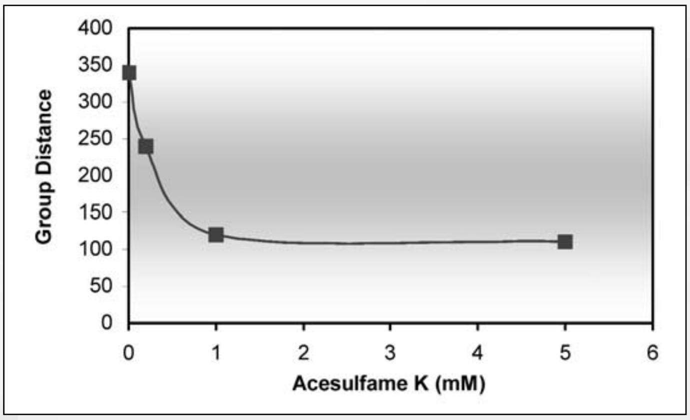

Figure 2 – Distances between formulation and placebo as a function of sweetener concentration

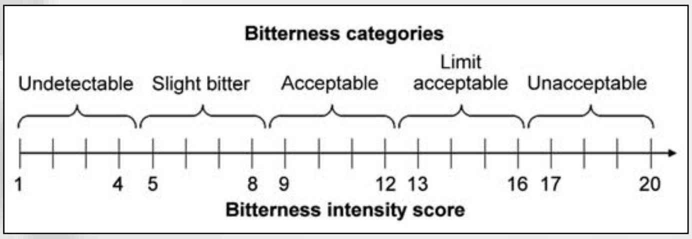

Figure 3 – Bitterness calibration scale

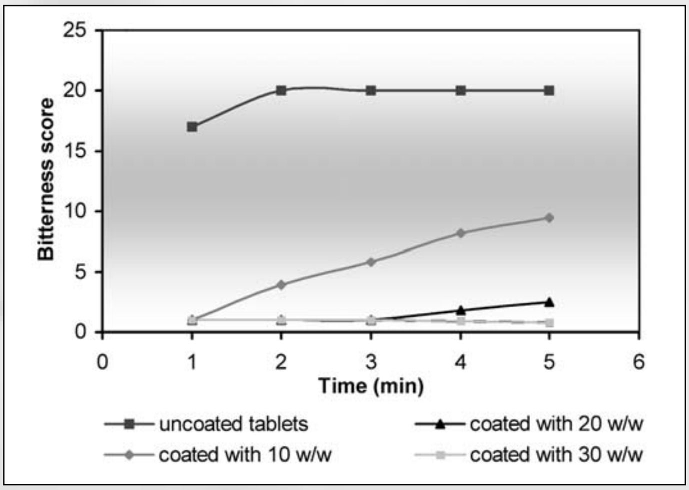

Figure 4 – Bitterness profile of uncoated and coated pellets over time

standard calibration scale ranking from 1 to 20 (Figure 3). Scores 1 and 20 respectively correspond to undetectable and unacceptable bitterness.

Without coating, the bitterness reached an unacceptable level (bitterness score = 16.5) within 1 minute. With 10% w/w of coating, a slight bitterness was reached after 2 minutes. With 20% and 30% w/w of coating, no bitterness was detected after 5 minutes. The use of the E-tongue analyzer allowed to determine that a 20% w/w coating was sufficient to mask the bitterness of quinine sulfate (Figure 4). This rapid measurement technique can be applied to significantly reduce formulation times.

QUANTIFICATION OF THE TASTE MASKING CAPABILITY OF ENCAPSULATION

Chewable tablets as a dosage form are becoming increasingly popular for both adolescent and geriatric populations due to their increased patient compliance. However, one drawback of this dosage form is that many pharmaceutical actives have an unpleasant bitter taste. Therefore, these formulations often require taste-masking strategies, such as encapsulation of the API to assure patient acceptability.

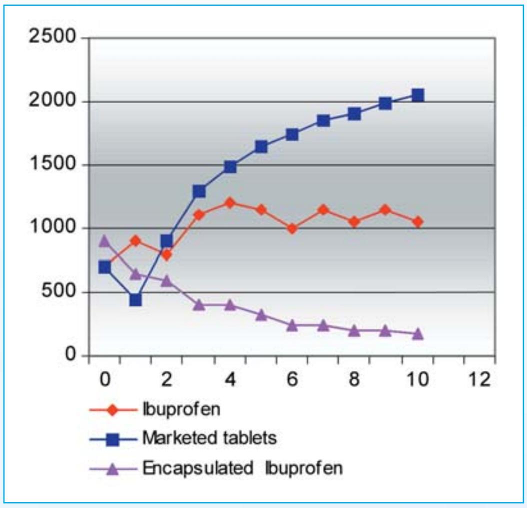

Figure 5 – Bitterness evolution over time

An Electronic Tongue was used to quantify the taste masking capability of encapsulation technology applied to chewable tablets containing a bitter API (Ibuprofen).The taste analyzer was coupled to a Solid Dynamic Form Analyzer (SFDA) in order to measure the evolution of taste over time during dissolution.

Chewable tablets containing 50 mg of encapsulated Ibuprofen, orange flavored chewable tablets, neat Ibuprofen and other known bitter compounds were dissolved in 20 mL of deionized water before analysis with the instrument.

Measurements of the taste over time show that the bitterness of both marketed tablets and neat ibuprofen increases during dissolution. On the contrary, the bitterness of encapsulated ibuprofen diminishes over dissolution.

The calculation of distances between samples allows to compare taste similarities and differences: the higher the distance, the more different the compounds.

Results (Figure 5) show that encapsulated Ibuprofen is closer to the placebo than to neat ibuprofen, and neat ibuprofen is nearer to other bitter compounds. This confirms that encapsulation does reduce the unpleasant taste that can be found in ibuprofen or other bitter compounds.

Moreover, by comparing the distances D1 (Neat Ibuprofen-Placebo) and D2 (Encapsulated Ibuprofen-Placebo), a 53% of taste improvement can be reached:

%Taste Improvement =
(D1-D2)/D1x100 = 53%

In this case, the analytical evaluation by the E-tongue prevented panelists from tasting unpleasant compounds.

Useful as a formulation tool to monitor taste, the Electronic Tongue can be an efficient instrument to speed up and optimize the pharmaceutical companies' efforts and work, while reducing safety concerns.