



Innovative Tools to Speed up Formulation Development while Decreasing Human Panel Tests

By Dr Jean Christophe Mifsud, President and Chief Executive Officer at Alpha M.O.S



Dr Jean-Christophe Mifsud is President and Chief Executive Officer of Alpha M.O.S. He founded the company in 1992, with the mission to develop instruments correlated with the human senses, particularly those of smell and taste. Previously he worked within the M&A department of Rhône-Poulenc Inc, USA, and as Marketing Manager for CIBA - GEIGY in Switzerland. He holds a degree in Chemical Engineering from Toulouse University, an MBA from the ESSEC business school in Paris and a PhD in Neurochemistry at Princeton University, New Jersey, USA. He also holds several patents in various fields.

Scientists have recently completed the development of sensing technologies that provide a full range of solutions, from chemical variation detection to taste and odour assessment for R&D and factory QC needs. The industry now has access to a breakthrough tool in the development of oral pharmaceutical formulations.

MEDICINE'S BAD TASTE AS THE MAJOR CAUSE OF NON-COMPLIANCE

Unpleasant or bitter taste is a common feature of many pharmaceutical drugs. However, sensory characteristics such as odour and taste significantly affect patient acceptance, preference and compliance and, after efficiency and safety, are of upmost importance in determining market success. For prescription drugs (Rx), a high palatability can ensure faster market success of a drug and patient dosage compliance. For a generic or OTC (over the counter) drug, it can be the single-most important factor in establishing or maintaining market leadership, and, increasingly, today's prescription drugs become tomorrow's OTCs or generics.

Another major market request is linked to nutritional foods. This has blossomed into a powerful entity in today's marketplace. For these new products and also new consumers, organoleptic properties are the challenge that has to be met in order to increase market share.

The major consequence of unpleasant taste is low compliance levels, particularly from infants, children and the elderly. Having difficulty swallowing solid dosage forms, these patients prefer oral solutions, suspensions and fast-dissolving tablets with a pleasant taste.



GOOD TASTE: A COMPLEX CHALLENGE

To avoid unpleasant sensory sensation, many scientific techniques have been developed, such as:

- The addition of aromas, sweeteners or cooling agents such as menthol and raspberry
- Other technological processes like microencapsulation, ion exchange resin and orally disintegrating tablets (ODT) technology

Moreover, it is important to have quality controls for aroma and flavours to ensure an excellent, reproducible and stable quality of pharmaceutical product over time in terms of taste and odour.

Due to these additional products and processes, formulation development time and costs of a pleasant taste-masked formulation have significantly increased and delayed the marketing of new drugs. To date, the main method of measurement of odour and taste intensity remains the human sensory test. However, the use of sensory panelists is very difficult, not only because of the subjectivity of panel members, but also because of the potential toxicity of drugs. Problems in recruiting and maintaining taste panelists are significantly more crucial when working with unpleasant products. Moreover, new drug entities before Phase I cannot be

Table 1 : The Primary Features of Electronic Testing Instruments		
	Electronic Nose	Electronic Tongue
Sensors	Metal Oxide	Specifically designed liquid sensors based on ChemFET technologies
Detection principle	Resistance variations	Potential variations
Compounds detected	Volatile	Dissolved
Sampling	Autosampler with numerous options (purge and trap, several options SPDE, SPME)	Autosampler with (16 or 48 beaker positions)
		

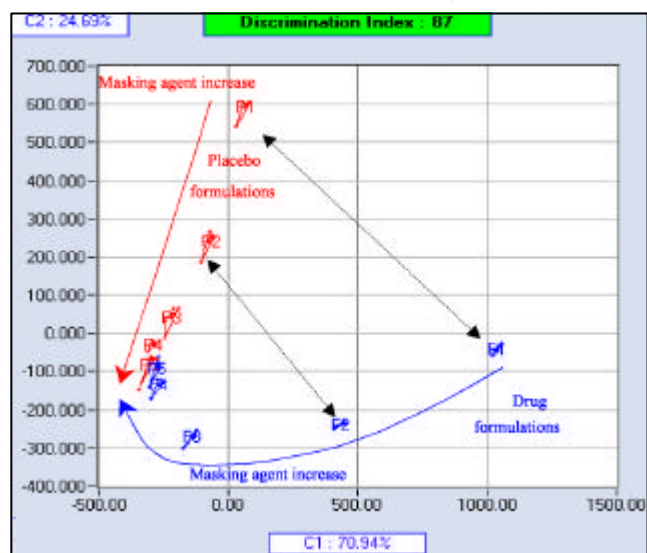
tasted ethically by human beings without tackling the issue of tests involving children. This is why formulators not only need safe and objective instruments to facilitate their work, but reliable and fast analysers in order to decrease formulation development times.

ELECTRONIC SENSING TECHNOLOGIES

Electronic smell and taste instruments have been developed and optimised in order to answer some of these issues: increasing formulation candidates in the prescreening steps, minimising human test panels and generating objective measurements of taste and reducing formulation development time and costs.

These instruments are sensor-based analysers that make a global analysis of the total complex chemistry of the sample (chemical fingerprint). They perform qualitative/quantitative analyses of organoleptic and chemical properties of products. The 'electronic tongue' performs analysis in liquid matrix such as gels, syrups, solutions, emulsions, tablets, lozenges, capsules or

Figure 1 : Bitterness Masking Efficiency
(Principal Component Analysis)



films, whereas the 'electronic nose' analyses a wide range of volatile organic compounds.

From a technical point of view, all detection methods used in these instruments are based on chemical variations. Table 1 presents the main features of each instrument.

Molecules of the tested sample interact with the active part of the sensor (metal oxide for the gas sensors and chemical sensitive layer for the liquid sensors). These bindings and interactions modify the physical properties of the sensor and generate either resistance or potential variations. In the case of the taste-sensitive instruments, the measurement consists of a potentiometric difference between each individual liquid sensor with a reference electrode (Ag/AgCl). Electronic parts of the instrument transduce physical variations into electrical ones, which are measured by the instruments. These electrical output signals are recorded over time.

Each sensor is partially selective to various chemical compounds and this partial selectivity differs between sensors. The cross-sensitivity and selectivity of sensor arrays allow them to track any variation in the headspace or liquid matrix of samples. Thus, a combination of several sensors will provide a unique global electronic fingerprint of the complexity of sample matrix instead of measuring one specific compound.

Raw data obtained by each sensor (between 6 and 18 metal oxide sensor for the 'electronic nose' dedicated to the R&D and seven liquid sensors for the 'electronic tongue') and recorded over time are processed with multivariate statistic tools integrated with software compliant with 21 CFR Part 11.

Electronic sensing Systems can give simple answers, like recognised as 'orange flavour', 'good conformity' or 'no conformity' or more sophisticated responses such as an odour or taste intensity, a molecule concentration, a score of bitterness or a measurement of bitterness-masking efficiency.

WHAT CAN ELECTRONIC SENSING TOOLS DO FOR PHARMACEUTICAL SCIENTISTS?

Through the utilisation of smell and taste sensitive technologies, the formulation and analytical departments in pharmaceutical companies can effectively conduct studies related to taste and flavour, packaging selection and stability studies. They can enable pharmaceutical scientists to:

- Speed up and optimise the formulation development process
- Evaluate and quantify bitterness scores of new chemical entities (NCE)

Figure 2 : Aroma Stability Over Time
(Principal Component Analysis)

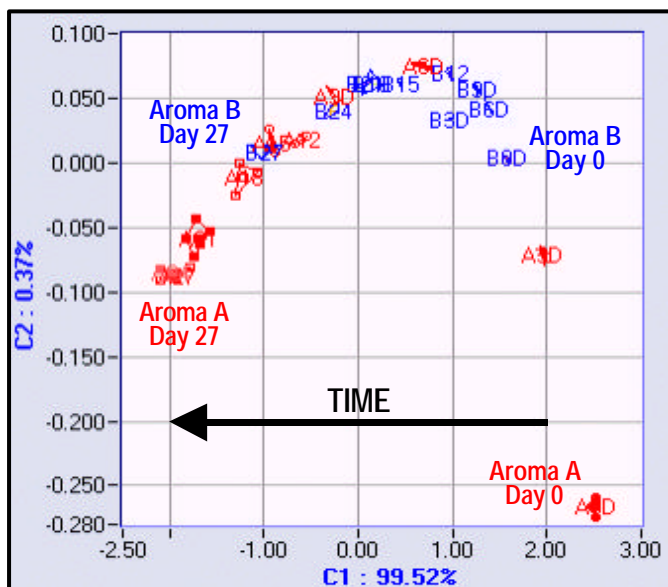
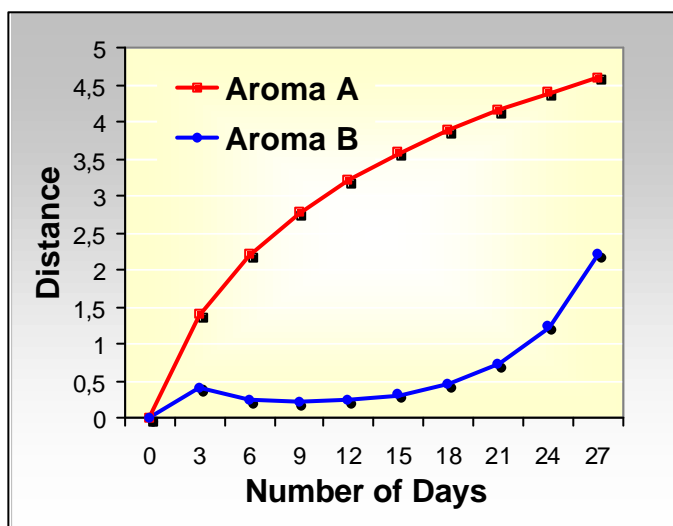


Figure 2 : Aroma Difference Between Fresh and Stored Samples



- Test more formulations trials with various combinations of sweeteners, enhancers, exhausters, aroma and masking agents and avoid sample preparation
- Compare the palatability of new formulations with competitors' products
- Avoid some risks during double blind clinical trials:
 - Developing placebos that match the active drug formulations from a taste, flavour and aroma perspective
- ? Simplify and accelerate conformity and stability tests:
 - Control raw materials such as fillers, binders, coatings, residuals and solvents
 - Monitor quality stability of the aroma and flavour suppliers

- Quantify excipients, additives, taste agents or active ingredients
- Define consistency of organoleptic quality throughout the scale-up process from small production batches to full-scale manufacturing
- Choose the best packaging according to its interaction properties with the product

A CASE STUDY: BITTERNESS MASKING

The methodology used with the taste-sensitive instrument when performing a masking study is based on a comparison of candidate formulations. Formulations under consideration often vary according to the type and level of sweeteners, flavours and/or masking agents. Each candidate formulation tested will be compared with the corresponding placebo formulation (see Figure 1, page 54). In order to choose the best flavour or concentration of a bitterness-masking agent, the distances between the drug and placebo formulations are calculated. The optimal bitterness-masking formulation will be the one with the smallest distance between the drug and placebo formulations.

STABILITY OF AROMA

After these bitterness-masking efficiency results are in, the two best aromas are selected and tested with the 'electronic nose' instrument for stability over time. They are stored under stressed conditions and analysed at various intervals. Figure 2 shows the drift of samples from day zero to day 27 and Figure 3 displays distances between fresh samples and samples stored over time for each aroma. In this example, Aroma B drifts significantly less than Aroma A: thus Aroma A is more stable in this formulation over time.

ELECTRONIC SMELL AND TASTE TECHNOLOGY REMOVES SAFETY AND LIABILITY CONCERNS

The minimal sample preparation required and the relative speed of analyses make these instruments very advantageous when compared to current methods for taste-masking, stability and consistency of formulations. A beneficial aspect of the automation and throughput of these Systems is the ability to objectively screen larger numbers of formulations and samples. By investigating the widest number of candidates and having the analytical capability to reduce the number of formulations and define the optimum tasting formulation, it is then possible to utilise a sensory panel only as a final validation of the chosen formulation.

Thus, smell and taste sensitive instruments increase screening possibilities, while reducing time development. These unique technologies are more cost-effective than human sensory panels and permit rapid analytical results. ?

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