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Electronic evaluation by sensing device

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ABSTRACT

Many active pharmaceutical ingredients usually associated with bitterness, can impart an unpleasant taste or odor. To produce a desirable oral drug product, especially if destined for pediatric use, development efforts focus on masking the unpleasant taste or odor, often by adding flavoring or sweetening agents to the formulation. The formulations organoleptic properties taste, odor, mouth-feel and appearance are of considerable importance in differentiating products in the market and can ultimately determine the success of a product. Organoleptic analysis of such prototype products is commonly performed by human taste panels. However, in an effort to eliminate human testing due to the safety risks and since it is time-consuming and expensive, alternative analytical means are being sought. The electronic tongue or electronic nose is such a system for automatic analysis and recognition of liquids or gases, including arrays of non-specific sensors, data collectors and data analysis tools. Electronic tongues are used for liquid samples analysis, whereas electronic noses for gases. The result can be the identification of the sample, an estimation of its concentration or its characteristic properties. The novel electronic tongue technology is being utilized by the food/beverage and pharmaceutical industries to evaluate product taste characteristics. The electronic-nose device may provide testing of odors and also provide physicians with a quicker and more accurate diagnostic tool for a number of diseases. Also it can be used for detection and identification of certain chemical compounds in exhaled air and excreted urine or body fluids related to specific metabolic conditions, certain skin diseases, or bacterial infections.

Keywords: Bitter, mouth feel, taste masking, human testing, electronic tongue, electronic nose.

INTRODUCTION

Sensing devices includes electronic devices which have the ability to sense and are used in many fields for various applications. Electronic tongue (E-tongue) and Electronic nose (E- nose) are two systems for automatic analysis and recognition of liquids or gases, including arrays of non-specific sensors, data collectors and data analysis tools. Electronic tongues are used for liquid samples analysis, whereas electronic noses for gases. The utilization of E- tongue or E-nose can be the identification of the sample, an estimation of its concentration or its characteristic properties. This new technology has many advantages over subjective evaluation. Problems associated with human senses, like individual variability, impossibility of on-line monitoring, subjectivity, adaptation, infections, harmful exposure to hazardous compounds, mental state, are of concern with E- sensors [1-5].

Table 1. 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).

Electronic Tongue

Human tongue can recognize principally five different taste which are sweet, sour, salty umani, and bitter. **Table 1** shows different compounds characterizing the different tastes mentioned above. Many active pharmaceutical ingredients can impart an unpleasant taste or odor, usually associated with bitterness. In addition to the medicinal value of drug actives, compounds for oral dosage also need to have good taste, a desirable texture and color. In essence, these oral treatments must be appealing to the consumer throughout the range of population, from pediatric to elderly patients. To produce a desirable oral drug product, especially if destined for pediatric use, development efforts focus on masking the unpleasant taste or odor, often by adding flavoring or sweetening agents to the formulation. 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 like 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 [2-8].

Organoleptic analysis of prototype products is commonly performed by human taste panels. 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. 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. Data derived by such a method is highly subjective, limited, and potentially biased.

However, in an effort to eliminate human testing due to the safety risks, alternative analytical means are being sought. The novel electronic tongue technology is being utilized by the food, beverage and pharmaceutical industries to evaluate product taste characteristics. It provides relative measurements of nonvolatile or low-volatile molecules and dissolved organic compounds that are responsible for taste and flavor sensations [2-8].

An electronic tasting apparatus such as the E-tongue (Alpha M.O.S., Toulouse, France) offers one solution to these challenges [1]. 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. The E-tongue technology offers the potential to provide taste evaluation during formulation development or to be used as a quality-control tool, and thus significantly reduce the amount of human testing. Another important benefit includes the reduction of the reliance on human panels. Human panels typically present several difficulties including health concerns, fatigue of tasters, maintaining the motivation for tasting unpleasant compounds and the lack of analytical standardization. While it is necessary to develop good tasting treatments, the use of sensory panelists is very difficult and problematic in this industry. This is due to the potential toxicity of drugs and subjectivity of taste panelists. Problems in recruiting taste panelists, motivation and panel maintenance are significantly more difficult when working with unpleasant products. Further, non-FDA approved molecules cannot be tasted [1].

Key benefits of E-tongue taste evaluation:

1) Helping to quantify bitterness of drug actives when limited basic taste information is available, especially if the drug supply is limited
2) Developing suitable matching bitter placebos for blinded clinical testing
3) Developing optimized taste-masked formulations
4) Measuring efficiency of complexation/ coating within formulation
5) Conduction comparator studies (benchmark analysis)
6) Serving a quality control traction 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) [9-13].

Electronic tongue is an analytical instrument comprising an array of non-specific, poorly selective, chemical sensors with partial specificity (cross-sensitivity) to different components in solution, and an appropriate method of pattern recognition and/or multivariate calibration for data processing. Of primary importance is stability of sensor behaviour and enhanced cross-sensitivity, which is understood as reproducible response of a sensor to as many species as possible. If properly configured and calibrated, the electronic tongue is capable of recognizing the quantitative and qualitative composition of multicomponent solutions of different natures. The main part of the electronic tongue is a set of potentiometric chemical sensors, applicable for liquid analysis. Sensor arrays include different types of sensors, conventional ones, specially designed non-specific sensors with enhanced cross-sensitivities or classical electrochemical electrodes are used depending on the task, sensor stability or cross sensitivity. The second essential part of the electronic tongue is data processing. Since the number of sensors in the array of an electronic tongue can reach 40, each of them producing a complex response in the multicomponent environment, a relevant multidimensional data processing must be performed. This is done by different pattern recognition methods such as artificial neural networks or multivariate calibration tools [9-13].

Researchers at the University of Texas are developing an electronic tongue that they hope will someday be able to taste the differences in a variety of liquids. With wine, for example, the tongue changes colors depending on how sweet or sour the vintage is. The electronic tongue contains tiny beads analogous to taste buds. Each bud is designed to latch onto specific flavor molecules and change colors when it finds one, be it sweet, sour, bitter or salty. The buds are housed in pits on the surface of the tongue itself, which is made of silicone. Each one of these pits looks like a little pyramid, and it's just the right size that we can take one of these taste buds and nestle it down inside, they also plan to go beyond the four tastes of the human tongue and use the device to analyze such substances as blood or urine, or to test for poisons in water. Some day, the tongue might speed up blood analysis by testing everything from cholesterol to medications in a person's bloodstream, all at the same time. The device, which has the potential to incorporate hundreds of chemical microsensors on a silicon wafer, has a multitude of potential uses. From the silicon tongue, the team hopes to create a process to make artificial tongues more cheaply and quickly, placing them on a roll of tape, for example, to be used once and thrown away. But the developers have a way to go before achieving their vision [14, 15, 23].

In one of a research work, it was shown that suppression of bitterness of quinine by sucrose can be quantified using a multi channel taste sensor. A multichannel taste sensor whose transducer is composed of several kinds of lipid/polymer membranes with different characteristics can detect taste in a manner similar to human gustatory sensation. Taste information is transformed into the pattern composed of the electric signals of the membrane potentials of the receptor part. The measurement was performed using the taste sensing system SA01 of Anritsu Co Ltd. The electrode set was attached to a mechanically controlled robot arm. The detecting sensor part consists of seven electrodes made of lipid polymer membranes (i.e. channels) Lipids used in the preparation of membranes are listed in **table 2**. Each lipid was mixed in a test-tube containing polyvinylchloride and plasticizer (dioctyl phenyl phosphonate), which were dissolved in tetrahydrofuran. The mixture was then dried in a glass plate that was set on a hot plate whose temperature was controlled at about 30^{o} C. The lipid/polymer membrane prepared in this way was a transparent and soft film about 200 µm thick. Each electrode was made of an Ag wire whose surface was plated with Ag/AgCl, with an internal cavity filled with 3 M KCl solution. The lipid/polymer membranes were pasted on the opening of the tube. The difference of the electric potential between the working electrode and reference electrode was obtained by means of high input impedence amplifier connected to a computer [14-18]. Performance of electronic tongue is represented in **table 3**.

The ASTREE Electronic Tongue system is an instrument equipped with an array of seven coated sensors for liquid analysis. It is fully automated with 15 positions for formulation samples providing four replicate measurements per sample. It provides fast comparative measurements of non/low volatile molecules and dissolved organic compounds that are responsible for taste and flavor sensations [18-23].

Table 2. Lipids used in Channels

Channel	Lipid
1	Decyl alcohol (DA)
2	Oleic acid (OA)
3	Dioctyl phosphate (DOP)
4	DOP:TOMA 5:5
5	DOP:TOMA 3:7
6	Trioctylmethylammoniumchloride (TOMA)
7	Olylamine (OAm)

Table 3. Performances of the Electronic Tongue [9-13]

Specification	Qualitative analysis	Quantitative performance
Typical sensor array size	20 – 40 sensors	10-30 sensors
Typical number of measuring sessions	4 – 8	12 - 50
Number of measurements within each measuring session	3	3 - 10

Electronic Nose

Flavor analysis during product development is typically performed by human organoleptic analysis, which is often expensive and less objective. A novel approach using a metal oxide sensor-based instrument (electronic-nose) for headspace analysis was explored to replace human sensory perception for consistent qualitative and quantitative analysis of flavors in a pharmaceutical formulation. The use of the electronic-nose can be employed to identify unknown flavors in drug formulation placebos. The quantitative method might be used to assay the flavor concentration during release testing of the oral solution formulation or to monitor flavor shelf-life in the marketed container. It can also be implemented for packaging selection for the formulation in order to ensure the flavor shelf-life [24].

An "electronic or artificial nose" is an instrument, which comprises a sampling system, an array of chemical gas sensors with differing selectivity, and a computer with an appropriate pattern-classification algorithm, capable of qualitative and/or quantitative analysis of simple or complex gases, vapors, or odors. An "electronic tongue" uses an array of liquid sensors. The artificial chemical senses include taste and olfaction. There are striking analogies between the artificial noses of man and the "Bio-nose" constructed by Nature. The human nose uses the lungs to bring the odor to the epithelium layer; the electronic nose has a pump. The human nose has mucous, hairs, and membranes to act as filters and concentrators, while the E-nose has an inlet sampling system that provides sample filtration and conditioning to protect the sensors and enhance selectivity. The human epithelium contains the olfactory epithelium, which contains millions of sensing cells, selected from 100-200 different genotypes that interact with the odorous molecules in unique ways. The E-nose has a variety of sensors that interact differently with the sample. The human receptors convert the chemical responses to electronic nerve impulses. The unique patterns of nerve impulses are propagated by neurons through a complex network before reaching the higher brain for interpretation. Similarly, the chemical sensors in the E-nose react with the sample and produce electrical signals. A computer reads the unique pattern of signals, and interprets them with some form of intelligent pattern classification algorithm [27, 28, 31-34]. **Table 4** gives comparison between the human and electronic nose.

Table 4. Schematic Comparison between Human and Electronic Noses [32].

Human nose	Electronic nose
10 million receptors, self generated	5 - 100 chemical sensors manually replaced
Saturates	Persistent
Identifies a large number of odors	Has to be trained for each application
Cannot detect some simple molecules	Can detect simple molecules (H_2, H_2O, CO_2)
Detects some specific molecules	Not possible in general at very low concentrations
Associative with sound, vision, experience, etc.	Multisensor systems possible
Can get infected	Can get poisoned

Advantages of Electronic Nose:

Our human nose is elegant, sensitive, and self-repairing, but the E-nose sensors do not fatigue or get the "flu". Further, the E-nose can be sent to detect toxic and otherwise hazardous situations that humans may wish to avoid. Sensors can detect toxic carbon monoxide, which is odorless to humans.

An electronic nose is an instrument comprised of three parts: (a) a sampling system, (b) an array of chemical gas sensors producing an array of signals when confronted with a gas, vapor, or odor, and (c) an appropriate pattern-classification system. The E-nose is typically applied to the qualitative or quantitative analysis of gases, vapors, odors, or complex chemical mixtures and has a conveniently simple output, such as a variety of coffee, or the identity of a solvent vapor. It is truly a separate class of analytical evaluation [31, 33].

Analytical Significance:

The rancidity of olive oil has been traced to the presence of one or two specific aldehydes that are formed during spoiling. These are readily detected by human olfactory systems as well as by chemical sensors. The E-nose and the human nose both effectively discriminate rancid olive oil from good oil. The E-nose can also create different patterns depending upon the concentration of aldehydes in the oil. This is an example of the analytical capability of the E-nose being similar to the human nose [25, 26].

One example of an important problem now being investigated with E-noses is that of detection and identification of bacteria and infectious disease. An illustration of how this might be done is as follows. The vapors above a bacterial culture are collected and a short "sniff" is introduced into the E-nose. As the bacteria grow, they eat specific compounds in the medium upon which they grow and they emit specific metabolites. These are partitioned along with all other chemicals in the liquid medium and the vapors above the medium. So the "sniff" contains a unique set of volatile compounds that are representative of the medium and bacteria. As they pass the sensors, they produce a pattern of responses. These signals can then be analyzed by the computer. The patterns generated by the vapors above a bacterial culture are different for different growth times as well as for different species. With the E-nose we can tell the age of the culture and the type of bacteria in this controlled laboratory experiment. It is still not possible to do this with "wild" samples collected from any field environment and not yet possible to do this with small populations of bacteria, such as those found in infections in medical practice. But the promise of the method to identify and quantify important vapor samples like these illustrates the tremendous future of the E-nose. If it is possible to quantify and identify bacterial with tiny chemical sensors, then inexpensive instruments that are small and portable could have this immense power. Research continues to overcome the barriers to such field application of the E-nose in this and other applications [25, 26, 34].

Scientists have developed a device, which they claim could save lives by smelling tuberculosis-causing bacteria. The electronic nose invented at Cranfield University in Bedfordshire can produce a reliable result in only four hours. Current laboratory methods of confirming infection take two days which the researchers say could make the difference between life and death in some cases. The sensors use artificial intelligence to identify bacteria in TB cases, as well as other respiratory diseases. The technique analyses sputum, saliva and mucus converted into gas form. Infected sputum contains various acids and other products of infected lung tissue. Current laboratory methods of analyzing sputum can only detect the infectious mycobacteria if it is present in large quantities. It cannot distinguish between different strains of the bacteria.
To do that can take up to six weeks, with scientists having to grow cultures in a laboratory. The scientists have proved the system works in laboratory tests [26, 27].

Medical Applications :
The electronic-nose device may provide physicians with a quicker and more accurate diagnostic tool for a number of diseases. Current interest focuses on the detection and identification of certain chemical compounds in exhaled air and excreted urine or body fluids related to specific metabolic conditions, certain skin diseases, or bacterial infections.

Scientists at Cranfield University (Cranfield, Bedfordshire, UK) are taking a different approach to diagnosing urinary tract infections. In a device called the Diag-Nose, they mix a patient's bacterially infected urine with a special growth medium that contains specially formulated compounds. Upon ingestion by the contaminating bacteria the compounds will release characteristic odors that can be detected by a sensor device, leading to a quick diagnosis and earlier treatment of the patient. Identifying the responsible bacterial organism usually takes up to two days; the method developed at Cranfield takes five to six hours. Initial clinical trials look very promising, according to a university spokesperson, and a much larger multicenter trial, involving thousands of patients, will commence soon. Other conditions that scientists are looking to diagnose include tuberculosis, gastric conditions such as ulcers, and cancers that could be potentially diagnosed through the breath, such as esophageal or lung cancer [28-34].

Researchers in the Dental School at the University of California, Los Angeles, are evaluating the potential of Cyrano's device for quantitatively measuring the vapors emitted from bacteria known to be sources of oral malodor (bad breath). The identification of specific odor-emitting bacteria could provide a method for treating oral problems which, left untreated, could lead to major problems affecting the gums or teeth. Odor-emitting Helicobacter pylori, a bacterium found to be responsible for intestinal ulcers, can also be detected and identified. Samples of urine contaminated with certain kinds of bacteria may also be tested in a rapid, cost-effective manner. Some researchers feel that the electronic nose will be helpful in monitoring patients with liver cirrhosis, as well as those with melanomas.

The electronic nose may also provide more-accurate, real-time patient monitoring during anesthesia administration. Cyrano is also conducting clinical trials with its device at Children's Hospital Los Angeles to investigate early detection and diagnosis of upper-respiratory infections. Electronic-nose detectors may also find use as an adjunct in monitoring diabetic or prediabetic patients, automobile drivers or drug abusers for alcohol or drug ingestion, or by animal breeders to evaluate times of estrus [34-40].

CONCLUSION

The simplicity, speed of analyses and the low requirement of sample preparation using Electronic Sensing Technologies make them very advantages versus current methods for the evaluation of the efficiency of sweeteners and flavor excipients for taste masking, level of residual solvents, stability and consistency of formulations.

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