Review Article

# Electronic tongue: An analytical gustatory tool

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## Abstract

Taste is an important organoleptic property governing acceptance of products for administration through mouth. But majority of drugs available are bitter in taste. For patient acceptability and compliance, bitter taste drugs are masked by adding several flavoring agents. Thus, taste assessment is one important quality control parameter for evaluating taste-masked formulations. The primary method for the taste measurement of drug substances and formulations is by human panelists. The use of sensory panelists is very difficult and problematic in industry and 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 difficult when working with unpleasant products. Furthermore, Food and Drug Administration (FDA)-unapproved molecules cannot be tested. Therefore, analytical taste-sensing multichannel sensory system called as electronic tongue (e-tongue or artificial tongue) which can assess taste have been replacing the sensory panelists. Thus, e-tongue includes benefits like reducing reliance on human panel. The present review focuses on the electrochemical concepts in instrumentation, performance qualification of E-tongue, and applications in various fields.

**Key words:** Electrochemical concepts, electronic tongue, taste, taste masking

## INTRODUCTION

Taste-sensing system is analytical sensory array units which can detect specific substances by means of different artificial membranes and electrochemical techniques.

There are various synonyms for these sensory array systems as taste sensors, taste chips, taste sensing system, electronic sensory array system, biomimetic sensor array system, or electronic tongue.[1] From analytical sense, they are composed of various sensors with unique properties and characteristics of partial selectivity or cross-selectivity. Their unique property is measurement and characterization of complex liquid matrices. Due to these features, they have been first used in area of food industry. Later, their use have been widely spread in monitoring environment, medical diagnostics, herbal products,[2] detection of endotoxins and pesticides, etc. The rationale to use electronic tongues for pharmaceuticals is rather new, but not surprising, as taste plays an important role in the development of a pharmaceutical formulation.

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Recent changes in European regulatory requirements[3] initiated the development of medicines intended for children use and demand the development of age-appropriate formulations. As lot of APIs show unpleasant taste, taste masking has become utmost importance. In order to understand concepts of electronic tongue, human tongue structure and mechanism are dealt here under.

## HUMAN TONGUE STRUCTURE

The tongue is a muscular hydrostat on the floors of the mouth of most vertebrate which manipulates food for mastication. It is the primary organ of gustation, as much of the upper surface of the tongue is covered in papillae and taste buds [Figure 1]. In human beings, in addition to tasting, the other function of the tongue is phonetic articulation. The tongue also serves as natural means of cleaning teeth.[4] On the surface of tongue is present pink tissue called mucosa. The function of mucosa is to keep

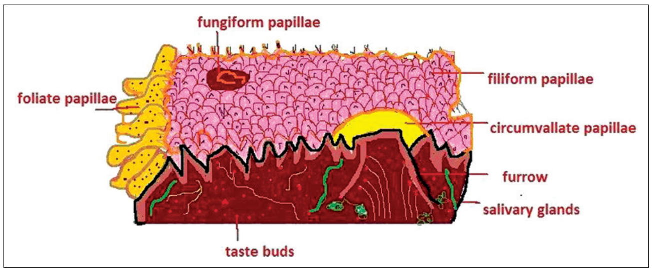


**Figure 1:** Anatomy of tongue

the tongue moist. Tiny bumps called papillae gives rough structure. Several thousands of taste buds are present on the surfaces of the papillae. Taste buds are collection of nerve cells that connect to nerves running into the brain. Different lipid molecules present in the taste buds of tongue plays a key role in sensing taste of food materials. The most common four tastes are sweet, sour, bitter, and salty. A fifth taste, called umami, results from tasting glutamate (present in MSG). The tongue has many nerves that help detect and transmit taste signals to the brain. Because of this, all parts of the tongue can detect these four common tastes.

## TASTE MECHANISM

Taste has been the Cinderella of the senses. The tasted substance, or tastant, is detected by receptors which are present on the apical surface[5-7] of taste cells, which are in contact with the oral compartment. It shows G-protein-coupled receptor activation, which in turn leads to the activation of intracellular enzymes that generate secondary messengers,[8] which in turn modulate a membrane ion channel, depolarizing the cell membrane potential causing an inflow of calcium ions and release of calcium ions from intracellular stores resulting in release of neurotransmitter molecules, which activate the post-synaptic sensory neurons. This is transduction mechanism. Another mechanism, which was recently revealed, was the involvement of transducin-like G protein. In addition to the above proteins, there exist another protein called as alpha-gustducin, which is specific for taste cells of the tongue and some chemoreceptor cells of intestine.[5,6] Studies conducted on mouse taste cells revealed that cAMP? being the secondary messenger transducing the sweet taste of sucrose.[7] In frog preparations, cAMP was found to inactivate a $K^+$ ion conductance, acting through the cAMP-regulated protein kinase A, and thereby to cause membrane depolarization.[8-10] Astringent taste is generally exhibited by tannic acid and aluminium salts shows inhibition of $Na^+$ influx transport across isolated epithelium.

## HOW TASTE BUDS WORKS

The taste buds are chemoreceptors, they transduce, or translate, chemical signals in food into electrical signals in the body called as action potentials [Figure 2], travel to the brain through the nervous system, allowing sensation

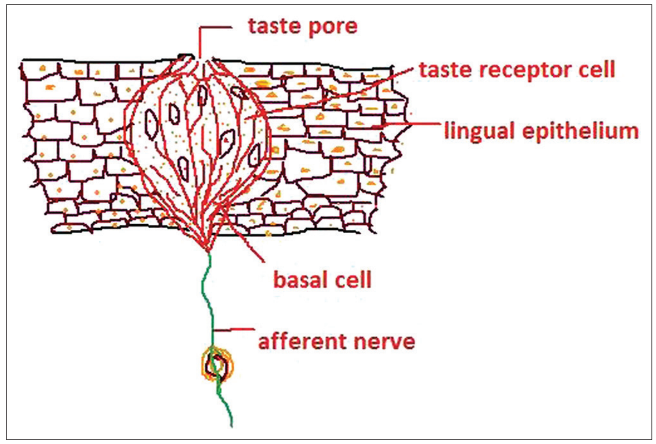


**Figure 2:** Anatomy of taste buds

of taste. The cranial nerves are responsible for carrying the action potential initiated in taste buds to the brain, where taste is ultimately registered.

The same concepts of human taste mechanism has been applied to electronic tongue and designed.

## INSTRUMENTATION

Electronic tongue or taste sensors[11] is an instrument, trained for screening the taste attributes of formulations in a rapid timeframe, when used in addition with human taste assessment data. Sufficient aqueous solubility of test compounds is necessary for application of the electronic tongue. Co-solvents like ethanol can be used to increase solubility of test compounds and the use of instrument can be widened. These devices have a same structure of three principal components, sensory array, the equipment of emitting and receiving signals, and pattern recognition. In recent years, three types of devices called electronic tongue, or taste sensors, had been developed, based on potential, impedance spectroscopy, and voltammetry. The gustatory sensors based on potential was first presented by Iiyama *et al*.[11] It is composed of several kinds of lipids/polyvinylchloride(PVC) membranes for transforming the taste quality information like saltiness, bitterness, etc., into electrical signals. Another type of potential taste sensors was presented by Vlasov *et al*.,[12] which was designed by several non-specific sensors based on chalcogenide glasses as transducer. The second electronic tongue which is based on impedance spectroscopy was first described by Riul and coworkers, in which the sensors were built by supramolecular thin films of conducting polymers with lipid-like material and were analyzed with impedance spectroscopy. The third kind being based on the principle of voltammeter was first designed by Winquist *et al*. It consists of several metallic electrodes (platinum, gold, palladium, iridium, rhenium, and rhodium) which work as working electrode (Ag/AgCl reference electrode and stainless steel electrode as counter electrode for standard three-electrode systems).

## BASIC PRINCIPLE

The main elements of an electronic taste-sensing system are number of different sensor types attached to arm, a sample table, an amplifier, and a computer for data recording. Figure 3 gives a basic principle of electrochemical taste-sensing system. This system imitates what is happening when molecules with specific taste nature interact with taste buds on the human tongue. The taste buds are represented by sensors which interact with these molecules at the surface initiating changes in potential. These signals are compared with physiological action potentials which are recorded by computer, which correspond to the neural network at the physiological level. The data obtained can further be evaluated on the basis of already existing matrix of sensor responses which can be compared with human memory or association to already existing taste patterns. The most applied principle is potentiometry. Electrochemical concepts of Electronic tongue are dealt here under.

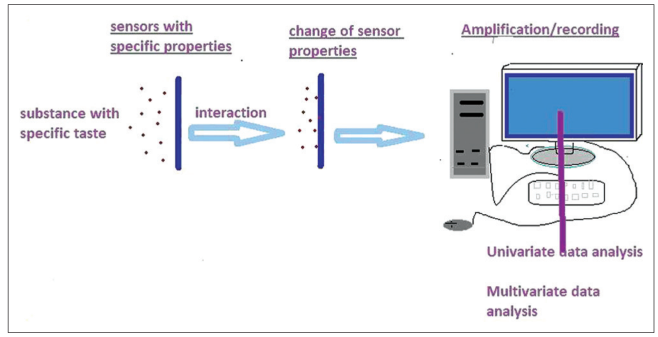


**Figure 3:** Basic principle of electronic taste sending system

## ELECTROCHEMICAL CONCEPTS

The general concepts of electronic tongue used for analysis involves application of an array of nonspecific or low-selective sensors in order to produce signals during analysis of samples. The idea behind using low-selective sensors is based on analogy to biological organization of taste systems in mammals. In the region of tongue, there are several millions of nonspecific receptors that respond to different substances. The taste buds possess several dozens of receptors on the tongue of mammals. The taste signals from the receptors are transmitted to the brain and processed by network of neurons. So, the image of the sensed object is created.

The idea of reproducing artificially the human response to external stimuli was first published in 1943.[13] Thus, this concept has been extended to build an "electronic brain" and artificial intelligence based on neural computing. The first analytical tool of these concepts was an "electronic nose" (1982)[14] used for analysis of gases. "Electronic tongue," introduced in 1995[15] is considered as a promising device in quantitative and qualitative analysis of multi-component matrices.

In literature, electronic tongue is defined as "The electronic tongue is an analytical instrument comprising of an array of nonspecific, low-selective, chemical sensors with high stability and cross-sensitivity to different species in solution, and an appropriate method of pattern recognition (PARC) and/or multivariate calibration for data processing."[16]

## SENSING MATERIALS FOR SENSOR ARRAYS

Based on the principle involved used, the sensing material for sensor arrays varies.[17] If the principle involved is potentiometry, then the materials used are Chalcogenide and oxide glasses,[16,18] noble metals for amperometric signal detection.[19] Sensing materials based on plasticized organic polymers have been applied for potentiometry[17,18] and optical sensors.[20] The selectivity and detection limits of a sensor array depend on composition and properties of the sensing materials.[21] The number of sensors in the array may range from 4 to 40.[20] Potentiometric sensors are the most widespread type of sensors used in electronic tongues system.

Selectivity of potentiometric sensors, such as ion-selective electrodes (ISE), defined by selectivity coefficient, $K_{ij}$, and primary ion, i, against the interfering ion, j, in the Nikolsky-Eisenman equation,

$$E = E^0 + \frac{RT}{Z_i F} \ln \left[ a_i + \sum_j K_{ij} (a_j)^{Z_i / Z_j} \right]$$

Where, $a_i$ and $a_j$ are activity of the primary ion and interfering ion, respectively; $K_{ij}$ is the selectivity coefficient; $E^o$ is the sum of the standard potential of the electrode and the junction potential; E is the potential difference for the electrochemical cell composed of the ion selective and reference electrode; $Z_i$ and $Z_j$ are charge numbers of the primary and interfering ion, respectively. A number of conventional ISEs, e.g., pH glass electrode, sodium and chloride–selective electrodes can also be included in the system. Potentiometric measurements must be carried out by using a multichannel voltmeter with high-input impedance. Values of the sensor potential should be measured against a conventional Ag/AgCl reference electrode and stored as computer data files.

Mathematical signal processing procedures like pattern recognition (PARC) and multivariate calibration (artificial neural network), principle component analysis, and self-organizing map techniques are used to analyze the response of the sensor array because output of the sensor array in a multispecies solution is complex and cannot be described by using theoretical equations (The Nernst or Nikolsky-Eisenman equation).

The most novel electrochemical techniques for electronic tongue developed was multifrequency large amplitude pulse voltammetry. It is designed by several large amplitude pulse voltammetry with deferent step lengths.[22]

## POTENTIOMETRIC CONCEPTS WITH LIPIDS AS TRANSDUCERS

In general, lipids are the most important material for transforming chemical information into electrical signals.[23-26] Taste substances are effective on membrane potentials because of their electric charges. Hence, multichannel taste sensors using 8 lipid membranes have been developed. Here, lipid membranes act as transducers of taste information and a computer as a data analyzer. It has sensitivity, durability, and superior to human tongue.[27-30] Here, lipid membrane is prepared by mixing lipid with PVC, Dioctylphenyl phosphate (plasticizer). This mixture is dissolved in tetrahydrofuran and mixture is transferred to Petri dish and stored at 300°C for 24 hours. This membrane possesses electric charge due to lipids. This acts as working electrodes. The reference electrode is made with Ag wire whose surface is plated with Ag/AgCl with an internal cavity filled with 3MKCl solution and opening tube filled with 100 mM KCl and agar.

Eight kinds of lipid membranes were studded on the multichannel electrode as shown in Figure 4.[31] The system contains Ag/AgCl electrode in 100 mM KCl solution/lipid membrane/reference electrode in taste solution. Taste substance change the membrane potential, and then the electric signal from each membrane is converted to digital code by a digital voltmeter through a high-input - impedance - amplifier and an eight-channel scanner, and finally recorded in a computer. The sensor output comprises of eight electric potentials from eight kinds of lipid membranes.

Various lipids which are used as multichannel transducers are as follows:

Toko *et al*.[30] prepared taste-sensing membranes by adding lipids with silicone rubbers. Lipids which are used are dioctyl phosphate, trioctyl phosphate, and methyl ammonium chloride and molar mixture of dioctyl phosphate and trioctyl methyl ammonium chloride. Riul Jr. *et al*.[32] designed an electronic tongue composed of polyaniline oligomers (16-mer) and polypyrrole (Ppy), which were able to distinguish salt, sweet, bitter, acidic solutions, different brands of mineral water, tea, and coffee, proving that conducting polymers are useful sensing materials.

Hayashi *et al*.[33] examined lipid and ion exchange cellulose as transducer materials of a taste sensor.

## PERFORMANCE QUALIFICATION OF SA402B TASTE-SENSING SYSTEM

Performance qualification of taste-sensing system SA402B (Insent Inc., Atsugi-chi, Japan) equipped with seven lipid membrane sensors for bitter taste assessment. These sensors represent the gustatory stimuli bitterness, umami, saltiness, saltiness, sourness, and the nociceptive sensation astringency. Specificity, linearity, range, accuracy, precision, and detection were established for each sensor type referring to ICH guidelines Q2 (R1). Standard substance used is quinine hydrochloride, as it is the bitterest one with bitter value 200 000. Equipment qualification contains four basic elements: DQ, OQ, IQ, and PQ.[34,35]

The underlying measurement principle is potentiometric and sensor response are recorded as mV values. According to Nernst equation, the electrode potential depends on activity of the substance.[36]

$$U = U^0 + \frac{RT}{zF}\ln a_i$$

Where, U is electrode potential; U° is standard electrode potential; R is universal gas constant; T is temperature (K); Z is ionic valence of the substance; F is Faraday constant; and $a_i$ is activity of the substance.

$$a_i = f_i c_i$$

Where, $c_i$ is the concentration of the substance; $f_i$ is the activity coefficient of the substances.

Sensor check is done routinely before every measurement to ensure that sensors are working in the correct mV range. Each sample was measured four times; one measurement cycle consisted of measuring the reference solution (Vr) for 30 seconds, then sample solution (Vs) for 30 seconds. The after taste was measured by determining change of membrane potential caused by adsorption of the substances to the lipid membrane after short cleaning procedure for 6 seconds, then washed with reference solution (Vr′) for 30 seconds and measured, followed by complete washing for 330 seconds.

Sensor output for taste, also called Relative value (R)

$$R = V_s - V_r$$

Sensor output aftertaste, also called CPA value (change of membrane potential caused by adsorption)

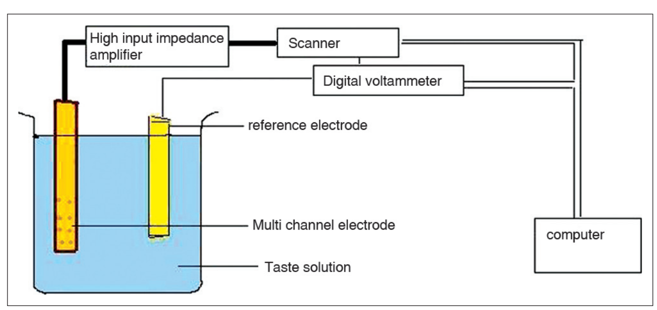


**Figure 4:** Experimental setup of potentiometric multichannel taste sensor system

$CPA = V_{r1} - V_r$

The whole procedure is done for all samples for four times [Figure 5].

## APPLICATIONS OF ELECTRONIC TONGUE

E-tongue is specially designed for taste analysis in R and D, formulation, food product Development, and food process improvement applications. It has got several applications in various industrial areas: The pharmaceutical industry, food and beverage sector, etc. It can be used to:

- Analyze human urine for the detection of urinary system dysfunction and creatinine levels.[37]
- Evaluate Italian wine for taste and flavor.[38]
- Detect alcohols in beverages by using porphyrin-based potentiometric electronic tongue.[39]
- Analyze flavor ageing in beverages (for instant fruit juice, alcoholic or non-alcoholic drinks, flavoured milk.
- Quantify bitterness or spicy levels of drinks or dissolved compounds.
- Quantify taste-masking efficiency of pharmaceuticals (tablets, syrups, powders, capsules, etc.).
- Analyze stability of medicines regarding taste.
- Benchmark the target products.
- Differentiate the different kinds of mineral water based on hardness of water.[40]
- Differentiate varieties of tomato by measuring crushed tomatoes.[41]
- Discriminate fresh from spoiled milk.[42]
- Differentiate different brands of coffee of different origin.[43]
- Monitor agriculture and industrial pollution of air and water.
- Identify toxic substances.
- Search for drugs, explosive.
- Searching for chemical/biological weapon.
- Identify unpleasant taste of pharmaceuticals.
- Quantify taste and foodstuff recognition.
- Monitor Herbal medicine.
- Monitor environment with respect to water, metal ions, endotoxins, pesticides.
- Characterize APIs like Caffeine, Paracetamol, phenylthiourea, Quinine hydrochloride, etc.
- Characterize amino acids like L-isoleucine, L-leucine, and L-phenylalanine.[44]
- Evaluate coated microparticles of Ibuprofen and roxithromycin.[45]
- Study sweet taste evaluation with lipid/polymer membrane.[46]
- Measure solid food.[47]
- Detect trace amounts of organic substances.[48]
- Evaluate taste of crude drugs and Kampo Formula.[49]

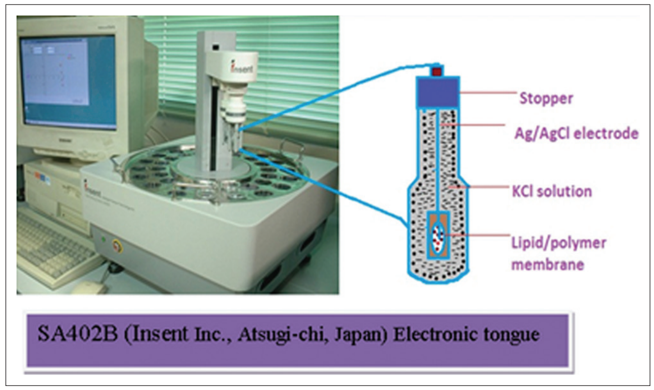


**Figure 5:** Electronic tongue

## CONCLUSION

Electronic tongues are emerging and promising fields in recent chemical sensor science. It has a concept of global selectivity. It is a valuable tool for assessment and prediction of the taste of pharmaceuticals and related products. It replaces human panels in routine analysis in pharmaceutical development and production. The exposure and risk of using human panel to test products is greatly reduced, permitting better analytical results to quickly define the best formulation and get the product to market.

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