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Taste sensing systems (electronic tongues) for pharmaceutical applications

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ABSTRACT

Electronic tongues are sensor array systems able to detect single substances as well as complex mixtures by means of particular sensor membranes and electrochemical techniques. Two systems are already commercially available, the Insent taste sensing system and the αAstree electronic tongue. In addition, various laboratory prototype versions exist.

Besides the successful use in food industry, the implementation for pharmaceutical purposes has strongly grown within the recent years. A reason for this is the increased interest of developing palatable formulations, especially for children. As taste assessment of drugs comes along with challenges due to possible toxicity and subjectivity of the taste assessors, electronic tongues could offer a safe and objective alternative.

In order to provide guidance on the use of these systems, possible fields of interest are presented in this review, as for example, system qualification, quality control, formulation development, comparison between marketed drug products, and the validation of the methods used. Further, different approaches for solid and liquid dosage forms are summarized.

But, also the difficulty to obtain absolute statements regarding taste was identified and the need of more validated data was discussed to offer guidance for the next years of research and application of electronic tongues for pharmaceutical applications.

1. Introduction

Taste sensing systems are analytical sensor array systems which are able to detect specific substances by means of different artificial membranes and electrochemical techniques.

There are various synonyms for these sensor array systems as for example taste sensor, taste chip, taste sensing system, electronic sensor array system, biomimetic sensor array system or electronic tongue (Ciosek and Wróblewski, 2007). From an analytical point of view they are a composition of different sensors with varying properties and characteristics of partial selectivity or cross-selectivity. Their ability to measure and characterize complex liquid matrices makes them unique in the field of analytical systems.

Due to these properties, they have been first used in the area of food industry for example for quality control, comparison of different product qualities as well as comparison to competitive products (Escuder-Gilabert and Peris, 2010). There are some recent reviews presenting the fields of application for electronic tongues. Fig. 1 summarizes these possible application areas based on the reviews by Vlasov et al. (2002), Ciosek and Wróblewski (2007), and Kobayashi et al. (2010).

Obviously, the analysis of food stuff and beverages represents the biggest part as different types of electronic tongues have been already used for the determination of fruit juice, onions, soft drinks, tea and herbal products, beverages, apples, milk, tomatoes, alcohol, coffee, sake, olive oil, beer, rice, cork, meat, and soya paste. In addition, other systems have been developed specifically for the monitoring of environment, as for example the analysis of water qualities, fermentation processes as well as the detection of endotoxines and pesticides. Some approaches were made in the area of medical diagnostics monitoring urine and blood samples as well as in the field of safety determining toxic substances.

With respect to herbal products, the non-specificity of the electronic tongue sensors is a major advantage of electronic tongue measurements. Herbal extracts are complex systems which are often hard and elaborate to characterize using common analytical techniques. This is why electronic tongues could help reducing efforts and cost while reliably detecting taste as well as quality of the extracts (Ahmad et al., 2006). The application of electronic taste sensing systems for the monitoring of herbal medicines will therefore also be included in this review.

The idea to use electronic tongues for pharmaceutical purposes is rather new, but not surprising, as taste plays an important role in the development of a pharmaceutical formulation. Recent

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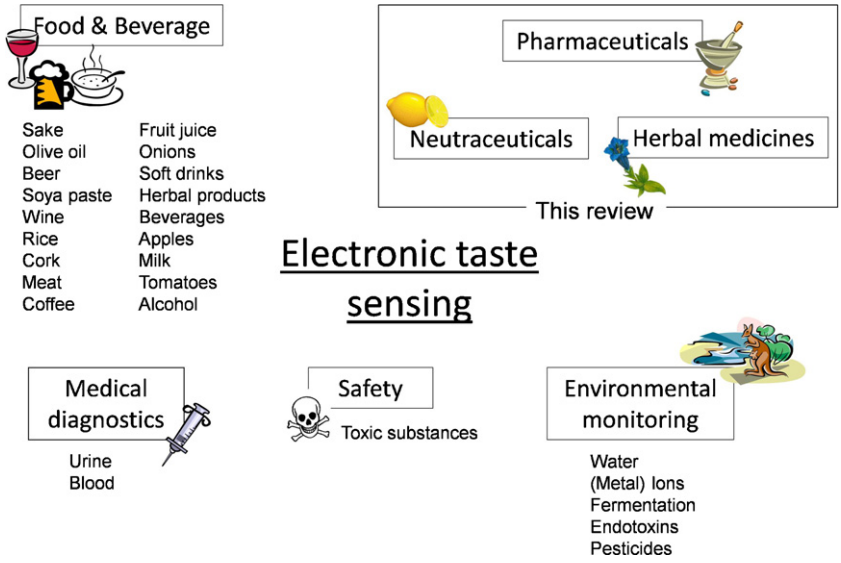

Fig. 1. Fields of application for electronic taste sensing systems (figure created according to Vlasov et al., 2002; Ciosek and Wróblewski, 2007; Kobayashi et al., 2010).

changes in European regulatory requirements (Regulation (EC) No 1901/2006, 2006) initiated the development of medicines intended for paediatric use and demand the development of age-appropriate formulations. Especially in children, taste of a medication is important with respect to adherence and compliance. As a lot of active pharmaceutical ingredients exhibit an unpleasant taste, taste masking has therefore become increasingly important. Researchers focusing on paediatric drug development, have early considered the use of electronic tongues, but they also claimed for more reliable data in order to use the taste sensing systems as adequate tools in taste assessment (Cram et al., 2009). In order to put the application of electronic tongues for pharmaceutical applications in the right context and to understand the motivations of using these systems in this particular area a short introduction about taste sensation, taste assessment and masking of unpleasant taste in medicinal products shall be given here.

Basically, taste is transmitted by the interaction of dissolved molecules with different targets located in taste buds on the tongue. The mechanisms of signal transduction after binding of the tasting substance can be different depending on the taste quality. Thus, sour and salty tastes are transmitted via ion channels whereas bitterness and umami are transmitted via G-protein coupled receptors. Sweet taste can be transmitted by both, ion channels and G-protein coupled receptors. In addition, interactions of different tastes can occur in the subsequent neural network (Gilbertson et al., 2000.). Further, human taste perception in general does not only happen on the tongue as there are other important factors as for example olfactory perception as well as limbic influences (Dulac, 2000).

A major group of taste masking strategies focuses on the inhibition of the substance receptor interaction, like for example coating of solid dosage forms or complexation of the drug substance by solid or soluble complexing agents. In addition, research focuses on the development of specific blockade of the taste receptor. Other techniques try to cover the taste by misleading the sensory system as for example by using sweeteners. Established taste masking technologies for pharmaceutical dosage forms were extensively described by Sohi et al. (2004), Ayenew et al. (2009), and Wagh and Ghadlinge (2009).

The assessment of successful taste masking can come along with challenges depending on the particular method, as for example analytical techniques, animal studies or human taste panels (Anand et al., 2007; Cram et al., 2009). In general, human sense of taste can be subject to physiological properties and individual preference. Especially for the paediatric population a general approach applicable for the specific characteristics of children at different development stages is not available yet (Davies and Tuleu, 2008) coming along with additional ethical concerns. The toxicity of new chemical entities plays a major role in early preclinical development and leads to limitations with respect to taste assessment. Therefore, electronic tongues may offer an objective and safe method for comparing different formulations with respect to their taste masking. Depending on the dosage form and based on the taste masking technology, taste assessment by an electronic tongue has to be carried out according to specific measurement setups. The mechanisms of detection by the sensors are different as well.

In this review guidance on how to deal with different dosage forms and taste masking techniques shall be provided based on the experiences of the recent years. Research with respect to feasibility and detectability of different active compounds shall be described. Further, the application of electronic tongue systems in the field of pharmaceutics will be elucidated, comprising quality assurance, quality control, taste characterization of active pharmaceutical ingredients, development of solid and liquid dosage forms, comparison of competitive products and taste characterization of already existing formulations, as well as validation of the results.

And finally, the limitations of electronic taste sensing systems shall be elaborated and notes of caution with respect to data interpretation and statistical performance will be provided.

2. Electronic tongues – types and setup

2.1. Main principle and general setup

The main elements of an electronic taste sensing system are a different number of various sensor types which can be attached to a robot arm, a sample table, an amplifier and a computer system for data recording.

Fig. 2 shows a rough sketch of the basic principle of electrochemical taste sensing. Basically, these systems try to represent and imitate what is happening while molecules with specific taste properties 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 electric potentials. These signals, which can be compared to physiological action potentials, are recorded by a computer system, which corresponds to the

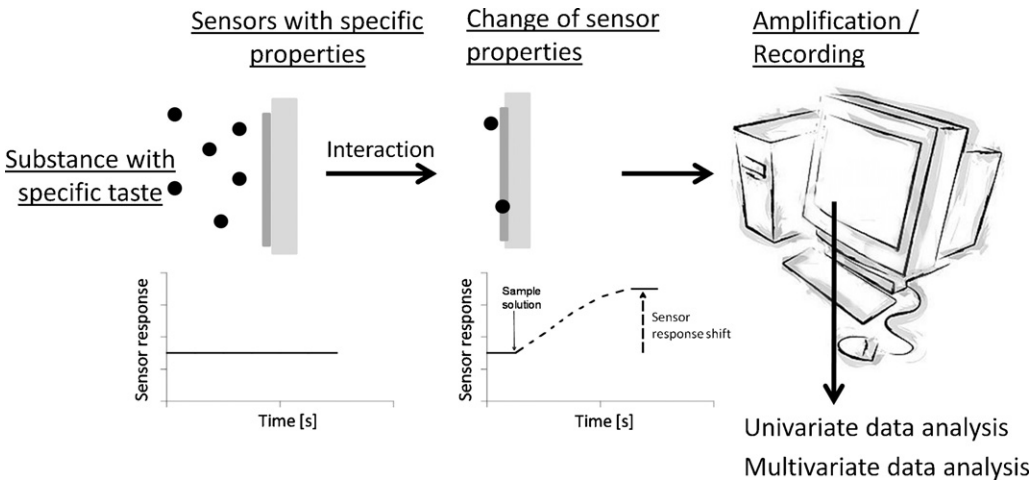

Fig. 2. Basic principle of electronic taste sensing systems.

neural network at the physiological level. The obtained data can be evaluated afterwards on the basis of an already existing matrix of sensor responses which is comparable with the human memory or association to already known taste patterns.

For most of the systems, during analysis, sensors are immersed in samples which are located on an auto sampler and voltage values (mV) are recorded over a specific time period followed by a washing step and measurement of the next sample (Legin et al., 2004; Turner, 2009; Kobayashi et al., 2010).

Sensor materials and membranes can be of different nature and contain different substances depending on the type of measurement principle used. There are, for example, lipid membranes consisting of differently charged lipids and different types of plasticizers as well as sensors with alcoholic compounds or inorganic salts. The most applied measurement principle is potentiometric and mV values are measured with respect to an Ag/AgCl reference electrode. Analogous to human taste, sensor responses depend logarithmically on the activity of the substances which are measured (Plambeck, 1982; Schindler and Schindler, 1983). This is described by the Nernst equation (equation (1)).

$$U = U^0 + \frac{R \times T}{z \times F} \times \ln a_i \quad (1)$$

where U = electrode potential; U^0 = standard electrode potential; R = universal gas constant; T = temperature (K); z = ionic valence of the substance; F = Faraday constant; a_i = activity of the substance.

$$a_i = f_i \times c_i, \quad (2)$$

where c_i = concentration of the substance; f_i = activity coefficient of the substance.

For human taste sensation, the Weber–Fechner law explains the logarithmic relationship between concentration of the taste stimulus and taste intensity (Mutschler et al., 2007; Schmidt, 2007). Therefore, reaching a particular concentration threshold, differences between taste intensities cannot be distinguished any more by human taste assessment.

In comparison to other commonly used techniques, complex mixtures of substances like active pharmaceutical ingredients and excipients for taste masking can be investigated by these electrochemical sensor array systems as sensors are non-specific (Woertz et al., 2010a). Nevertheless, a limitation might be that samples need to be liquid for investigation. In addition, particles in the liquid should be removed as they could damage the sensor or sensor membranes. Therefore, in order to investigate solid dosage forms, an indirect determination has to be carried out, as for example dissolving and subsequent filtration or time-dependent dissolution testing. Guidance on sample preparation with respect to the particular dosage form is shown in Fig. 3.

Table 1 shows electronic tongues, which have been used for pharmaceutical purposes. To date, two systems are commercially available whereas the others are laboratory prototype systems.

2.2. Insent taste sensing system

The Insent taste sensing system (Fig. 4a) is a potentiometric multichannel taste sensor developed over a couple of years by scientists at Kuyushu University in Japan and is now distributed by Intelligent Sensor Technology (Insent) Inc. (Atsugi-shi, Japan). Kobayashi et al. (2010) describe the used sensors, the principles of measurement, the design of the taste sensor as well as the whole development of this electronic tongue in a recent review. It summarizes about 34 research papers which were published by the working group of Toko (Information science and electrical engineering, Kyushu University, Japan) in the years 1980–2008 showing the continuous development of this electronic tongue.

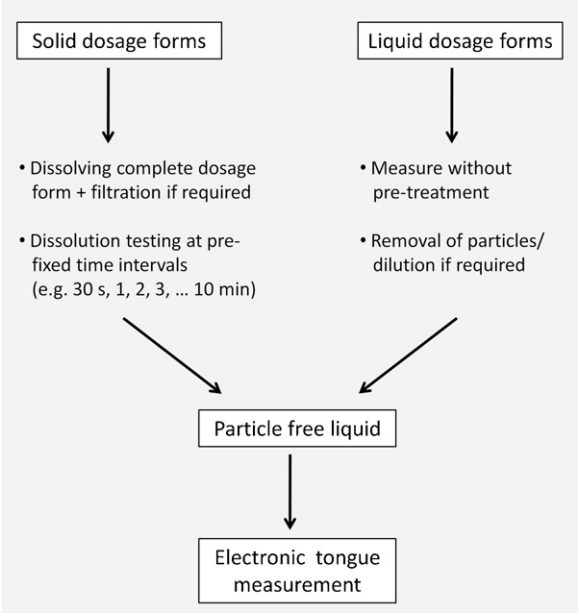

Fig. 3. Sample preparation with respect to the dosage form.

Table 1
Electronic tongues used for pharmaceutical applications.

Electronic tongue	Measurement principle	Sensor type	Number of sensors	Working group /Distributor
αAstree electronic tongue	Potentiometric	ChemFET	17 (3 different sensor sets with 7 sensors each)	Alpha MOS (Toulouse, France)
Insent taste sensing system TS-5000Z	Potentiometric	Lipid membrane sensors	8	Information science and electrical engineering, Kyushu University, Japan Intelligent Sensor Technology (Insent) Inc. (Atsugi-shi, Japan)
Laboratory version	Potentiometric	Modified chalcogenide glass or plasticized PVC membranes	Up to 30	Chemistry Department, St. Petersburg University (St. Petersburg, Russia)
Laboratory version	Potentiometric	Ion selective electrodes	8	Warsaw University of Technology, Faculty of Chemistry (Warsaw, Poland)
Laboratory version	Impedance spectroscopy	Nanostructured films adsorbed onto Pt interdigitated electrodes	6	Faculdade de Ciencias e Technologia, UNESP (Sao Paulo, Brazil)
Laboratory version	Potentiometric	Lipid membrane sensors	8	School of Pharmaceutical Sciences, Universiti Sains Malaysia (Penang, Malaysia)
Laboratory version	Potentiometric	Ion selective electrodes coated with PVC membranes	1/drug	Department of Physical Chemistry, Kyoto Pharmaceutical University (Kyoto, Japan)

In brief, the taste sensing system can be equipped with up to eight lipid membrane sensors, each representing a gustatory stimulus or mouth feeling as for example sourness, saltiness, astringency, sweetness, umami, and three types of bitterness specific for molecules with different ionic character. It has a sample table with two parallel circles of sample positions. Each sample needs to be placed in duplicate on both circles as sensors are attached on two different sensor heads in order to avoid cross contamination. Therefore, 10 samples can be measured within one cycle. Today's commercially available system is the TS-5000Z. By implementation of an Ag/AgCl reference electrode, which is separately attached to each sensor head, the change of membrane potential is measured after immersing sensors in the sample solution and mV values are obtained consequently. The sample value is determined relatively with respect to a preliminary measured standard solution consisting of potassium chloride and tartaric acid. In addition, a so called after taste value can be measured by immersing sensors into the standard solution after sample measurements and two short cleaning steps (2×3 s). Therefore, the adsorption of the substance to the membrane is measured. The obtained value is called CPA value ("change of membrane potential caused by adsorption"). After 30 s measurement of the sample value and the aftertaste value, respectively, sensors are cleaned in ethanolic solution and the next sample is measured. The measurement time of 30 s is set as default value by the supplier, but can be changed manually.

2.3. αAstree electronic tongue

The αAstree electronic tongue (Fig. 4b) is a potentiometric based system with a seven-sensor probe, an Ag/AgCl reference electrode and an auto sampler with 16 or 48 possible sample positions. The seven-sensor probe can differ in composition of different sensors and therefore three types of sensor sets are available, one set for food applications (sensors ZZ, BA, BB, CA, GA, HA, JB), one set for pharmaceutical applications (sensors ZZ, AB, BA, BB, CA, DA, JE) and one set which is described as set for bitterness intensity measurement of new chemical entities (sensors BD, EB, JA, JG, KA, OA, OB). In contrast to the Insent taste sensing system these sensors measure in a cross-selective way meaning that they are not assigned to a specific taste quality or gustatory feeling. The underlying sensor technology is based on chemically modified field effect transistor technology (ChemFET) which is similar to the ion selective FET technology, but sensors are coated with specific materials. These ChemFET sensors are composed of two highly conducting semiconductor regions: a source and a drain. Those regions are surrounded with an insulator. A sensitive layer (coated membrane) is

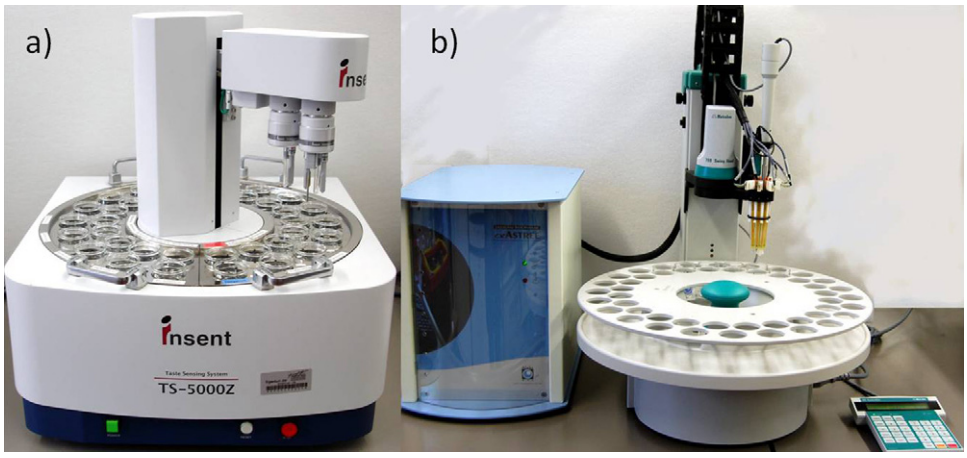

Fig. 4. Commercially available electronic tongues: a) Taste sensing system TS-5000Z (Insent Inc., Atsugi-shi, Japan); b) αAstree2 (AlphaMOS, Toulouse, France).

deposited above the insulator between the source and the drain. The type and composition of materials in the layer is not disclosed, but they are able to form specific interactions, like hydrogen bonds and van der Waals interactions with the chemical substances measured (AlphaMOS, 2004). Together with a set of seven sensors, the reference electrode and a stirrer are attached to the sensor head. Samples are measured for 120 s and the timeframe, in which the obtained sensor response values are averaged, can be chosen manually. Again, the measurement time of 120 s is recommended by the supplier, but can be changed.

2.4. Other

There are various types of other electronic tongues which are experimental laboratory setups and not commercially available (Table 1). For example, the working group of Legin at St. Petersburg University (Chemistry Department, St. Petersburg University, Russia) has published at least 73 research papers within the years 1996–2010. A detailed list of publications is available online at www.electronictongue.com. Most of these papers are dealing with the application of their electronic tongue to the analysis of different food stuff, but there are also few pharmaceutical projects. This potentiometric working electronic tongue can be equipped with various sensors either being solid state sensors consisting of modified chalcogenide glass or specially designed non-specific sensors with enhanced cross-sensitivities based on plasticized PVC membranes (Legin et al., 1997, 2004). In addition, a reference electrode and a standard glass pH electrode are included. The measurement time is 5 min in order to allow the sensors to reach equilibrium potential and a washing step with distilled water follows. Signals are recorded by a computer over a multichannel electronic high impedance voltmeter, AD converter and multiplexor.

Another electronic tongue potentially useful for pharmaceutical purposes was introduced by Aoki et al. (2008). Platinum sensors coated with different materials were able to detect different concentrations of methylene blue in water based on impedance spectroscopy. This might therefore be a reasonable approach using a measurement technique other than potentiometry.

A system similar to the Insent taste sensing system was developed by Ahmad et al. (2006). The sensors are also coated with lipid membranes and the measurement principle is potentiometric. Eight sensors are available having partial overlapping selectivity and cross-sensitivity. A conditioning of the sensors is carried out in 1 mM potassium chloride 1 h before measurement and sensors are washed with deionized water afterwards. The measurement time is 2 min per sample.

A potentiometric system using one ion selective electrode for a particular drug was described for a taste masked formulation by Funasaki et al. (2006). The electrodes are coated with a PVC membrane specific for a particular drug and electromotive forces are recorded during the sample measurement which lasts about 2 min.

Other electronic tongue types are based on optical sensor arrays or mass sensors and also miniaturized e-tongues are under development (Ciosek and Wróblewski, 2007). However, an application for pharmaceutical purposes has not been described for these systems so far.

3. Data treatment and evaluation

3.1. General

The data of electrochemical sensors, which is obtained as a result of direct measurement or relative measurement of the sample in mV, can be processed either univariate or multivariate. Data evaluation methods used for electronic tongue measurements of pharmaceutical samples are listed in Tables 2–4 together with the type of drug substance, excipients which were used, dosage form, the type of electronic tongue, the purpose of the study, and the type of validation method. It becomes obvious that multivariate statistics are used in most of the studies, but univariate data evaluation is used for sensors of the Insent taste sensing system as well. Both approaches are useful and provide different options for interpretation of the experimental results. An example for the data processing of data from the two commercially available potentiometric electronic tongues is shown in Fig. 5. Caffeine citrate was used as a model drug here with concentrations of 0.026–45.3 g/100 ml demineralized water.

3.2. Univariate data evaluation

The best way to get a first impression about the complex data of the measurement is a univariate evaluation of the sensor responses. To do this, for both commercially available sensor systems, the first measurements should be discarded and only the last three runs of the measurement should be taken for further examination. This can be explained by a conditioning phase of the sensors which is advantageous to obtain stable results. As shown in Fig. 5, a drift of the sensor responses over measurement time can occur leading to misinterpretation of the data. Therefore, only stable signals should be used and the mean together with the standard deviation can be calculated. It is necessary to know that the sensor values (mV) are not a measure for the real taste intensity. Even if one sensor is associated with a particular taste quality, as for the TS-5000Z, results need to be interpreted in relation to previous calibrations with excipients and the drug substance. This can be explained by the dependency of sensor responses on the chemical characteristics of the substances, because adsorption to the sensor membrane can occur due to hydrophobic and hydrophilic interactions, as well as ionic interactions (Kobayashi et al., 2010). As unpleasant taste cannot be directly associated with certain chemical characteristics, the obtained values are hard to compare between different unpleasant tasting substances. If possible, an individual substance calibration curve of all excipients and drugs used for the formulation should therefore be established (Woertz et al., 2010b). Based on this, sensors for evaluation of a multicomponent formulation by multivariate statistics can be chosen and a comparison of the actual value with values from the concentration series by one sensor can be done as well.

3.3. Multivariate data evaluation

Since always more than one sensor and up to 40 sensors can be used, multivariate statistics make it easier to evaluate the results of a measurement with many sensors and many samples at a glance. This makes sense especially when multicomponent mixtures should be evaluated where different sensors show different behavior leading to the main conclusion whether taste masking was achieved or not. In detail, a mixture of unpleasant tasting API and masking agents can be evaluated as not masked or only partially masked by one sensor which is more specific for the drug. On the other hand it can be evaluated as taste masked by a sensor which is more specific for the masking excipients.

This is caused by the non-specificity of sensors. Combination of sensor responses which were chosen based on the univariate interpretation is then advantageous for taste prediction. Various statistical methods can be generally applied to the data analysis of sensor data. Those which are mostly used are principal component analysis (PCA) and partial least square regression (PLS). Principal

Table 2
Pharmaceutical applications of the αAstree electronic tongue.

Drug substance	Excipients	Dosage form	Purpose	Electronic tongue type	Data analysis	Validation by reference method	Reference
15 nutritive drinks (Thiamine and thiamine derivates, medicinal plant ingredients)	–	Liquid	Characterization of products	αAstree (Food sensor set) & FOX 4000 nose sensor	Univariate and multivariate (PCA)	Adult human taste panel ($n = 11$)	Kataoka et al. (2005)
Doxycycline hyclate (D), ciprofloxacin hydrochloride (C), potassium iodide (P)	D: Apple juice with sugar, low-fat milk, low-fat chocolate milk C: Maple syrup, chocolate syrup, apple juice P: Orange juice, raspberry syrup, chocolate milk	Ground tablets in mixture with different food stuff and drinks	Palatability (+ stability and dose uniformity) in household food and drinks	αAstree (pharmaceutical sensor set)	Multivariate (PCA – Euclidean distances)	Adult human taste panel ($n = 30$; $n = 20$ for D)	Sadrieh et al. (2005)
Quinine sulphate	Acesulfame K, sodium acetate, sodium chloride, Prosweet® flavor, Debittering® powder, Coca-Cola®, Sprite®, Diet Sprite®, Dr. Pepper®	Oral liquid	Formulation development	αAstree (pharmaceutical sensor set)	Multivariate (PCA – Euclidean distances)	None	Zheng and Keeney (2006)
Caffeine anhydrous, paracetamol, phenylthiourea, prednisolone sodium, quinine hydrochloride, ranitidine hydrochloride, sucrose octaacetate	–	–	Characterization of APIs				
Undisclosed model drug	Amberlite IRP64/Carbopol 971P	Liquid ODTs	Formulation development	αAstree (sensors not specified)	Multivariate (PCA – Euclidean distances)	Adult human taste panel ($n = 5$) Drug release profiles (HPLC)	Li et al. (2007)
Quinine sulphate	Eudragit® E PO	Pellets	Formulation development	αAstree (Bitterness prediction module)	Multivariate (PLS – Bitterness prediction module)	Dissolution testing, bioavailability study in adults ($n = 12$) and children <5 years ($n = 56$)	Kayumba et al. (2007, 2008)
Sodium benzoate	κ-carrageenan, MCC, Witocan® 42/44, Precirol®, Dynasan 114®	Pellets	Electronic tongue evaluation Formulation development	αAstree (pharmaceutical sensor set)	Univariate and multivariate (PCA – Euclidean distances)	Adult human taste panel ($n = 9$), dissolution testing, drug release in food	Krause (2008)
Quinine anhydrous, hydrocortisone, prednisolone	Erythritol, acesulfame K, sucrose Tangerine, strawberry, cherry HP-β-cyclodextrin, Me-β-cyclodextrin	Oral liquid	Formulation development	αAstree (pharmaceutical sensor set)	Univariate and multivariate (PCA – Euclidean distances, PLS)	Adult human taste panel ($n = 12$)	Turner (2009)
Unknown (slightly to moderately bitter taste), acetaminophen, diphenhydramine hydrochloride, oxybutynin chloride	Sorbitol, citric acid, sodium citrate, artificial cherry flavor, sodium benzoate, acesulfame K, aspartame, sodium saccharin, high fructose corn syrup, sweetness enhancer type A/B	Oral liquid	Formulation development	αAstree (pharmaceutical sensor set)	Multivariate (PCA – Euclidean distances, DFA, PLS)	Adult human taste panel ($n = 4$–6)	Lorenz et al. (2009)
Famotidine	Aspartame, other excipients	Orally disintegrating tablet	Comparison of original and eight generic products	αAstree (Food sensor set)	Multivariate (PCA – Euclidean distances)	Adult human taste panel ($n = 11$), drug release profiles (HPLC)	Tokuyama et al. (2009)
Epinephrine bitartrate	Acesulfame K, aspartame, citric acid	Sublingual tablet	Formulation development	αAstree (Bitterness prediction module)	Multivariate (PLS – Bitterness prediction module)	None	Rachid et al. (2010)

Table 3
Pharmaceutical applications of the Insent taste sensing system.

Drug substance	Excipients	Dosage form	Purpose	Electronic tongue type	Data analysis	Validation by reference method	Reference
Quinine HCl, trimebutine maleate, dibucaine HCl, metronidazole, betamethasone-21-phosphate, salicylic acid, benzoic acid, diclofenac sodium, theophylline, acetaminophen, caffeine anhydrous	(Sucrose, aspartame)	Liquid	Characterization of APIs	Insent taste sensing system SA402	Univariate (CPA value of eight sensors compared to bitterness strength evaluated by human panel)	Adult human taste panel ($n = 15$)	Uchida et al. (2000)
Quinine HCl, amitriptyline HCl, D-chlorpheniramine maleate, dextromethorphan HBr, dibucaine HCl, diltiazem HCl, imipramine HCl, promethazine HCl, propranolol HCl, trimebutine maleate	–	Liquid	Characterization of APIs Electronic tongue evaluation	Insent taste sensing system SA402	Multivariate (MRA of two sensors and human taste panel data)	Adult human taste panel ($n = 11$)	Uchida et al. (2001)
Quinine hydrochloride, L-tryptophan, magnesium chloride, sodium chloride, hydrochloric acid, sucrose, monosodium glutamate	BMI-60 (bitter masking substance consisting of 15–20% phosphatidic acid, 40% phosphatidyl-inositol, 10–15% phosphatidyl-ethanolamine, and 5% phosphatidyl-choline	Liquid	Electronic tongue evaluation	Insent taste sensing system SA401 (seven sensors)	Univariate and multivariate (PCA)	Adult human taste panel ($n = 5$)	Takagi et al. (2001)
Quinine hydrochloride	Sucrose, aspartame, sodium chloride, phosphatidic acid, tannic acid	Liquid	Formulation development Electronic tongue evaluation	Insent taste sensing system SA402	Univariate (CPA value of one sensor compared to bitterness strength evaluated by human panel)	Adult human taste panel ($n = 11$), binding study (HPLC)	Nakamura et al. (2002)
L-isoleucine, L-leucine, L-valine, L-phenylalanine, L-tryptophan	–	Liquid	Characterization of amino acids	Insent taste sensing system SA402 (eight sensors)	Univariate and multivariate (PCA)	Adult human taste panel ($n = 9$)	Miyanaga et al. (2002)
Clarithromycin, erythromycin, cefdinir, vancomycin HCl, doxycycline HCl, tetracycline HCl, oxytetracycline HCl, minocycline HCl, bacampicillin HCl	–	Liquid	Characterization of APIs	Insent taste sensing system SA402B	Univariate and multivariate (PCA, MRA of two sensors and human taste panel data)	Adult human taste panel ($n = 9$)	Uchida et al. (2003)
Clarithromycin dry syrup		Oral liquid	Characterization of formulation				
Clarithromycin	Water, coffee, tea, green tea, cocoa, milk, sports drink	Powder, dry syrup	Characterization of a product modified by commercially available beverages	Insent taste sensing system SA402B (eight sensors)	Univariate and multivariate (MRA of two sensors and human taste panel data)	Adult human taste panel ($n = 9$)	Tanigake et al. (2003)
Aminoleban EN®	Flavors: pineapple, apple, milky coffee, powdered green tea, banana	Liquid	Electronic tongue evaluation Formulation development	Insent taste sensing system SA402 (eight sensors)	Univariate	Adult human taste panel ($n = 9$)	Miyanaga et al. (2003)

component analysis is a tool to summarize and reduce data by transforming a number of variables, here: sensor responses, to a smaller number of variables, so called principal components (PC), in order to describe the objects, here: measured samples, in a new space with less dimensions (Kessler, 2007). As a result, samples can be compared more easily, but with ideally the same amount of information. A typical PCA map consists of a two dimensional graph, whose axes optimally represent 100% of the information in

Table 3
(*Continued*)

Drug substance	Excipients	Dosage form	Purpose	Electronic tongue type	Data analysis	Validation by reference method	Reference
Protein-based nutrients: Clinimeal®, Ensure®, Harmonic-M®, Racol® Peptide-based nutrients: Enterued®, Twinline® Amino-acid-based nutrients: Elental®, Hepan ED® Aminoleban® EN	Coffee flavor, milk flavor, pineapple, apple flavor, fruit-mix, and powdered green tea flavor	Oral liquid	Characterization of products	Insent taste sensing system SA402 (eight sensors)	Univariate and multivariate (PCA)	Adult human taste panel ($n = 9$)	Mukai et al. (2004)
Ampicillin, amoxicillin, cefaclor, cefdinir, cefcapene, cefteram, faropenem, cefditoren, azithromycin, clarithromycin, erythromycin, fosfomycin, midecamycin, norfloxacin, sulfamethoxazole/trimethoprim, aciclovir, oseltamivir, amantadine	Acidic sports drink (Pocari sweat®)	Dry syrup, fine granules, tablet	Characterization of products modified by commercially available acidic sport drinks	Insent taste sensing system SA402B (eight sensors)	Univariate and multivariate (MRA of two sensors and human taste panel data)	Adult human taste panel ($n = 7$)	Ishizaka et al. (2004)
Amitriptyline HCl, calcium pantothenate, D-chlorpheniramine maleate, dextromethorphan HBr, dibucaine HCl, diltiazem HCl, imipramine HCl, promethazine HCl, trimebutine maleate, quinine HCl	–	Liquid	Characterization of APIs Electronic tongue evaluation	Insent taste sensing system SA402B (eight sensors)	Univariate and multivariate (PLS)	Adult human taste panel ($n = 11$)	Hashimoto et al. (2006)
Trimebutine maleate	Polyvinylacetal diethylamino-acetate (AEA)	Micro-spheres	Formulation development			Drug release profiles	
Clarithromycin, azithromycin	Chocolate jelly, paste jelly, water jelly	Dry syrup	Characterization of products modified by commercially available jellies	Insent taste sensing system SA402B (eight sensors)	Univariate and multivariate (MRA of two sensors and human taste panel data)	Adult human taste panel ($n = 5$ or 6), drug content (HPLC), dissolution testing	Tsuji et al. (2006)
Famotidine, quinine sulphate	Sucrose, sorbitol, erythritol, xylitol, mannitol, lactitol, maltitol	Liquid	Electronic tongue evaluation (new sensor)	Insent taste sensing system SA402B (eight sensors)	Univariate	Adult human taste panel ($n = 9$)	Hashimoto et al. (2007)
Famotidine		ODT	Characterization of formulation			Dissolution testing	

total gained from a number of sensor responses. The location of samples in this map should be regarded with respect to the amount of information represented by each axis. If the *x*-axis, which is mostly PC-1, carries a higher amount of information, differentiation of the samples along the *x*-axis carries more weight than differences along the *y*-axis. A PCA map as shown in Fig. 5 can be evaluated visually by the location of samples on the map. In addition, so called Euclidean distances between the different samples can be calculated. The closer the formulation is located to the placebo and the larger the distances to the pure unpleasant API are, the better the taste masking is. The distance between the samples can be calculated as shown in equation (3).

$$d(p, q) = \sqrt{\sum_{i=1}^{n} (p_i - q_i)^2} \quad (3)$$

With $d(p,q)$ = Euclidean distance between the samples p, q; i = principal components; n = number of principal components of the model.

Discriminant functional analysis (DFA) is a modification of the PCA where correlations in data are explained. It can be therefore

Table 3
(*Continued*)

Drug substance	Excipients	Dosage form	Purpose	Electronic tongue type	Data analysis	Validation by reference method	Reference
11 medicinal plants (Gentian, swertiae herb, bitter orange peel, picrasma wood, coptis rhizome, phellodendron bark, geranii herb, houttuyania herb, rhubarb, lupli strobilus, chinese nutgalls) and 10 chinese medicines (Orengedokuto, Unseiin, Akadama abdomen medicines)	–	Liquid	Characterization of herbal products Quality control	Insent taste sensing system SA402 (five sensors)	Univariate and multivariate (PCA – Euclidean distances)	HPLC	Kataoka et al. (2008)
Sodium benzoate	Eudragit® E κ-carrageenan, MCC, Witocan® 42/44, Precirol®, Dynasan 114®	Pellets	Electronic tongue evaluation Formulation development	Insent taste sensing system SA402B (four sensors)	Univariate and multivariate (PLS)	Adult human taste panel ($n = 9$), dissolution testing, drug release in food	Krause (2008)
Quinine hydrochloride (quinine benzoate, quinine sulphate, acetaminophen, sodium benzoate, sodium saccharin)	–	Liquid	Performance qualification	Insent taste sensing system SA402B (seven sensors)	Univariate and multivariate (PCA)	–	Woertz et al. (2010a)
Propiverine hydrochloride, quinine hydrochloride, donepezil hydrochloride, eperisone hydrochloride, ticlopidine hydrochloride, azelastine hydrochloride	–	Liquid	Characterization of APIs	Insent taste sensing system SA402B (six sensors) combined with a disintegration testing apparatus ODT-101	Univariate and multivariate (PCA)	Adult human taste panel ($n = 6$)	Harada et al. (2010)
Propiverine hydrochloride	Sucrose, pectin, agar, λ-, κ-, ι-carrageenan	ODTs	Formulation development				
Sodium diclofenac	Sucralose, xylitol, saccharine, mint flavor, licorice flavor, soft fruits flavor	Liquid Fast-dissolving oral film	Formulation development	Insent taste sensing system SA402B (three sensors)	Multivariate (PCA – Euclidean distances, MRA)	Adult human taste panel ($n = 10$)	Cilurzo et al. (2010)
Quinine hydrochloride	Sucrose, glucose, fructose, mannitol, sucralose, sodium saccharin, acesulfame potassium, monoammonium glycyrrhizinate α-cyclodextrin, β-cyclodextrin, hydroxypropyl β-cyclodextrin, sulfobutyl ether β-cyclodextrin, γ-cyclodextrin, maltodextrin Amberlite IRP69, Amberlite IRP88, Indion 234	Oral liquid	Formulation development	Insent taste sensing system TS-5000Z (eight sensors)	Multivariate (PCA – Euclidean distances, PLS)	UV-spectroscopy, FT-IR spectroscopy, human taste assessment data from already existing literature	Woertz et al. (2010b)

used for the prediction of unknown samples. Nevertheless, the more often used prediction methods are multiple regression analysis (MRA) or projection to latent structures by means of partial least squares (PLS). PLS can be seen as a particular regression technique for modeling the association between a matrix *y*, for example taste scores from human taste panel, and the complex data space *x* of variables and observations obtained from electronic tongue measurements (Eriksson et al., 2006). The difference to multiple

Table 4
Pharmaceutical applications of other electronic taste sensing systems.

Drug substance	Excipients	Dosage form	Purpose	Electronic tongue type	Data analysis	Validation by reference method	Reference
Eurycoma longifolia Jack	–	Liquid (herbal extract)	Electronic tongue evaluation (quality control)	Malaysia laboratory system (eight sensors)	Univariate and multivariate (PCA)	None	Abdullah et al. (2004)
Quinine, caffeine, four undisclosed drugs	Aspartame, acesulfame K, sucrose, sodium chloride, sodium benzoate, flavors: peach, strawberry, orange	Powder, tablets (dissolved)	Characterization of substances Electronic tongue evaluation	St. Petersburg laboratory system (30 sensors)	Multivariate (PCA, DFA, PLS)	None	Legin et al. (2004)
Eurycoma longifolia	–	Liquid (herbal extract)	Quality control Electronic tongue evaluation	Malaysia laboratory system (eight sensors)	Univariate and multivariate (PCA – Euclidean distances)	None	Ahmad et al. (2006)
Propantheline bromide, oxyphenonium bromide	34 possible taste masking excipients (e.g. native and modified cyclodextrins, saccharides, surfactants, organic acids, nonionic and anionic polymers)	Oral liquid	Formulation development	Kyoto laboratory system (one sensor per drug)	Univariate	Adult human taste panel ($n = 5$)	Funasaki et al. (2006)
Methylene blue	–	Liquid	Electronic tongue evaluation	Sao Paulo laboratory system (six sensors)	Multivariate (PCA)	–	Aoki et al. (2008)
Ibuprofen, roxithromycin	Hypromellose, Eudragit® L30D-55	Coated microparticles	Electronic tongue evaluation Formulation development	Warsaw laboratory system (eight sensors)	Multivariate (PCA)	None	Jańczyk et al. (2010)

regression analysis is that the data space x is considered for model building and data correlation assuming a correlation between x and y. MRA does an independent correlation between both variables mostly resulting in a worse model, which is closer to reality. Nevertheless, when the relationship between x and y variables is found in univariate data evaluation, a multivariate correlation can be done by means of partial least square regression.

The αAstree e-tongue offers a bitterness prediction module for data evaluation which is based on partial least square regression. There, a standard set of bitter tasting substances like caffeine monohydrate, acetaminophen, quinine hydrochloride, prednisolone metasulfobenzoate sodium, loperamide hydrochloride, and famotidine in different concentrations is correlated with in vivo data obtained by human taste panel. Partial least square regression is used for correlation and a R^2 of 0.8 or more should be obtained according to the supplier's recommendation. According to the supplier, substances with unknown bitterness intensities can be predicted by the established model afterwards. In order to predict the bitterness in this way, only the specific set of sensors for bitterness measurement can be used. For the Insent taste sensing system, such a prediction tool has not been established yet.

In conclusion, multivariate data analysis can be used to visualize the results obtained from many sensors and to understand possible correlations between the samples as well. Nevertheless, it should be handled with caution as calculations are based on algorithms included in the particular software. Therefore, it is advisable to take a look at the raw data as well as to consider results from univariate evaluation in order to prevent misinterpretation of the results.

4. Pharmaceutical applications

4.1. Qualification

As electronic tongues are analytical instruments and not physiologically working body tissues, they are required to work according to analytical standards. Therefore, particular tests for qualification should be performed in order to assure the fitness for purpose of these systems. Qualification consists of four major points: design qualification (DQ), installation qualification (IQ), operation qualification (OQ), and performance qualification (PQ) (Burgess et al., 1998). Both commercially available systems are setup with control and calibration tools which offer the level of operation qualification. A so called "sensor check" is performed with the Insent taste sensing system by measuring the standard solution right before every measurement which assures that sensors are in the correct working range. In addition, a monthly performed maintenance measurement, where solutions representing the different taste qualities are measured, is another way to ensure that sensors are working according to the specifications of the manufacturer. The αAstree system has three tests, which have to be passed at the beginning of every week of measurement or storage of the sensors in dry state for more than 2 days: a "conditioning" and a "calibration" where sensors are immersed in 10^{-2} M of hydrochloric acid and specific sensor values have to be reached. And a "diagnostic" where three samples representing salty (sodium chloride 10^{-1} M), sour (hydrochloric acid 10^{-1} M), and umami (mono sodium glutamate 10^{-1} M) taste need to be identified and distinguished. After passing these tests, sample measurements can be performed.

Some of the laboratory systems were also tested for reproducibility of the sensor outputs, but no reference solutions, as described above, were investigated to confirm stability of the data.

A protocol for performance qualification has been recently established by Woertz et al. (2010a) for the Insent taste sensing system SA402B using quinine hydrochloride as a model drug. As sensors of the newer taste sensing system TS-5000Z are the same compared to the SA402B, results are transferrable. This approach was based on the requirements of ICH guideline Q2 on validation of analytical procedures. All topics required by the guideline like linearity, range, specificity, accuracy, precision, as well as

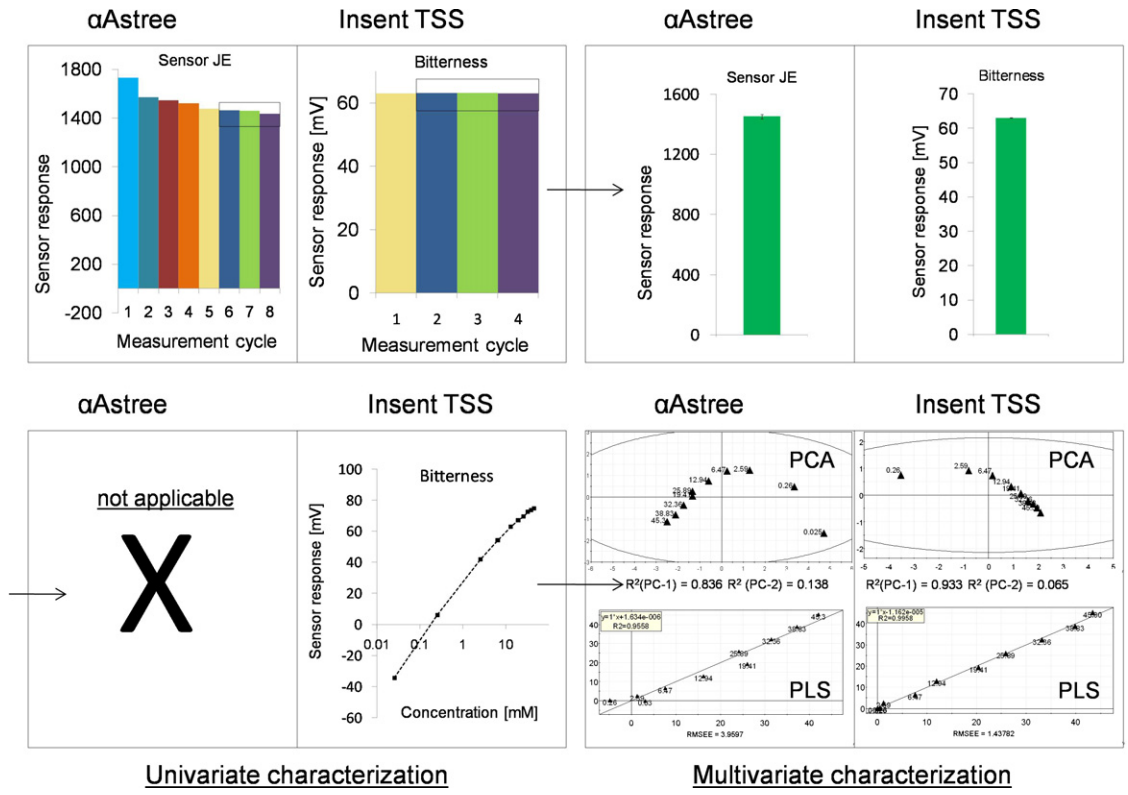

Fig. 5. Treatment and evaluation of electronic tongue data exemplarily shown for two commercially available electronic tongues, the αAstree electronic tongue and the Insent taste sensing system (TSS); univariate characterization with sensors JE and a bitterness sensor as an example; multivariate characterization with seven sensors respectively; model drug: caffeine citrate 0.026–45.3 g/100 ml.

detection and quantitation limit were tested and items not applicable were modified. Therefore, a valuable guidance how to apply this guideline to an electronic taste sensing system was offered. It was found that the intermediate precision was not sufficient, which was explained in the robustness part. Sensors were susceptible to changes in temperature and further previous measurements and the age of sensors could affect the sensor response values. Consequently, it was suggested to use an external standard for all measurements in order to compare results over long time periods and normalize to the standard if necessary.

In conclusion, the capability of these systems to work in correct working ranges is an important factor to serve as a reliable analytical system. Therefore the items of qualification should be considered for every system and an external standard should be used in the field of pharmaceutical applications.

4.2. Quality control

Research showing the implementation of electronic tongues in pharmaceutical quality control is rather rare. Nevertheless, the control of herbal medicines quality is a good example for the rational use of an electronic tongue system in this field. Ahmad et al. (2006) describe the application of their in-house fabricated electronic tongue for the determination of batch-to-batch uniformity, stages of maturity, and differences between extracts obtained by different solvents of eurycoma longifolia. Different concentrations of aqueous solutions of the spray dried herbal powder were investigated before (Abdullah et al., 2004). The different concentrations could be distinguished by the electronic tongue system and were used as a training set. Based on this, unknown concentrations could be predicted. The three quality control approaches could be successfully performed and differences were detected by the electronic tongue. Nevertheless, the authors additionally recommend further investigations quantifying the marker compounds in the complex herbal mixture for fully demonstrating the fitness of the system in quality control.

Kataoka et al. (2008) also showed the quality control of 11 medicinal plants and 10 chinese medicines by use of the Insent taste sensing system SA402. Groups of secoiridoid glucosides, triterpene derivates, and alkaloids of berberine type could be identified by the electronic tongue. Further, two medical plants as well as the same plants coming from different locations were compared with each other. A good correlation between electronic tongue measurements and HPLC detection of berberine amount was found. Again, limitations were discussed, as differences in chirality of substances could not be detected by the taste sensing system.

Nevertheless, these first approaches show the possibility to use an electronic tongue in quality control. After system qualification and method validation electronic taste sensing systems could therefore offer a promising rapid and cost-saving tool in quality control.

4.3. Characterization of active pharmaceutical ingredients

The taste characterization of active pharmaceutical ingredients by implementation of a human taste panel reveals challenges with respect to ethical concerns. This is especially true for new chemical entities with unknown toxicity. Electronic tongues are therefore tried to use as taste prediction tools in early drug development in order to prevent possible safety concerns.

Zheng and Keeney (2006) did the first steps in evaluating the feasibility of the αAstree electronic tongue to differentiate bitter tasting drugs and to rank them according to their bitterness. Caffeine anhydrous, paracetamol, phenylthiourea, prednisolone sodium, quinine hydrochloride, ranitidine hydrochloride, and sucrose octaacetate were investigated at the same concentration and a bitterness ranking was conducted by distance calculation to demineralized water. Nevertheless, validation by a human taste

panel was not performed and it is described that the relationship between distance calculation and bitterness intensity needs to be further investigated. A validation of a ranking of bitter tasting substances measured by the αAstree electronic tongue was done by using reference values of human taste assessment for substances recommended by the supplier (Rachid et al., 2010). This model was then used as the bitterness prediction module in this study in order to predict the masking efficiency of different excipients for epinephrine.

Legin et al. (2004) introduced their electronic tongue system for the quantification of tastes and masking effects in pharmaceutics and showed that discrimination between different drugs was possible. Substances with different tastes could be distinguished and substances with the same taste could be identified. Also possible masking effects after the addition of sweeteners and flavors could be detected. Nevertheless validation by a reference method was not carried out and it was therefore concluded that a wider range of bitter substances whose bitter taste have been assessed by human taste panel should be investigated in order to obtain an adequate calibration of the electronic tongue. As briefly discussed in the data evaluation section, sensor responses depend on the chemical characteristics of the substances investigated.

Uchida et al. (2000, 2001) investigated 17 different drugs with known bitter taste in two studies using the Insent taste sensing system SA402. A correlation between human taste panel and some substances could be established using one sensor out of eight available sensors. Nevertheless, it became obvious that sensor responses of a particular sensor are dependent on molecule characteristics. Drugs with amino groups, like for example quinine hydrochloride, were detected with a good correlation to human assessment, but anionic drugs, like diclofenac sodium were detected more precisely by another sensor and neutral drugs were hard to detect at all.

An acceptable prediction of the bitterness intensity of propiverine hydrochloride based on a model consisting of five other bitter tasting drugs was established using the Insent taste sensing system SA402B (Harada et al., 2010). But, again, as sensor responses depend on the structure of the molecules, the number of reference samples would be too small to predict the taste of other compounds reliably.

These studies show the difficulty to compare active pharmaceutical ingredients with different molecular structures with respect to their taste. Consequently, so called bitterness prediction modules have to be considered with caution and should only be used after extensive validation.

4.4. Formulation development

4.4.1. General

Two approaches for the development of a taste masked formulation are possible (Figs. 6 and 7). On the basis of an unpleasant tasting API possible taste masking excipients can be added and screened for taste masking efficiency by the electronic tongue. Finally, a taste masked product should be different to the pure API and similar to the pleasant tasting placebo formulation with respect to sensor output values. The other approach is based on an already existing taste masked formulation. After measurement of such formulations, sensor responses can be evaluated and a new formulation can be developed based on the qualitative information about excipients and sensor response values. Differences between the existing product and the new taste masked formulation should be small with respect to sensor responses. This strategy can be especially helpful in comparing and developing generic formulations.

In general, it has to be distinguished between the development of solid and liquid dosage forms as taste masking strategies are different.

4.4.2. Development of solid dosage forms

Much less papers in literature are found for the development of taste masked solid dosage forms using an electronic tongue compared to liquid dosage forms (Tables 2–4). The reason might be the different taste masking strategies as well as the sample preparation (Fig. 3). As conventional solid dosage forms cannot be directly investigated by an electronic tongue other analytical techniques might be more useful. If taste masking of the solid, e.g., pellet, tablet, or granule preparation, is intended by introducing a coating barrier, characterization of a delayed drug release by dissolution testing might be sufficient to evaluate the taste masking efficiency. A good example for this was shown by Kayumba et al. (2007), where quinine sulphate pellets were coated with Eudragit® E PO. A modified dissolution profile with poor drug release in the first 5 min could be observed by UV-spectroscopy and reduced bitterness values were detected by the αAstree electronic tongue using the bitterness prediction module. In addition no discomfort or rejection of the pellets

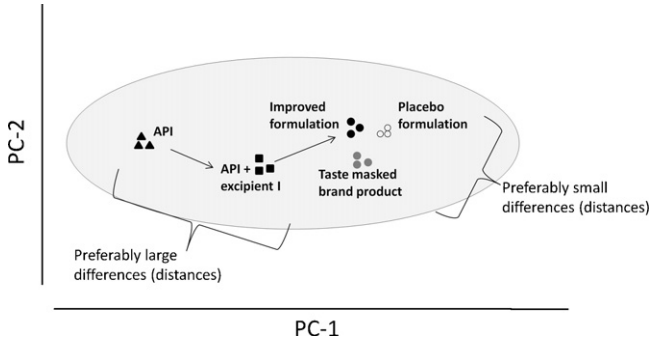

Fig. 7. Rational development of a new drug formulation with improved taste guided by an electronic tongue.

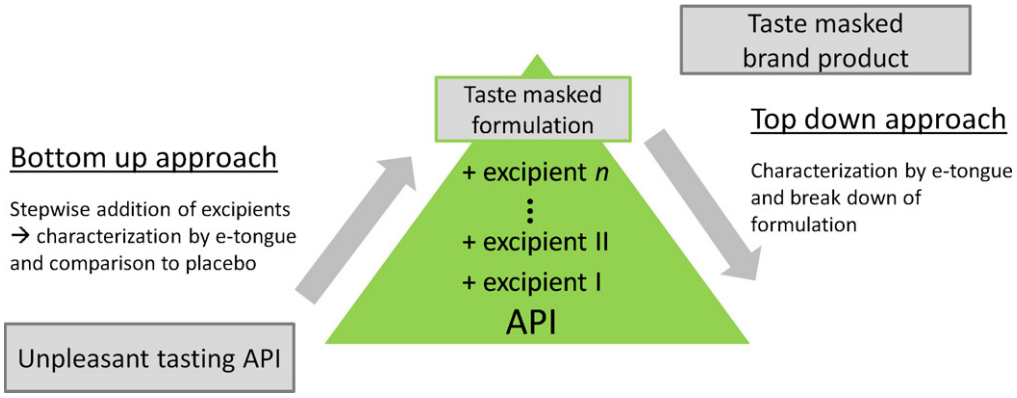

Fig. 6. Top–down and bottom–up approaches for development of a pharmaceutical formulation guided by an electronic tongue.

was reported in a subsequent bioavailability study in 56 children and 12 adults. A correlation between electronic tongue measurements, UV-spectroscopy and human taste panel data was done by Krause (2008) using the Insent taste sensing system as well as the αAstree electronic tongue. By comparing sodium benzoate pellets with different lipid binders and a Eudragit® E coated pellet formulation lipid pellets were found to be better taste masked. Both electronic tongue systems were able to detect the free amount of drug and therefore acceptable correlations were obtained, whereas the αAstree data was better for correlation with human data, the Insent taste sensing system was more reliable for correlation with the actual concentration. Altogether, the Insent taste sensing system was described as slightly superior.

Jańczyk et al. (2010) showed the taste masking of ibuprofen and roxithromycin in microparticles using a laboratory system equipped with eight potentiometric sensors. By investigating a suspension of these microparticles, taste masking by Eudragit® L30D-55 could be shown in comparison to hypromellose microparticles which were not taste masked. Again, the detection of taste masking was related to the amount of released drug from the microparticles.

Nevertheless, if other substances of the tablet formulation could either interfere with UV detection or should simultaneously be detected as they could influence the overall taste sensation, an electronic tongue could offer additional benefits (Tokuyama et al., 2009). Furthermore, depending on the substance, the detection limit of electronic tongue sensors can be lower than the detection limit of UV-spectroscopy and therefore enable a more sensitive detection.

Rachid et al. (2010) used the αAstree electronic tongue for the development of a sublingual tablet, with epinephrine, but taste masking by citric acid, acesulfame potassium and aspartame was only shown in aqueous solution based on the bitterness prediction module of the software.

Orally disintegrating tablets could be developed containing an unpleasant tasting drug masked by two polymers, Amberlite IRP64 and Carbopol 971P (Li et al., 2007). The optimal polymer ratio together with the pH optimum was evaluated by measurements with the αAstree by means of design of experiments. A good correlation between human taste assessment and distances between formulations and corresponding placebos was obtained by electronic tongue measurements. In addition, the drug release from orally disintegrating tablets in water was limited compared to drug release in 0.1N HCl.

A taste masked fast-dissolving oral film made of maltodextrin and diclofenac sodium could be developed based on electronic tongue measurements. After a screening of different taste masking excipients in combination with the drug using three bitterness sensors with the Insent taste sensing system, a pleasant tasting film formulation could be developed. Results from electronic tongue measurements of the film formulation were consistent with statements from human taste panel.

A new disintegration apparatus for use with the Insent taste sensing system SA402B in order to determine the taste masking efficiency of ODTs was introduced by Harada et al. (2010). Based on this, samples which were possibly taste masked by different soluble complexing agents were measured after 15 s and after complete disintegration. The influence of both effects, the modified disintegration time and taste masking by complexation could be evaluated by use of this method. Therefore an additional benefit was offered here, as sole disintegration testing and detection via UV-spectroscopy might not have taken the effect of taste masking by complexation into account.

In conclusion, taste masking characterization of solid dosage forms which are of orally disintegrating or fast disintegrating type can be improved by implementation of electronic tongue systems whereas coated formulations could be determined via dissolution testing and common analytical techniques like UV-spectroscopy.

4.4.3. Development of liquid dosage forms

Liquid dosage forms, in addition to the orally disintegrating solid dosage forms, require special interest with respect to taste masking, as already dissolved molecules can directly interact with taste buds on the human tongue. Further, oral liquids are still preferred by the European Medicines Agency for younger age groups as they are assumed to be easy to administer and swallow (EMA, 2006).

Zheng and Keeney (2006) showed the evaluation of the effect of different sweetening substances and soft drinks on the bitter taste of quinine sulphate dehydrate using the αAstree electronic tongue. Distance calculations based on principal component analysis were performed and a reduced distance between quinine and water could be observed after adding these substances. These results were not validated as a reference method was not described. It is further said that substances which are added to improve the taste of a liquid formulation are usually used in low concentrations. Their influence on taste properties might therefore be overlapped by other higher concentrated substances of the formulation. Therefore, the electronic tongue was described to be less useful comparing complex liquid formulations.

Lorenz et al. (2009) showed the implementation of the αAstree electronic tongue for formulation development of an unknown API and provided a decision tree when an electronic tongue can be used. Nevertheless, this decision tree is based on data obtained by human taste panel which might be difficult for some substances depending on the stage of development. Formulations which were compared were of very different nature (different drugs, different excipients) which might lead to wrong results as these electrochemical sensors should be calibrated by the substances first. Further, statistical evaluation of multivariate data analysis was only little described which could question the reliability of this electronic tongue for taste assessment in formulation development here.

The taste masking of quinine, hydrocortisone and prednisolone with different cyclodextrins, sweetening agents and flavors was evaluated by the αAstree electronic tongue as well as by human taste panel (Turner, 2009). The electronic tongue was capable of screening and discriminating optimal taste masking concentrations of the cyclodextrins. However, results had a high variability as the method was not robust and after the addition of sweetening agents and flavors, only partial correlation with human taste panel could be achieved.

Sadrieh et al. (2005) used the αAstree electronic tongue to determine the palatability of doxycycline, ciprofloxacin and potassium iodide in different food and drink matrices commonly available in households in order to be prepared for administration to a child. The applicability of each sensor was tested before by measuring the test matrix alone and determination of the relative standard deviation in between several investigations. Based on this, sensors for the multivariate data analysis were chosen and distances between the matrix and the formulation were calculated. Validation of electronic tongue results by human data showed that the ranking of palatability was different. Nevertheless, the pure drugs in water were always evaluated with lowest palatability by human panel and electronic tongue respectively. Therefore, the electronic tongue could be used auxiliary to identify taste masked samples, but absolute statements regarding palatability were difficult to obtain.

The working group of Uchida investigated different liquid solutions as well as formulations containing unpleasant tasting APIs over a couple of years using Insent taste sensing systems (2000–2007). They mainly focused on the evaluation of electronic tongue performance but also on taste masking of various antibiotics, antidepressants, and other unpleasant active pharmaceutical ingredients. In addition, a validation by human taste panels was

done in almost every study. As a result, newly developed sensors were introduced and their ability to detect taste masking efficiency could be shown. Therefore, data evaluation was often based on a single sensor. A large range of different active pharmaceutical ingredients (see Table 3) was tested in these studies over a period of 7 years with different sensors. From a pharmaceutical point of view it would be interesting to repeat these trials with the actual sensor set of eight sensors in order to transfer the results to the actually marketed taste sensing system TS-5000Z.

A screening of about 34 possible taste masking excipients was carried out to mask the bitter taste of propantheline bromide and oxyphenonium bromide by Funasaki et al. (2006). Electronic tongue measurements were potentiometric, but only one ion selective electrode per drug substance was used. Depending on the taste masking approach, the correlation between human taste assessment and bitterness prediction was therefore not always possible. Limitations were reached for taste masking techniques which intend to overcome the taste (e.g. sweeteners) and viscosity enhancers covering the taste receptor. Nevertheless, the bitter taste of both substances could be successfully masked using cyclodextrins and λ-carrageenan. However, this study showed that the implementation of systems with more than one sensor could be beneficial for reliable assessment of taste masking.

How a taste masked liquid formulation can be rationally developed guided by a multichannel taste sensing system was demonstrated by Woertz et al. (2010b). In this paper, various taste masking excipients were screened in order mask the bitter taste of the model drug quinine hydrochloride. A rational approach for developing a taste masked formulation was shown using the Insent taste sensing system TS-5000Z. In addition, validity of the method was either shown by referring to existing literature or the implementation of analytical techniques like UV-spectroscopy or FT-IR spectroscopy.

In conclusion, electronic tongues could be successfully used for the development of a taste masked liquid formulation and validity of the results could be shown. Nevertheless, results of the electronic tongue taste prediction depend on the characteristics of the molecules as well as the taste masking strategy. A reliable assessment was obtained in the cases were taste masking was based on the prevention of interaction of the dissolved molecules and the taste buds on the tongue. Complexation of the unpleasant tasting drug is a good example for this. When, however, taste masking is based on overlapping effects by, for example, sweeteners, beverages or food stuff, electronic tongue results should be handled with caution. A reliable assessment could then only be done when the formulation is detected by the electronic tongue with the same characteristics as a pleasant tasting placebo formulation.

4.5. Comparison to competitors and product characterization

In order to compare different products with each other the non-specificity of sensors is an important advantage. A mapping of the mostly complex mixtures can be performed and product characteristics evaluated.

A good example was shown by Mukai et al. (2004) evaluating 15 different nutritive drinks using the Insent taste sensing system. Kataoka et al. (2005) also investigated 15 other nutritive drinks with the αAstree electronic tongue. Both systems were able to distinguish samples based on their product characteristics by means of univariate and multivariate data evaluation. In the study with the αAstree e-tongue, products were classified into four groups and products containing medical plants were evaluated with the lowest palatability whereas fruity samples were assessed as most pleasant. Products used in the study with the Insent taste sensing system, were either protein-based, peptide-based, or amino-acid based. The three groups could be detected by the electronic tongue as well as a fourth group after the addition of sour flavors. Both studies showed good correlation with human data, indicating that a product characterization can be reliably done.

The comparison between eight generic famotidine orally disintegrating tablets with the original product was investigated by Tokuyama et al. (2009) using the αAstree electronic tongue equipped with the sensor set for food application and the 16-position auto sampler. A mapping of all products could be established ranking generic products with respect to the original one. An acceptable correlation ($R^2 = 0.8965$) with a gustatory sensation test could be achieved showing that the electronic tongue was a useful tool for characterization of these products. It could be further shown that comparison of drug release profiles alone was not sufficient for comparison of the products with respect to their taste properties as taste was influenced by the released drug as well as by released aspartame.

4.6. Validation

As can be seen from Tables 2–4 and as described above, the validation of electronic tongue results has been carried out by human gustatory panels and common analytical techniques like UV-spectroscopy, dissolution testing and detection by UV, or HPLC analysis and detection by UV.

The correlation with, for example, dissolution testing can be done in the case of a coated dosage form, were the delayed release of the active pharmaceutical ingredient indicates a taste masking effect (Kayumba et al., 2007). In the case of orally disintegrating tablets or other liquid multicomponent mixtures these common analytical techniques easily reach their limits. This can be explained by the specificity of these methods to only one substance in most cases. Therefore, human taste panels would be the adequate reference method here to assess whether the electronic tongue prediction is reliable.

Most of the studies summarized here were validated by human taste assessment. The number of adult human volunteers varied from 5 to 30, but the average participant number was 10.

Acceptable correlations to human data were obtained in most cases. Nevertheless, it has to be distinguished between the pure characterization and ranking of an unpleasant, mostly bitter tasting API and the assessment whether this kind of API could be successfully taste masked. For the latter, correlation between human taste assessment and comparative placebo and formulation measurements are sufficient in many cases. However, the comparative characterization of drugs is much more difficult. This can be explained by the fact that compositions quite different from each other are easier to distinguish by the electronic tongue and also by human taste assessors. Compounds which are only varying in bitterness intensity are more difficult to differentiate by humans due to physiological and individual preference, and, as discussed above, they are harder to map by electronic tongue measurements due to different molecular characteristics. Further, there are still gaps in knowledge about the detailed mechanisms at the sensor membranes and whether human taste is represented in an appropriate way by these sensors.

As a result, at least one reference technology, which is appropriate for the API and the drug dosage form, should still be used to verify results from electronic tongues and to establish more validated data. Based on this, electronic tongue data could be handled without using a reference in the future.

5. Discussion and future trends

With respect to the application of electronic tongues in terms of formulation development and comparison to competitors, most investigations are reported dealing with the αAstree electronic

tongue. These investigations were mostly performed within the past 5 years. In contrast, analytical investigations, variations of sensors and the evaluation of rather simple systems have been described more extensively by use of the Insent taste sensing system covering the past 10 years. The reason for this is that the Insent taste sensing systems were developed based on research at a university whereas the αAstree system was directly marketed by its developing company. Therefore experiences with variations of sensor membrane composition, an increased or decreased sensitivity to substances and approaches for better understanding mechanisms of detection by the sensors are only described for the Insent system. Further, types of taste sensing systems change over the years showing the ongoing development. In contrast, published research for the αAstree electronic tongue is just showing examples of pharmaceutical applications with one system. Due to development over the years, types and number of sensors used for the different studies with the Insent taste sensing system are different. Only one study shows the application of the eight commercially available sensors (Woertz et al., 2010b), although not all of them were included in multivariate data analysis. Therefore other investigations described here might need to be verified by using the actual commercially available sensors.

Differences in data evaluation can be seen as all data obtained from the αAstree electronic tongue is interpreted by multivariate statistics (PCA – Euclidean distances or PLS – Bitterness prediction module) whereas data from the Insent taste sensing system is additionally evaluated by univariate statistics. As discussed above, having an additional look at the raw data and results from univariate data evaluation could prevent misinterpretation of the multivariate statistics.

In general, most of the reported pharmaceutical applications are based on the development of drug formulations. These investigations show that electronic tongues are analytical instruments which can be recommended for evaluation of taste masked pharmaceutical formulations. It has been further shown that they often offer a first clue about feasibilities of taste masking strategies in formulation development as well as the comparison of already existing products.

Nevertheless, for the whole field of electronic tongue research a lot of physiological conditions are not taken into account yet, which makes it difficult to provide absolute statements regarding the taste of a specific compound. Therefore, more validation of the data by human assessment is needed in order to find out feasibilities and limitations.

A matrix containing more validated data from human taste panels could be established in order to predict the taste of a formulation based on just the excipients and excipient drug combinations. In addition, taste prediction by means of cell based systems is an increasingly attractive field which offers promising results (Wang et al., 2010). Up to now, only a rough reflection to what is happening in reality in the taste buds on the human tongue can be obtained by electronic tongue measurements. Therefore, sensor systems based on membranes which are closer to humans taste cells should be developed. In the best case a combination of electronic taste sensing system and living cells would work in order to measure how and to what extent interactions between the formulation and human gustatory sensation are existent. This could further be extended by simulating the volume and composition of saliva while measuring.

However, it will never be possible to include all sensory (e.g. olfactory, thermo-mechanical signals), physiological (e.g. transmitter release, neural transduction), and psychological aspects of human taste sensation into a single analytical procedure.

Research, so far, shows that electronic tongues are promising instruments to predict taste and to reduce the number of required human taste tests. They can be further used as analytical tools measuring and comparing complex mixtures in a reproducible manner. Therefore the way towards the development of a "real artificial tongue" approaching physiological taste processes is opened, but there is still a long way to go.

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