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Independent comparison study of six different electronic tongues applied for pharmaceutical analysis

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ABSTRACT

Electronic tongue technology based on arrays of cross-sensitive chemical sensors and chemometric data processing has attracted a lot of researchers' attention through the last years. Several so far reported applications dealing with pharmaceutical related tasks employed different e-tongue systems to address different objectives. In this situation, it is hard to judge on the benefits and drawbacks of particular e-tongue implementations for R&D in pharmaceutics. The objective of this study was to compare the performance of six different e-tongues applied to the same set of pharmaceutical samples. For this purpose, two commercially available systems (from Insent and AlphaMOS) and four laboratory prototype systems (two potentiometric systems from Warsaw operating in flow and static modes, one potentiometric system from St. Petersburg, one voltammetric system from Barcelona) were employed. The sample set addressed in the study comprised nine different formulations based on caffeine citrate, lactose monohydrate, maltodextrine, saccharin sodium and citric acid in various combinations. To provide for the fair and unbiased comparison, samples were evaluated under blind conditions and data processing from all the systems was performed in a uniform way. Different mathematical methods were applied to judge on similarity of the e-tongues response from the samples. These were principal component analysis (PCA), RV′ matrix correlation coefficients and Tuckerís congruency coefficients.

1. Introduction

Evaluation of taste parameters and taste-masking efficacy gains importance, especially in the development of pediatric drug formulations. The traditional way to assess the taste is obviously based on human sensory panels. However, besides ethical aspects, this method is associated with numerous problems, such as sensory panel fatigue or dependency of sensory scores on the health conditions of a panelist. Artificial taste assessment of pharmaceutics seems to be a very attractive alternative, since it provides a fast and objective formulation evaluation. The first works dealing with bitter taste sensing by e-tongue were presented by Toko [1]. Since then, multichannel taste sensor that later became a fundamental part of commercial taste sensing system by Insent had been used for quantification of basic taste sensations in large variety of samples [2–4]. Various studies were devoted to the application of different versions of e-tongues for the assessment of taste in pharmaceutical samples [5–16]. A variety of sensors and sensor systems were developed and applied in these research efforts, based on both, commercial [5,6,9,10,13–15] or laboratory instrumentation [7,8,11,16]. Most of these reports are focused on the development of new drug formulations by choosing appropriate taste masking strategies. Besides, original and generic products were compared [12,13], products modified with commercially available beverages or jellies characterized [14,15], the effect

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of micro encapsulation [16] or oral film formulations [17] on taste-masking efficacy assessed and stability and dose uniformity studies [18] presented. In a recent study, the capability of HPLC and e-tongue analysis was compared with human taste panels regarding taste assessment and the applied e-tongue was proven to be even more sensitive than the human taste panels [19].

The idea of "e-tongues" is based on the application of an array of cross-sensitive chemical sensors combined with multivariate data processing techniques to yield quantitative and qualitative information about studied sample [20]. Chemical sensors in an array can be based on various principles of signal transduction: potentiometry, voltammetry, optical sensing, surface acoustic waves, etc. The first two mentioned transduction schemes gained widest acceptance in research these days [21]. This is probably due to the ease of instrumentation required for implementation of these techniques and broad options to modify sensor response in order to fit it to particular analytical task.

The electronic tongue TS-5000Z and SA402B (Insent Inc., Atsugi-Shi, Japan) and those multisensor systems from the laboratories of Warsaw (Department of Microbioanalytics, Warsaw University of Technology; Poland) and St. Petersburg (Institute of Chemistry, St. Petersburg State University/Laboratory of Artificial Sensory Systems, ITMO University; Russia) are based on direct potentiometric measurements with sensors based on PVC-plasticized membranes [4,7,8,10,16]. The differences between these systems are in the number and composition of sensor membranes leading to the fact that all these systems have somewhat different sensitivity to the components in the analyzed media. In case of FIA version from Warsaw the kinetics of interaction of various components with membrane material is also taken into account thus providing for additional source of chemical information. The α-Astree e-tongue (AlphaMOS, Toulouse, France) is based on ISFETs (ion-selective field effect transistors) with polymeric sensor membranes [10], which are generally similar to those employed in systems from Warsaw and St. Petersburg. However, the measuring principle is not direct potentiometric, but based on recording the feedback gate potential constantly keeping the FET current. The voltammetric e-tongue from the Sensors and Biosensors Group Barcelona (Department of Chemistry, Universitat Autònoma de Barcelona) registers RedOx processes taking place at the surface of differently modified working electrodes [11,21]. Unlike potentiometric sensors this type of measurements can provide information on non-ionic substances in the media which can be reduced/oxidized under experimental conditions.

So far, comparability studies have been performed based on the two commercially available systems [22,23] or proving the inter-lab comparability of the Insent taste sensing system [24]. Since the sensor systems applied for pharmaceutical analyses are based on different principles and may have different functionality, it seems timely to perform independent comparison of the several above mentioned e-tongues in the framework of an interlaboratory experiment to reveal possible differences and special aspects associated with each of the systems. The purpose of this study was an independent comparison of six different multisensor systems applied to the same set of samples. In order to eliminate subjective factors all the raw data from the systems, obtained in blind conditions, were processed in centralized way with the same algorithms and approaches.

2. Materials and methods

2.1. Materials

Caffeine Citrate (Fagron, Barsbuettel, Germany), maltodextrin (Kleptose® linecaps 17, Roquette Frères, France), citric acid (J.T. Baker, Griesheim, Germany), saccharin sodium (Caesar & Loretz, Hilden, Germany), lactose monohydrate (granuLac® 140, Meggle Pharma, Wasserburg, Germany) were used to prepare the samples. Potassium Chloride (Gruessing, Filsum, Germany), tartaric acid (AppliChem, Darmstadt, Germany), hydrochloric acid (Merck, Darmstadt, Germany), potassium hydroxide (Gruessing, Filsum, Germany) and absolute ethanol (VWR international, Darmstadt, Germany) were used to prepare the washing solutions for the Insent e-tongue. Potassium chloride, used at the University of Barcelona, was purchased from Merck KGaA (Darmstadt, Germany) and the solutions were prepared using deionised water from a Milli-Q system (Millipore, Billerica, MA, USA). Purified water was produced by appropriate methods, such as reverse osmosis at the Heinrich-Heine-University of Duesseldorf (Germany) and at Warsaw University of Technology, Poland (Millipore Elix3) and double distillation with GFL-2101 system (GFL, Germany) at St. Petersburg University.

2.2. Sample preparation

To perform a concentration series based on caffeine citrate, 0.386 g caffeine citrate was dissolved in 100.0 ml of purified water, resulting in a 10 mM stock solution. Based on this stock solution, a serial dilution series (10–1 mM, then 1–0.1 mM, then 0.01–0.001 mM) were performed for the e-tongues based on potentiometric signal acquisition. For the voltammetric e-tongue sensitivity of the sensors was proven by measuring a concentration series including 0.38 mM, 0.57 mM, 0.95 mM, 1.88 mM, 3.68 mM and 7.02 mM in an aqueous KCl solution (10 mM).

Samples for the taste-masking experiment were prepared according to Table 1. The substances were precisely weighed into 100 ml flasks and shipped to all research groups involved in the study. Each sample was then diluted at site with 100.0 ml of purified water according to a shared protocol and measured under blind conditions. The pH values of samples 1–4, 6, 8, 9 were around 2.5 and for samples 5 and 7 (containing neither caffeine citrate nor citric acid) the pH was around 5.5.

2.3. Description of the applied electronic tongues and measurement protocols

2.3.1. TS-5000Z (Insent, Inc., Atsugi-Shi, Japan) (Fig. 1a)

The TS-5000Z e-tongue system (abbreviation: I) was equipped with the commercially available sensors SB2AC0, SB2AN0 and SB2BT0 (dedicated to bitter cationic substances), SB2AAE (dedicated to umami), SB2CT0 (dedicated to saltiness) and SB2CA0 (dedicated to sourness), SB2C00 (dedicated to bitter anionic substances) and SB2AE1 (dedicated to astringent substances) and Ag/AgCl-reference electrode. The measurement followed the standard procedure as described by Woertz et al. [22,25], using the recommended measurement setup ABCABC (A, B, and C are representatives of sample beakers). Prior to each measurement, a sensor check was performed and only proper working sensors were applied further. The washing steps were conducted in the recommended washing solutions (−)-solution: 100 mM hydrochloric acid diluted with ethanol (30% (w/w)) for negatively charged sensors, (+)-solution: 100 mM potassium chloride and 10 mM potassium hydroxide in ethanol (30 % (w/w)) as well as in the standard solution (0.3 mM tartaric acid and 30 mM potassium chloride in distilled water). The whole measurement procedure was carried out 4 times in a row. Regarding the conditioning of the sensors, only the results of the last three runs were considered for evaluation.

Measurement of the samples followed the procedure described by Pein et al. [24], starting with the bitter sensors SB2AC0, SB2AN0 and SB2BT0 in the first cycle, followed by a second run with the other 5 sensors.