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Interlaboratory testing of Insent e-tongues

Miriam Pein[a,*], Xolani Dereck Gondongwe[b], Masaaki Habara[c], Gesine Winzenburg[d]

[a] Institute of Pharmaceutics and Biopharmaceutics, Heinrich-Heine University Duesseldorf, Universitaetsstr. 1, 40225 Duesseldorf, Germany
[b] University College London, School of Pharmacy, 29-39 Brunswick Square, London, UK
[c] Insent (Intelligent Sensor Technology), Inc., Atsugi, Kanagawa, Japan
[d] Novartis Pharma AG, Basel, Switzerland

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ABSTRACT

The first interlaboratory testing of electronic taste sensing systems was performed within five participating centers, each working with the Insent (Insent Inc., Atsugi-Shi, Japan) e-tongue. Preparation of the samples for the comprised four experiments, shipping of the samples and evaluation of the results was performed at the University of Duesseldorf. The sensitivity (in this case the difference between lowest and highest sensor response) and slope of the regression line values, obtained within Experiments 1 and 2, have been found to serve as applicable evaluation criterions for interlaboratory comparability. Modified sensor responses could be attributed to aged sensors, but did not influence the results of either Experiment 3, dealing with the evaluation of film formulations, or Experiment 4, dealing with the evaluation of minitablet formulations, in a great amount. Presented PCA Score and Loading Scatter Plots as well as Euclidean distance patterns based on the raw sensor responses confirmed the comparable performance of Insent e-tongues of the participating centers.

1. Introduction

Multi-sensor arrays for automatic analysis, evaluation and classification of liquid samples, so called “electronic tongues”, have gained importance in the development of pharmaceutical drug formulations in the past few years (Anand et al., 2007; Legin et al., 2004; Maniruzzaman et al., 2012; Woertz et al., 2010b, 2011b,c; Zheng and Keeney, 2006). The EU legislation on medicines for children from 2007 and the fact that taste-masking attributes of medicinal products are nowadays often required by regulatory authorities (Breitkreutz, 2008) emphasize the need for objective tools to evaluate the taste(masking) of drug formulations. The successful performance qualifications (Pein et al., 2013; Woertz et al., 2010a) support the application of the two commercially available e-tongues αAstree (AlphaMOS, Toulouse, France) and the TS5000Z (Insent, Atsugi-Shi, Japan) in the pharmaceutical development. But even though interlaboratory comparability of analytical instruments is mandatory for their application in quality assurance of pharmaceutical products, this topic has not been addressed so far. Previous studies from our group only compared the performance of one taste-sensing apparatus of the Insent company with the performance of one αAstree (Eckert et al., 2013; Preis et al., 2012; Woertz et al., 2011a). Proving comparable e-tongue performances in different laboratories and different operators would however be of great importance, as many factors can influence data obtained by electronic tongues, e.g. the history, storage and handling of the applied sensors (Pein et al., 2013; Woertz et al., 2010a). Especially with regard to the assessment of taste-masked drug formulations, also the time point and duration of sampling can have a great impact on electronic tongue results (Pein et al., 2014).

Therefore, the present study is the first approach to evaluate interlaboratory comparability. Experiments have been conducted within the “e-tongue usergroup”, which was set up in 2012 on behalf of the European Paediatric Formulation Initiative (EuPFi):

* Corresponding author. Tel.: +49 211 8114225; fax: +49 211 8114251.
E-mail addresses: miriam.pein@hhu.de (M. Pein), x.gondongwe@ucl.ac.uk (X.D. Gondongwe), habara.masaaki@insent.co.jp (M. Habara), gesine.winzenburg@novartis.com (G. Winzenburg).

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five different laboratories out of four different countries have been invited to participate in a round robin test, which comprised the evaluation of drug concentration series as well as drug-loaded orodispersible film and minitablet formulations. The definition of criteria to judge about interlaboratory comparability is one of the main aims of this study. To obtain least biased data, the experiments should be conducted based on the same samples, the same sample preparation and measurement protocol. Sample production and shipment as well as the data evaluation should be done by one center (University of Duesseldorf) to avoid systematic errors. Each participating center worked with one of the Insent taste-sensing systems (SA402B or TS5000Z, Insent Inc., Atsugi-Shi, Japan).

2. Participants

The Institute of Pharmaceutics and Biopharmaceutics at the University of Duesseldorf (HHUD, Duesseldorf, Germany) guided the interlaboratory experiment and was responsible for the sample preparation and the data evaluation. All investigated samples were shipped to the participating centers Novartis (Basel, Switzerland), the School of Pharmacy at the University College of London (London, England) and the company Insent Inc. (Intelligent Sensor Technology, Inc., Atsugi-Shi, Japan). Every center worked with the Insent taste sensing system (Atsugi-Shi, Japan). Novartis, the University College London and the company Insent used the system TS5000Z, while the University of Duesseldorf (HHUD) used the TS5000Z and the SA402B, both with different sensor sets. In total, the results of 5 participating centers were the basis of this study.

Independent of the participating center, experiments with the TS5000Z were performed at ambient temperature. The samples measured with the SA402B at the HHUD were kept at 20 °C by water cooling.

3. Materials and methods

3.1. Chemicals

Quinine hydrochloride was purchased by Caesar & Loretz (Hilden, Germany) and potassium chloride by Gruessing (Filsum, Germany). Each film formulation contained 15% (w/w) of the film forming agent hydroxypropyl methylcellulose (Pharmacoat® 606, Harke Group, Mühlheim a. d. R., Germany), 10% (w/w) ethanol (96%, VWR international, Darmstadt, Germany), 7% (w/w) of anhydrous glycerol and the coloring agent E 124 (both excipients purchased by Caesar & Loretz, Hilden, Germany). Film formulations A1 and B1 contained 3% (w/w) of dimenhydrinate, and film formulations B1 and D1 were sweetened with 0.5% of a 1:10 mixture of saccharin sodium:sodium cyclamate (both sweeteners purchased by Caesar & Loretz, Hilden, Germany). The minitablet formulations were prepared according to Stoltenberg based on the ready-to-use tableting excipient Pearlitol® flash (provided by Roquette, Lestrem, France) (Stoltenberg, 2012). Minitablets A2, B2 and D2 contained 0.16% (w/w) of zinc sulphate (Riedel-de Haen, Sigma–Aldrich, Seelze, Germany), minitablets A2, C2 and D2 contained 9.8% of sodium chloride (analytical grade, VWR international, Darmstadt, Germany) and minitablets B2, C2 and D2 contained 18.5% of a 1:10 mixture of saccharin sodium:sodium cyclamate.

Samples E1–G1 and E2–G2 were physical mixtures, containing the API (sample E1 and E2), the API and the taste-masking excipients (F1 and F2) or the taste-masking excipients (G1 and G2). Since they are dissolved prior to measurement, the samples were not explicitly mixed. The weights of the excipients in the physical mixture samples correspond with the amounts in the formulation samples. Each sample has precisely been weighed in for every participant (Table 1). The sample compositions reduced to the API and the taste-masking excipient(s) are summarized in Table 1.

3.2. Preparation of the film and tablet formulations

To prepare the drug containing film formulations (film A1 and B1), dimenhydrinate (DMH) was dissolved in ethanol and added to a stirred water–glycerol mixture. To prepare film B1, the sweetener mixture was additionally added, while it was solely added to prepare film C1. To each of the solutions, the film forming agent was added stepwise. After 24 h of continuous stirring, the viscous solutions were poured onto a release liner (Erichsen film applicator, Erichsen, Hemer, Germany) and casted directly afterwards at a speed of 6 mm/s.

The minitablets were compressed on a rotary die press (Pressima MX-Eu-B/D, IMA Kilian, Cologne, Germany) with 2 mm biconcave punches. Prepared minitablets weighed 6.2 mg ± 0.26 mg.

3.3. Electronic tongue measurements

3.3.1. Standard and washing solutions

Dependent on the incorporated artificial lipids, sensors should be dipped into either the (−)- or the (+)-washing solution. The (−)-washing solution was prepared by diluting 100 mM hydrochloric acid with ethanol (30% (w/w)) and used for sensors with negatively charged lipids. The (+)-washing solution was used for sensors with positively charged lipids and prepared by dissolving 100 mM potassium chloride and 10 mM potassium hydroxide in ethanol (30% (w/w)). The standard solution, which served as cleaning and reference solution, was prepared by dissolving 0.3 mM tartaric acid and 30 mM potassium chloride in distilled water.

3.3.2. General procedure

Using the recommended measurement setup ABCABC (A, B, and C are representatives of sample beakers), the e-tongue measurement followed the standard procedure as described by (Woertz et al., 2010a,b, 2011a,b). The washing steps were conducted in the recommended (−)- or (+)-washing solution (see also Section 3.3.3) as well as in the standard solution (preparation according to Section 3.3.1). The whole measurement procedure was carried out 4 times in a row. Both, sensor responses and CPA (change of membrane potential due to adsorption) values were recorded.

3.3.3. Specific procedure

To measure the samples with all 7 sensors, two measurement cycles have to be performed. For the first measurement cycle, the outer sensor head was equipped with sensor SB2AC0 at position 1 and SB2AN0 at position 2. During the washing procedure these sensors dipped into the (−)-washing solution.

After the first measurement cycle, the reference solution in the washing beakers was exchanged. For the second measurement cycle, the outer sensor head was then equipped with the sensors SB2AAE (position 1), SB2CT0 (position 2) and SB2CA0 (position 3), and the inner sensor head with sensors SB2C00 (position 5) and SB2AE1 (position 6). The sensors at the outer sensor head dipped into the (−)-washing solution, whereas the sensors at the inner sensor head dipped into the (+)-washing solution.

3.4. Experiments 1–4 and sample preparation

A solution of quinine hydrochloride (0.5 mM, 0.1985 g/l) served as external standard, which was placed in the first sample beaker position (position sample A) for every experiment. A serial dilution series of quinine hydrochloride was prepared in water (Experiment 1) and in an aqueous 10 mM KCl-solution (Experiment 2). For

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