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Taste masking analysis in pharmaceutical formulation development using an electronic tongue

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Abstract

The purpose of this study is to assess the feasibility for taste masking and comparison of taste intensity during formulation development using a multichannel taste sensor system (e-Tongue). Seven taste sensors used in the e-Tongue were cross-selective for five basic tastes while having different sensitivity or responsibility for different tastes. Each of the individual sensors concurrently contributes to the detection of most substances in a complicated sample through the different electronic output. Taste-masking efficiency was evaluated using quinine as a bitter model compound and a sweetener, acesulfame K, as a bitterness inhibitor. In a 0.2 mM quinine solution, the group distance obtained from e-Tongue analysis was reduced with increasing concentration of acesulfame K. This result suggests that the sensors could detect the inhibition of bitterness by a sweetener and could be used for optimization of the sweetener level in a liquid formulation. In addition, the bitterness inhibition of quinine by using other known taste-masking excipients including sodium acetate, NaCl, Prosweet® flavor, and Debittering® powder or soft drinks could be detected by the e-Tongue. These results further suggest that the e-Tongue should be useful in a taste-masking evaluation study on selecting appropriate taste-masking excipients for a solution formulation or a reconstitution vehicle for a drug-in-bottle formulation. In another study, the intensity of the taste for several drug substances known to be bitter was compared using the e-Tongue. It was found that the group distance was 695 for prednisolone and 686 for quinine, which is much higher than that of caffeine (102). These results indicate that the taste of prednisolone and quinine is stronger or more bitter than that of caffeine as expected. Based on the group distance, the relative intensity of bitterness for these compounds could be ranked in the following order: ranitidine HCl > prednisolone Na > quinine HCl∼phenylthiourea > paracetamol ≫ sucrose octaacetate > caffeine. In conclusion, the multichannel taste sensor or e-Tongue may be a useful tool to evaluate taste-masking efficiency for solution formulations and to compare bitterness intensity of formulations and drug substances during pharmaceutical product development.

Keywords: Taste sensor; e-Tongue; Bitterness; Quinine; Caffeine; Formulation; Solution; Excipients; Principal component analysis; Bitterness inhibition; Preformulation

1. Introduction

Excessive bitterness of the active pharmaceutical ingredients in oral liquid or suspension formulation, sublingual or buccal formulation is a major taste problem facing pharmaceutical scientists. In the early development stage, bitterness of formulations can have an impact on clinical study design when a double-blinded trial is needed. Later, the bitterness of formulations can influence pharmaceutical selection by physicians and patients and thus affect acceptance and compliance. To inhibit or block the bitterness, both physical and chemical methods have been employed. Use of capsules, polymer coatings, microencapsulation, complexation, taste-masking excipients, and chemical modifications have been reported (FuLu et al., 1991; Ueda et al., 1993; Fukumori et al., 1988; Bechtol et al., 1981; Katsuragi et al., 1997; Mullarney et al., 2003). Generally speaking, taste is comprised of five basic qualities: sourness produced by hydrogen ions such as HCl, acetic acid, and citric acid; saltiness produced mainly by NaCl; sweetness produced by sugars; and bitterness produced by quinine, caffeine and $MgCl_2$. The last one is umami, which is the Japanese term for “deliciousness”, and is produced by monosodium glutamate contained in seaweeds, disodium inosinate in meat and fish and disodium guanylate in mushrooms (Pfaffmann, 1959; Kawamura and Kare, 1987). Biologically, the sensations of taste in humans occur when molecules trigger signals in the mouth

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that are sent to the brain, where a specific taste sensation is registered. The taste transduction is mediated by specialized neuroepithelial cells, referred to as taste receptor cells, organized into groups of 40–100 cells, which form taste buds. Taste buds are ovoid structures, the vast majority of which are embedded within the epithelium of the tongue. Different taste modalities appear to function by different mechanisms. For example, a salty taste appears to be mediated by sodium ion flux through apical sodium channels (Keast et al., 2001), while a sour taste seems to be mediated via a hydrogen ion blockade of potassium or sodium channels (Kinnamon and Roper, 1988). Sweet and bitter tastes are transduced by G protein-coupled receptors (Kinnamon and Cummings, 1992). To date, more than 80 putative bitter receptors have been identified (Matsunami et al., 2000). Nevertheless, the taste transduction mechanisms are complex and not fully elucidated.

The main method for the taste measurement of a drug substance or a formulation is by human sensory evaluation, in which tasting a sample is relayed to inspectors. However, this method is impractical for early stage drug development because the test in humans is expensive and the taste of a drug candidate may not be important to the final product. Therefore, taste-sensing analytical devices, which can detect tastes (especially bitterness) have been desired for a long time. It has been reported that a multichannel taste sensor (i.e., an electronic tongue or e-Tongue), whose transducer is composed of several kinds of lipid/polymer membranes with different characteristics can be used to detect taste (Toko, 1996). Taste information is transformed into a pattern composed of the electronic signals of the lipid membrane potentials. The sensor measures taste quality since different electric potential patterns are obtained for substances producing different taste quality. Also, similar patterns are obtained for substances producing the same taste quality (Takagi et al., 1998; Miyanaga et al., 2002). However, those reported studies were conducted by pilot e-Tongues with short life sensors, which significantly limited its application. Recently, a taste analyzing system manufactured by Alpha MOS has become commercially available. The taste sensors consist of silicon transistors with an organic coating that governs sensitivity and selectivity of each individual sensor. The life of the sensors could last as long as 1 year.

In this work, the e-Tongue with seven taste sensors was evaluated for its application in taste masking analysis during pharmaceutical formulation development. Objectives of this study were: (1) to assess the response and selectivity of seven sensors to compounds with different tastes; (2) to evaluate the feasibility to utilize e-Tongue in liquid formulation design; (3) to investigate the potential use of e-Tongue in ranking relative bitterness of compounds.

2. Experimental

2.1. Materials

Quinine HCl, quinine sulfate dehydrate, caffeine anhydrous, ranitidine HCl, phenylthiourea, sucrose octaacetate, and tartaric acid were purchased from Sigma Chemical Co. (St. Louis, MO). Sodium chloride, sodium acetate, and sodium saccharin were purchased from Fisher Scientific, (Pittsburgh, PA). 0.1 M Sodium L-glutamate (MSG), 0.1N HCl, 0.1 M NaCl, prednisolone Na, and paracetamol were from Alpha MOS Inc. (Hillsborough, NJ). Acesulfame K, pharma grade, was supplied from Nutrinova (Summerset, NJ). Soft drinks—Coca-Cola®, Sprite®, Diet Sprite®, and Dr. Pepper® were purchased from various supermarkets. Debittering flavor® and Prosweet flavor®, commercial bitterness-suppressing agents, were supplied by Flavors of North America (Carol Stream, IL) and Virginia Dare (Brooklyn, NY), respectively. All chemicals were of the highest grade available and used without further purification.

2.2. Equipment

An αAstree liquid and taste analyzer (e-Tongue) connected with LS16 autosampler unit, taste sensors and reference electrode was purchased from Alpha MOS Inc., and the system was equipped with a data acquisition and analysis software package. A taste sensor set—KIT #2 for pharmaceutical application (ZZ2806, AB2806, BA 2806, BB2806, CA2910, DA2806, and JE2806) was also from Alpha MOS Inc. The reference electrode (Ag/AgCl) was from Metrohm AG.

2.3. Methods

2.3.1. General sample preparation and analysis

The compounds tested were weighed out and dissolved in purified water. All testing beakers contained 80–100 mL of solution. When the reference electrode and sensors were dipped into a beaker containing a test solution, a potentiometric difference between each individually coated sensor with the Ag/AgCl reference electrode was measured and recorded by the e-Tongue software. Each sample was analyzed for 120 s. The liquid sensors and the reference electrode were then rinsed with purified water for 10 s after each sample analysis. Using well-conditioned sensors, each sample was usually tested eight times by the rotation procedure (i.e., the first round of measurements of all samples was completed before the next round of measurements was started).

2.3.2. Cross-selectivity test

Five compounds were used for the cross-selectivity test including tartaric acid (sourness), sodium saccharin (sweetness), quinine (bitterness), NaCl (saltiness), and MSG (umami). Tartaric acid, sodium saccharin, NaCl and MSG were made at the same concentration (10 mM) while quinine was made at 1 mM. Solutions were analyzed using the e-Tongue as described above.

2.3.3. Bitterness-masking of quinine

Solution samples (250 mL) were prepared using purified water for evaluation of suppression of bitterness of quinine by a sweetener, acesulfame K and other known bitterness taste-masking excipients. Quinine was kept at a constant level of 0.2 mM with varying concentrations of acesulfame K (0.1, 1.0,