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Research Article

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Suitability of E-tongue Sensors to Assess Taste-Masking of Pediatric Liquids by Different Beverages Considering Their Physico-chemical Properties

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ABSTRACT. Manipulation of liquid oral drugs by mixing them into foodstuff is a common procedure for taste-masking of OTC pharmaceuticals when administered to children. However, the taste-masking capability of such application media is not systematically evaluated, and recommendations for suitable media are hardly published. In this study, a sensor array of commercially available and self-developed electronic tongue sensors was employed to assess the taste-masking efficiency of eight different beverages (tap water, apple juice, carrot juice, fennel tea, fruit tea, milk, cocoa, and Alete meal to drink) on the OTC pharmaceuticals Ambroxol-ratiopharm®, Cetirizin AL, and Laxoberal® by multivariate data analysis. The Euclidean distances between each pure application medium and its corresponding drug mixture were used as an indicator for the taste-masking efficiency and correlated to the physico-chemical properties of the beverages. Thus, the pH value, the viscosity, as well as the fat and sugar content of the beverages were included, whereas only the viscosity appeared to be insignificant in all cases. The sugar content as well as the fat content and pH value emerged to be a significant variable in taste-masking efficiency for some of the tested drug products. It was shown that the applied electronic tongue sensors were capable to demonstrate the impact of the physico-chemical properties of the application media on their taste-masking capacity regardless of their non-selectivity towards these characteristics.

KEY WORDS: fat content; pH; sugar content; taste-masking assessment; viscosity.

INTRODUCTION

A large variety of over-the-counter (OTC) pharmaceuticals for pediatric use is available on the market and frequently used in the treatment of prevalent diseases. Many of these pharmaceuticals are supposed to be orally administered and commonly available as oral liquids, such as syrups, drops or suspensions or oral solids, such as tablets, capsules, or granules (1). However, since most children are not able to swallow ordinary tablets (2) but (so far hardly marketed) mini-tablets (3), many parents, pediatricians, and pharmacists tend to access liquid oral drugs (1). Although these dosage forms are easy to administer (4), they are often developed based on adult's formulation and might therefore not meet the requirements for suitable pediatric dosage forms (5), in particular regarding palatability. In worst case, the drug will be rejected due to longer-lasting bad taste (6,7). Within recent years, palatability and taste became thus key factors in the development of pediatric drug formulations (8–11). Industry and academia put huge effort into the development of properly taste-masked pharmaceuticals (12–15). However, since more rather than less frequently used pediatrics do not taste well, compliance issues are still common (16). In particular with oral liquids, the advantages of maximum dose flexibility and ease of physical swallowing might go at the expense of proper taste (4). Parents but also nurses therefore often manipulate the drugs by adding for example soft food or beverages (2); and also some manufacturers recommend to take liquid drugs dispersed in other liquids (17,18). Besides the critical aspect of stability of the drugs, it remains unclear whether the manipulation really leads to proper taste masking.

A common step to evaluate palatability in pharmaceutical industry in the US is besides conducting taste panel studies using electronic tongues (19). According to the IUPAC technical report from 2005, an electronic tongue is defined as "a multisensor system, which consists of a number of low-selective sensors and uses advanced mathematical

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procedures for signal processing based on Pattern Recognition and/or Multivariate data analysis..” (20). Several published studies, correlating data of human taste panels and electronic tongue results, have proven that those instruments are at least with some reservations able to predict the taste (21–24). With regard to taste-masking evaluation of pharmaceutics, usually principal component analyses (PCA) are performed and according results plotted in PCA maps. This evaluation method enables assessing the differences of samples with regard to their detection by applied sensors. The more similar the samples are detected by the applied sensors, the closer their data points are located within the PCA map. Proper taste-masking is therewith assumed, the closer the data point of a taste-masked sample is located towards the API free placebo (22,25). Besides chemical properties of the drugs, such as pH, ion strength or type of counter ion also physical properties, such as the viscosity, influence sensor’s signals.

In particular with oral liquids, the advantages of maximum dose flexibility and ease of physical swallowing might go at the expense of proper taste (4). Especially with drops, where the drug is dissolved and little viscosity enhancer can be added, proper taste-masking is a severe problem—which might be manageable by manipulation with beverages. But besides the critical aspect of drug stability, it remains so far questionable whether the manipulation leads to proper taste masking. According information could just be obtained retrospectively, and no systematic studies have been performed so far.

Assuming the stability of the APIs and the physicochemical properties of the investigated drug formulations, we aim to prove suitability of electronic tongue sensors combined with multivariate data analysis for taste-masking evaluation. Drugs of interest are three over-the-counter (OTC) ready-to-use pediatrics, which were mixed with various application liquids differing in pH, viscosity, sugar and fat content. Commercially available and self-developed sensors have been applied to evaluate the benefit of using one or the other or both type of sensors arrays in this regard.

MATERIALS AND METHODS

Materials

OTC Ready-to-use Pediatrics

The three over-the-counter (OTC) ready-to-use drops Ambroxol-ratiopharm® (ratiopharm GmbH, 7.5-mg ambroxol hydrochloride/mL), Cetirizin AL (ALIUD PHARMA®, 10-mg cetirizin dihydrochloride/mL) and Laxoberal® (Boehringer Ingelheim, 7.5-mg sodium picosulfate/mL), approved for children (aged 2–6 years) (Table I), were dispersed in different application liquids (3.1.2).

Application Liquids

Tap water (TapWat), apple juice (AplJuice, babylove), fruit tea (FruTea, Alnatura), milk (Milk, 1.5% fat), fennel tea (FenTea, Rewe Bio), Alete Meal to Drink 8 Grains and Honey (Alete, Nestlé®), Carrot Juice (CarJuice, Hipp GmbH & Co), and Cocoa (Cocoa, Nesquik Nestlé®) were used as application liquids.

Electronic Tongue Measurements

Potassium chloride (Gruessing, Filsum, Germany), tartaric acid (AppliChem, Darmstadt, Germany), potassium hydroxide (Gruessing, Filsum, Germany), hydrochloric acid (Merck, Germany), and absolute ethanol (VWR international, Darmstadt, Germany) were used for the preparation of the washing and standard solutions for the electronic tongue.

The measurements were performed with a sensor array consisting of 15 different sensors. Eight of the sensors were commercially available (Insent Inc., Atsugi-Shi, Japan) and each dedicated to a defined taste: SB2AAE: umami taste, SB2CT0: saltiness, SB2AE1: astringency, SB2CA0: sourness SB2AC0: bitterness (cationic substances), SB2AN0: bitterness (cationic substances), SB2BT0: bitterness (cationic substances), SB2C00: bitterness (anionic substances). Moreover, seven self-developed membrane electrodes (3.1.4.) were applied.

Sensor Preparation of Self-Developed Sensors

Polyvinyl chloride (PVC, Sigma-Aldrich, Steinheim, Gemany), isopropylmyristate (IPM, Cognis GmbH, Duesseldorf, Germany), 2-nitro-phenyl octyl ether (NPOE, Fluka Analytical, Steinheim, Germany), trioctylmethyl ammonium chloride (TC, Alfa Aesar, Karlsruhe, Germany), bis (2-ethylhexyl) phosphate (BP, Sigma-Aldrich, Steinheim, Germany), oleic acid (OA, Fluka Analytical, Steinheim, Germany), hydroxypropyl-ß-cyclodextrin (HPßCD, Roquette, Lestrem, France), a cyclodextrin oligomer (CDO, HHU, Duesseldorf, Germany), tetrahydrofuran (THF, VWR international, Darmstadt, Germany), absolute ethanol (Sigma-Aldrich, Steinheim, Germany), and acetone (VWR international, Darmstadt, Germany) were used for the preparation of the electronic tongue sensors 1–7 (Table II).

Methods

Sensor Preparation of Self-Developed Sensors

Sensor membranes were prepared by dispersing different amounts and types of a plasticizer, ionophore, and artificial lipids with PVC and the organic solvents. The prepared polymer suspensions were casted on a Hostaphan® foil (Wiesbaden, Germany) with a coating knife of 1000 µm gap width on a coatmaster (Erichsen, Sweden). The dried polymer membranes were cut into pieces of 1.2×0.8 cm and attached to a sensor head blank (Insent, Japan). The sensors were filled with an internal solution of 3.33 M potassium chloride in saturated silver chloride. A silver/silver chloride wire was put into the sensor head functioning as the working electrode. The prepared sensors were conditioned in standard solution (0.3 mM tartaric acid and 30 mM potassium chloride in distilled water) for 24 h before the measurements.

Table I. Composition and Indication of the Investigated OTCs

OTC product	Drug substance	Indication	Excipients
Ambroxol-ratiopharm®	Ambroxol hydrochloride	Cough	Potassium sorbate, hydrochloric acid, purified water
Cetirizin AL	Cetirizin dihydrochloride	Allergy	Acetic acid 99%, glycerol, methyl-4-hydroxy benzoate (Ph. Eur.), sodium acetate, propyl-4-hydroxy benzoate (Ph. Eur.), propylene glycol, saccharin sodium, purified water
Laxoberal®	Sodium picosulfate	Constipation	Sodium benzoate, sorbitol solution 70%, sodium citrate dihydrate, citric acid monohydrate, purified water

Sample Preparation

The sample solutions were prepared by mixing a single dose of the OTC drops with 40 mL of each of the different application liquids as this volume was required by the manufacturer of the taste sensing system (Insent Inc., Atsugi-Chi, Japan) (3.1.2). A single dose and thus the sample solutions contained either 7.5-mg ambroxol hydrochloride, 2.5-mg cetirizin dihydrochloride, or 2.78-mg sodium picosulfate. Taste samples (salty, sour, umami, bitter, and astringency) for the sensor performance tests were prepared according to Kobayashi *et al.* (24). Further sensor performance was evaluated by analyzing pure application liquids and measuring sugar solutions containing either 5 or 10% D (+)-Saccharose (Carl Roth, Germany) in water and samples comprising of a single dose of either one of the OTC drugs in 5 or 10% sugar solution.

Electronic Tongue Measurements

Electronic tongue measurements were performed according to the measurement protocol of Woertz *et al.* (26) with a stability criterion of 2 mV. The measurements were performed five times, and only the three last runs were used for data evaluation.

Data Evaluation

Microsoft Excel®, Origin Pro 9G, and SIMCA 13.0 (Umetrics AB, Umea, Sweden) were used for the data evaluation. Sensor signals were corrected by an external standard solution of quinine hydrochloride dihydrate (Buchler GmbH, Germany) 0.5 mM. The mean of the last three runs of every experiment was calculated and used for multivariate data analysis.

Table II. Composition and Labeling of the Self-Developed Sensor Membranes 1–7

Sensor	Plasticizer	Ionophore	Artificial lipid	Oleic acid
1	IPM	CDO	TC-BP	x
2	IPM	CDO	TC-BP	x
3	NPOE	HPßCD	TC	x
4	NPOE	HPßCD	TC	x
5	NPOE	HPßCD	TC	x
6	IPM	HPßCD	TC-BP	x
7	NPOE	HPßCD	TC	x

Viscosity of the Application Liquids

Viscosity was analyzed by a rheometer (Kinexus Rheometer, Malvern Instruments, Germany), equipped with a 60-mm cone-plate system (CP1/60:PL60). Measurements were performed at 25°C and flow characteristics investigated performing a shear ramp from 0.1 to 100 s^{-1} and from 100 to 0.1 s^{-1}. The shear viscosity was evaluated at a shear rate of 20 s^{-1} and measured in triplicates.

Stability Testing

Stability of the APIs with regard to critical aspects of the application liquids, such as pH and calcium concentration, was evaluated by HPLC. Methanol for HPLC (VWR international, Darmstadt, Germany) and demineralized water with either 5% hydrochloride acid (Merck, Germany) or 5% sodium hydroxide (AppliChem, Darmstadt, Germany) were used as mobile phase and for the sample preparation for HPLC analysis. The HPLC instrument (Agilent Technologies 1260 Infinity) was equipped with a pump, autosampler, injector, UV detector, a C18 column (Nucleosil-100-5-C18, 250 × 4.6 mm, 5 µm) (Macherey-Nagel, Dueren, Germany), data evaluation was performed with LC Open Labs software.

Pure ambroxol hydrochloride (Fagron, Germany), cetirizine dihydrochloride (Buchler GmbH, Germany), and sodium picosulfate (Ph. Eur. Reference Standard, S07850000, EDQM, Strasbourg, France) were dissolved three different solutions: in diluted hydrochloride acid (Merck, Germany), pH = 3 sodium hydroxide (AppliChem, Darmstadt, Germany) solution of pH = 8, and calcium phosphate dihydrate (Carl Roth GmbH, Germany) solution (1.25 mg/ml). Each stability sample was measured immediately after preparation, 1 hour after preparation and 24 h after preparation.

RESULTS

Physico-Chemical Properties of the Application Liquids and Their Influence on Drug Stability

Prior to taste-masking assessment, chosen application liquids were analyzed according to their pH value and viscosity. Furthermore, fat and sugar content as provided by the producer were listed in Table III.

Moreover, potential food-drug interactions leading to degradation of the API were examined. Pure APIs were therefore stressed in solutions simulating the most critical characteristics of the used application liquid (high pH, low

Table III. Physico-chemical Properties of the Application Liquids: 1: Measured, 2: as Stated by the Supplier

Application liquid	pH value[1]	Viscosity (mPa·s)[1]	Fat content (%)[2]	Sugar content (%)[2]	Taste
Tap water	5.8	1	0.0	0.0	Neutral
Apple juice	3.6	4	0.04	11.0	Sour/sweet
Fruit tea	4.0	1	0.0	0.3	Sour
Milk	6.6	2	1.5	4.5	Slightly sweet, fatty
Fennel tea	7.6	1	0.0	0.0	Neutral
Alete	6.3	321	2.9	11.3	Sweet, fatty
Carrot juice	5.4	2	0.1	4.5	Slightly sweet
Cocoa	6.7	27	1.6	11.6	Sweet, fatty

pH and Ca^{2+} concentration) individually. Preparing these potentially critical solutions allows for the individual evaluation their impact on the API stability. Therewith, the complexity of the application media is reduced, and potential effects could be detected in a precise manner. The concentration of the pure API substances in demineralized water was compared to their concentration (after storage) in either solutions with pH 3, pH 8 (with regard to Table III) or with 50 mg Ca^{2+} in 40 ml (comparable to calcium content in milk (27)) (Table IV). Samples were taken and measured (a) directly after dissolving the APIs in the three critical solutions, (b) after 1 hour, and (c) after 24 h of storage. Neither one of the stress solutions nor the prolonged storage time led to degradation of the APIs ambroxol hydrochloride (content >98%) and cetirizin dihydrochloride (>97%). Sodium picosulfate remained stable in each of the stress solutions for 1 hour (content >98%). After 24-h storage, drug content in the water solution was decreased to 95% and in the calcium containing solution to 89%. High standard deviations prove decreased stability of sodium picosulfate over storage.

Considering an application directly after manipulation, chosen application liquids can be assumed to be suitable for taste-masking application.

Sensor Performance

Impact of Different Tastants on Sensor Responses

To classify the performance of the applied sensors (self-developed and commercial ones), solutions used as references for saltiness, sourness, umami, cationic and anionic bitterness as well as astringency (24) were analyzed, and the according sensor responses are displayed in Fig. 1.

All 15 sensors showed sensor responses arranged as a recognizable spectrum. In this experiment, the commercially available sensors from Insent Inc. (Atsugi-Shi, Japan) behave contrary to the self-developed sensors. To the taste samples salty, sour, cationic and anionic bitterness as well as to astringency, sensors from Insent responded with different negative potentials. For the same samples, the self-developed sensors showed positive sensor signals. The umami sample induced negative sensor responses for all sensors regardless of their origin. Even if no sensor signal of the employed sensor types was alike another, the sensor signals of the self-developed sensors were much more related to each other. However, the individual sensor signals for the different taste samples were proven to behave selective for the different basic tastes.

Table IV. Drug Content

	Ambroxol hydrochloride	Cetirizin dihydrochloride	Sodium picosulfate
(a) Drug content directly after dissolving the drug			
pH 8	103.43 ± 4.21	98.66 ± 0.97	100.95 ± 2.60
pH 3	100.83 ± 1.41	97.36 ± 1.15	98.83 ± 2.52
Ca^{2+}	102.06 ± 0.65	98.01 ± 0.56	100.43 ± 2.16
H_2O	98.52 ± 1.46	97.26 ± 1.43	100.09 ± 2.30
(b) Drug content after one hour of storage at RT			
pH 8	103.64 ± 1.75	97.57 ± 2.28	98.74 ± 2.93
pH 3	100.50 ± 1.17	97.19 ± 0.91	98.33 ± 2.47
Ca^{2+}	102.07 ± 1.57	97.29 ± 0.70	98.60 ± 1.99
H_2O	99.58 ± 1.95	98.13 ± 1.24	98.49 ± 1.43
(c) Drug content after 24 h of storage at RT			
pH8	104.12 ± 2.08	97.55 ± 1.45	98.54 ± 1.99
pH3	101.04 ± 0.50	97.84 ± 0.34	98.42 ± 1.78
Ca^{2+}	102.65 ± 1.20	97.96 ± 1.15	89.21 ± 7.93
H_2O	100.34 ± 1.58	100.42 ± 1.58	95.37 ± 3.72

(mean ± s, $n = 3$)

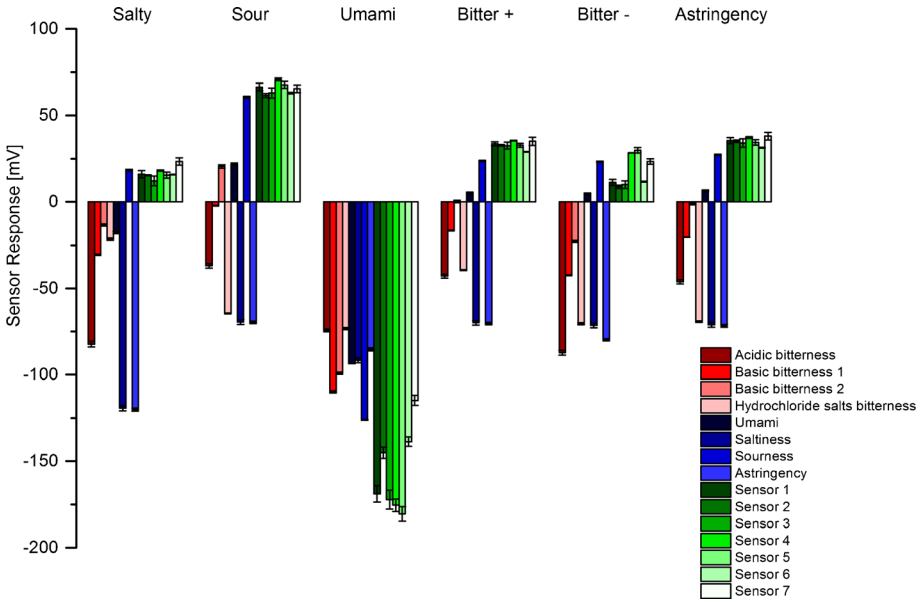

Fig. 1. Sensor responses of the used sensors to the basic taste samples. ($n = 3$, mean ± s)

Impact of Sugar on Sensor Responses

The impact of sugar in the different beverages on the sensor signals was evaluated by measuring (a) aqueous solutions containing 5 and 10% of pure sugar and (b) the ready-to-use drugs spiked with 5 and 10% of sugar. Twelve out of fifteen sensors were suitable to differentiate between the two pure sugar concentrations, resulting in decreasing sensor responses with increasing sugar content: self-developed: sensor 1 (difference of 8.47 mV ± 0.36 between 5 and 10% sugar solution), sensor 2 (9.69 mV ± 1.26), sensor 3 (9.00 mV ± 1.21), sensor 4 (1.24 mV ± 1.15), sensor 5 (6.38 mV ± 1.44), sensor 6 (0.98 mV ± 0.47), sensor 7 (10.24 mV ± 1.67); commercial ones: SB2C00 (acidic bitterness) (6.09 mV ± 0.39), SB2AE1 (astringency) (4.52 mV ± 0.46), SB2BT0 (hydrochloride salts bitterness) (10.37 mV ± 1.36), SB2CT0 (saltiness) (1.29 mV ± 0.35), and SB2AN0 (basic bitterness 2) (1.46 mV ± 0.42).

Ten out of fifteen sensors moreover detected significant differences of samples containing Laxoberal® spiked with either 5 or 10% sugar solution. Contrary to the pure sugar solutions, solutions containing Laxoberal® showed increasing sensor signals with increasing sugar content. These sensors were able to distinguish between the two different concentrated sugar media: self-developed: sensor 1 (difference of 5.49 mV ± 0.92 between Laxoberal® in 5 and 10% sugar solution), sensor 2 (5.41 mV ± 0.75), sensor 3 (6.08 mV ± 0.25), sensor 5 (1.80 mV ± 0.19), sensor 7 (6.01 mV ± 1.14); commercial ones: SB2C00 (acidic bitterness) (6.37 mV ± 0.52), SB2AE1 (astringency) (17.58 mV ± 2.37), SB2BT0 (hydrochloride salts bitterness) (4.04 mV ± 0.21), SB2CT0 (saltiness) (4.09 mV ± 0.68), and SB2CA0 (sourness) (2.75 mV ± 0.75).

Ability to Discriminate the Application Liquids

Application liquids (3.2.1) were analyzed by using on the one hand the commercial sensor array (SB2AAE, SB2CT0, SB2AE1, SB2CA0, SB2AC0, SB2AN0, SB2C00) and on the other hand by using the self-developed sensor array (according Table II). In a multivariate evaluation, commercial sensors showed difficulties to differentiate between Alete® and Carrot Juice and milk and cocoa (PC2, R^2 0.889), while self-developed sensors detected fennel tea, milk, and cocoa very much alike (PC2, R^2 0.998). Combining the information of both sensor arrays led to a good discrimination of fennel tea, carrot juice, Alete®, and milk/cocoa, which were still detected comparably.

On the basis of the sensor performance results, we expect improved results for the sensorial assessment, if the information of all employed sensors is used to assess taste-masking efficiency of the chosen application liquids on the OTCs.

Taste-Masking Evaluation

Principal Component Analysis

Taste-masking efficiency of the application liquids was assessed by multivariate analysis including the responses of all 15 employed sensors. For each OTC pediatric, a principal component analysis (PCA) was performed, using the sensor responses as x-variables (Fig. 2, left). The closer the pure application liquid sample is located to the according application liquid-OTC sample, the better taste-masking was assumed.

For Ambroxol-ratiopharm®, samples comprising a milk-based application liquid are arranged in the lower left

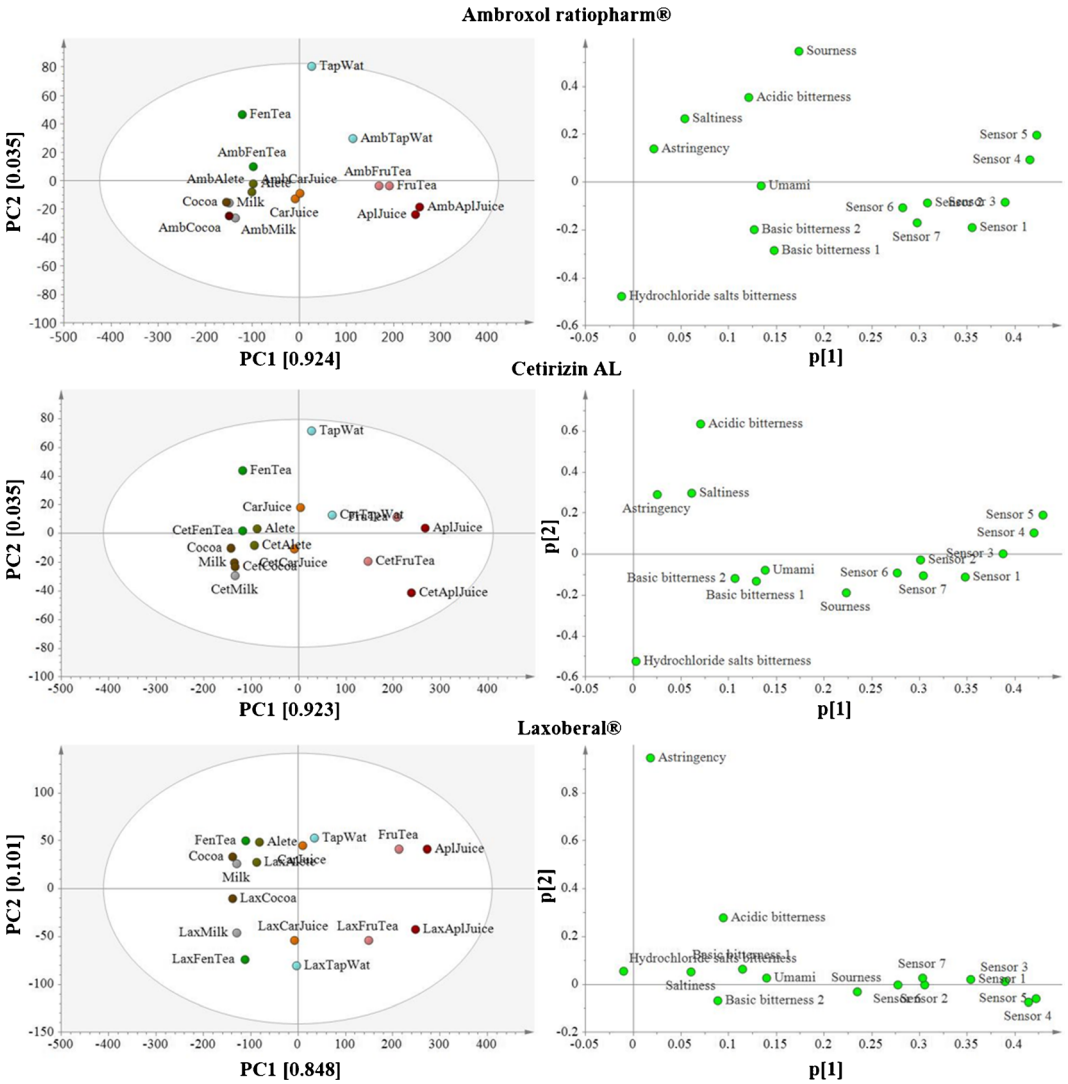

Fig. 2. Score scatter plots (PCA map) and corresponding loading scatter plots for the three OTC pediatrics Ambroxol-ratiopharm® ($R^2 = 0.959$, $Q^2 = 0.913$), Cetirizin AL ($R^2 = 0.957$, $Q^2 = 0.901$), and Laxoberal® ($R^2 = 0.949$, $Q^{2=}0.825$) containing the information of all samples based on the detection by the 15 employed sensors; each sample was measured in triplicate but displayed as mean; data is ctr scaled

quadrant. On the opposite site, the lower right quadrant, fruit tea and apple juice samples are found. The samples in this quadrant are dominated by the signals of the sensors for basic bitterness, umami, and the sensors 1,2,3,6, and 7 depicted in the loadings plots (Fig. 2, right). The samples located in the upper right quadrant are based on tap water and are represented by the sensors for acidic bitterness, astringency, saltiness, sourness, and the sensors 4 and 5. The samples containing fennel tea is to be found in the upper left quadrant, featured by no specific sensor as well as the sample based on carrot juice, which is located near the origin.

While tap water samples showed apparently the largest distance, milk-based samples containing either milk, cocoa, or Alete featured very high capacities to mask the taste of Ambroxol-ratiopharm®, expressed in small differences between the corresponding samples. In addition to this, carrot juice and apple juice showed also good taste-masking efficiencies with small differences between their corresponding samples.

In the PCA map for Cetirizin AL again samples containing milk-based beverages are arranged in the lower left quadrant, only pure Alete is located in the upper left quadrant even though on the lower boarder. The samples comprising fruit tea or apple juice are situated either in the upper right quadrant, if consisting of the pure application liquid, or in the lower right quadrant, if consisting of the drug containing mixture. Since the lower right quadrant is dominated by the sensor signals of sensors for basic bitterness and hydrochloride salts bitterness among others (Fig. 2, right), these signals are most likely provoked by cetirizin dihydrochloride. The fact that the corresponding samples are located in opposite quadrants indicates a low capability of fruit tea and apple juice to mask cetirizin dihydrochloride. Samples containing tap water are located in the upper right quadrant, dominated by the signals of sensors for acidic bitterness, saltiness, and astringency as well as of sensors 4 and 5 (Fig. 2, right). Tap water features similar distances and taste-masking abilities like fruit tea and apple juice. Fennel

tea and carrot juice showed regular taste-masking properties on cetirizin dihydrochloride. The carrot juice samples are located near the origin while the fennel tea samples are situated in the upper left quadrant.

Corresponding samples of Laxoberal® showed considerably larger distances within the PCA map indicating bigger differences in taste. It is noticeable that all pure application liquids are located in the upper quadrants while all drug containing mixtures are located in the lower quadrants. This indicates high sensitivity of the astringency sensor to sodium picosulfate and thus low taste-masking efficiency of each application liquid. Only Alete was able to properly taste-mask sodium picosulfate, since the corresponding samples are located in the upper left quadrant with a low distance.

Even though all three OTC pediatrics show different PCA map patterns and the impact of the application liquids on the sensor signals of the drug products differed from each other, milk-based liquids seemed to show better taste-masking properties than the other employed beverages. This could be shown for all drug products. However, the distances between the corresponding samples are difficult to be estimated reliably and therefore hard to compare.

Euclidean Distances

Due to the abovementioned reason, the Euclidean distances between the sensor signals of the pure application liquids and the drug containing mixtures were calculated (Fig. 3) (28). By doing so, differences between the application liquids and application liquid-OTC samples become more assessable. The Euclidean distances were calculated from the sensor responses of all 15 sensors after a z-transformation to ensure comparability of the different sensor signals. The lower the Euclidean differences, the more similar the sensor responses have been and the better the taste-masking efficiency is assumed.

As a tendency for all drug formulations, it is seen that tap water, fruit tea, and fennel tea showed the lowest taste-masking capabilities. On the contrary, cocoa and Alete feature the best taste-masking properties for all investigated drug formulations. Milk, apple juice, and carrot juice have differing effects on the taste of the OTCs. In the diagram, it is also visible that Ambroxol-ratiopharm®—regardless of the highest drug concentration applied in this study (7.5 mg/40 mL)—can be better taste-masked compared to the other OTCs, since it shows the lowest Euclidean distance obtained in this study (cocoa) and moreover a recognizable low Euclidean Distance for apple juice.

In detail, Ambroxol-ratiopharm® showed the lowest Euclidean distances for cocoa, followed by Alete, apple juice, and milk. Cetirizin Al on the other hand is best masked by milk followed by cocoa and Alete. Apple juice does not seem to have a remarkable taste-masking efficiency on Cetirizin Al. Laxoberal® shows the lowest Euclidean distances for Alete and cocoa.

DISCUSSION

Selection of OTC Pediatrics and Application Liquids

Ambroxol-ratiopharm®, Cetirizin AL, and Laxoberal® were chosen as OTCs for pediatric use for this study. This antitussive, antihistamine, and laxative are commonly used for the treatment in children as oral liquids. However, they are furthermore known to be often rejected by children, which was confirmed by local pharmacy specialized for

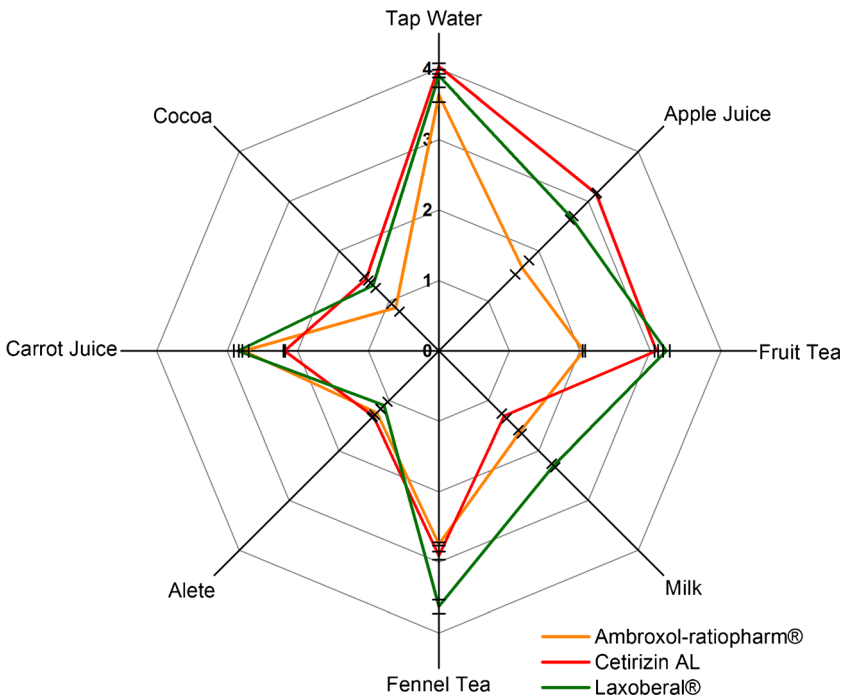

Fig. 3. Euclidean distances (mV) of all samples for the liquid drugs Ambroxol-ratiopharm®, Cetirizin AL, and Laxoberal® based on the detection by all 15 sensors (z-transformation, $n = 3$, mean ± s)

pediatric drugs (Apotheke in Wersten, Duesseldorf, Germany). Due to this bad taste-related rejection, the employees of the local pharmacy recommend to administer those drugs dispersed in various beverages to mask the bad taste of the drug formulation and to simplify the drug intake. A dilution of the drops in beverages is also suggested by some manufacturers (17,18).

As target group served children between 2 and 6 years and had to be taken into consideration for the selection of the investigated application liquids. As a result of a short parent's interview, eight beverages for pediatric nutrition with different tastes and ingredients or nutrient profiles, respectively, were selected to be mixed with the OTCs. Tap water was included as a negative reference for taste-masking efficiency but also as a reference for the drug stability within the application media. As milk-based media, pure milk with 1.5% fat, cocoa, and Alete were used. In addition, fruit tea and fennel tea as media with a low sugar content and apple juice with a high sugar content but low fat content in comparison to cocoa were chosen. Although it was not mentioned by the parents, carrot juice was also included, as it is often consumed by children of the target group.

Taste-Masking Evaluation by Multivariate Data Analysis

The differences between the e-tongue sensor signals of the pure application liquid and the OTC-application liquid mixture demonstrate the capacity of the media to mask the taste of the drug formulations. The closer the two corresponding samples are arranged in the PCA maps, the more successful the taste-masking of the particular application liquid is assumed. For all three OTC pediatrics, milk-based beverages seemed to show better taste-masking properties than the other employed beverages, which is in good agreement with the results of Sadrieh *et al.* (28) and well explainable by the natural attraction of children to milk. The included fat can moreover coat the taste-buds and thus avoid the contact between an unpleasant tasting API and taste receptors A more detailed and comparable look onto this result was made by calculating the Euclidean distances of each particular application liquid to each of the three OTC pediatrics. Low Euclidean distances corresponding to a high taste-masking efficiency could again be seen for cocoa, Alete and milk, but regarding Ambroxol-ratiopharm®, also apple juice seemed to be well taste-masking. Since these results are (besides the chemical properties of the APIs) due to the physico-chemical characteristics of the application liquids, pH, content of fat, and sugar and the viscosity were therefore considered for more detailed evaluation. All these properties are supposed to positively affect taste-masking capacity: An increased viscosity decelerates the diffusion of the drug to the taste buds (15), resulting in potential taste-masking efficacy. Sugar (sucrose) is known to have the capability to mask the bitter taste of drugs (29) and is despite its risk to provoke caries (30) still used in drug products for this purpose (1,7). Lipids can increase the viscosity in the mouth, which leads to a coating of the taste buds and mask the bad taste (7). But more likely, drug molecules partition into the lipid phase and thus reducing their concentration in the aqueous phase (as reported for quinine (31,32)) and thereby reducing the perceived bitterness (14). Furthermore, since children are more attracted by sourness than adults (33), the pH value also plays an important role for proper taste-masking of pediatrics.

Due to the postulated assumptions, the Euclidean distances were correlated to the key characteristics of the application media. Therefore, partial least squares projections to latent structures were prepared (PLS). The pH value, viscosity, fat content, and sugar content (input) are suspected to be responsible for the formation of the Euclidean distances. Thus, the Euclidean distances are set as the Y-variable (output) while the input variables are set as the X-variables (Fig. 4).

The Score Scatter plots for the three evaluated OTCs showed very comparable information. Cocoa and Alete are located in the lower left quadrant, apple juice in the upper right quadrant, milk and fennel tea in the lower right

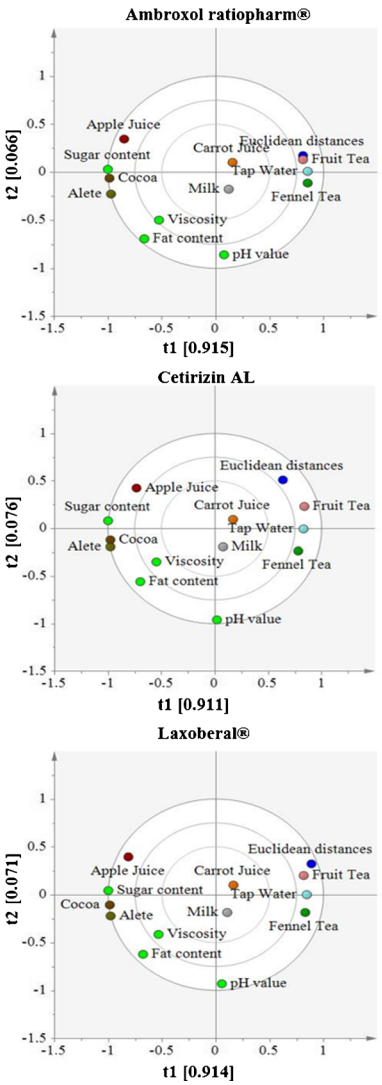

Fig. 4. Biplots showing scores and loadings of the PLS models for the three tested OTCs Ambroxol-ratiopharm® (R^2_x 0.981, R^2_y 0.683, Q^2 0,417) Cetirizin AL (R^2_x 0.987, R^2_y 0.669, Q^2 0.456), and Laxoberal® (R^2_x 0.986, R^2_y 0.892, Q^2 0.768). The model contains the pH value, viscosity, fat content and sugar content as X-variables and the Euclidean distances as Y-variable; data was ctr scaled

quadrant, fruit tea and carrot juice in the upper left quadrant, and tap water on the baseline between the upper and lower right quadrant. As indicated by the loadings in the biplot in Fig. 4, the sugar content, located in the upper left quadrant, is correlated to the Euclidean distances in a negative manner, meaning a high sugar content leads to low Euclidean distances. The pH value and the fat content are slightly negatively correlated to the Euclidean distances, while viscosity has a comparably lower impact (located nearest to the origin). Although viscosity of applied liquids is except Alete (321 mPas) quite low, as for example compared to the dosing vehicle ORA-BLEND® SF (1000 mPas (34)), this is in good agreement with the finding of Woertz *et al.* (35), who could not prove an impact of viscosity on sensor's signals.

The above-discussed correlations between the Euclidean distances to each of the X-variables are also semiquantitatively evaluated by according coefficient plots in Fig. 5. For Ambroxol-ratiopharm®, none of the physico-chemical properties showed a significant influence on the taste-masking capacity. This is in good agreement with the Euclidean distances in Fig. 3. The taste-masking of Ambroxol-ratiopharm® is overall the best of all three OTC drugs. Neither high sugar content (apple juice) nor a high fat content (milk) nor high pH value was found to have a higher impact on the Euclidean distances than another. All three aspects appear to have good taste-masking capacities for Ambroxol-ratiopharm®. The coefficient plot for Cetirizin AL features a high impact of pH and fat content on the taste-masking efficiency. Both characteristics are significant variables. This is again confirmed by results displayed in Fig. 3. Milk-based media with a higher fat content and pH value showed the best taste-masking efficiency. Even if cocoa and Alete also feature a higher sugar content, apple juice with a high sugar content but low pH value and no fat content were not able to taste-mask Cetirizin AL in a comparable manner. The taste-masking efficiency on Laxoberal® was inferior to the other drug products. Only a high sugar content combined with a higher fat content could show better capabilities to taste-mask Laxoberal®. In this manner, only cocoa and Alete feature low Euclidean distances while milk (higher fat content) and apple juice (high sugar content) did not. This is confirmed by the coefficient plot in Fig. 5, where fat and sugar are determined as significant variables for the taste-masking of Laxoberal®.

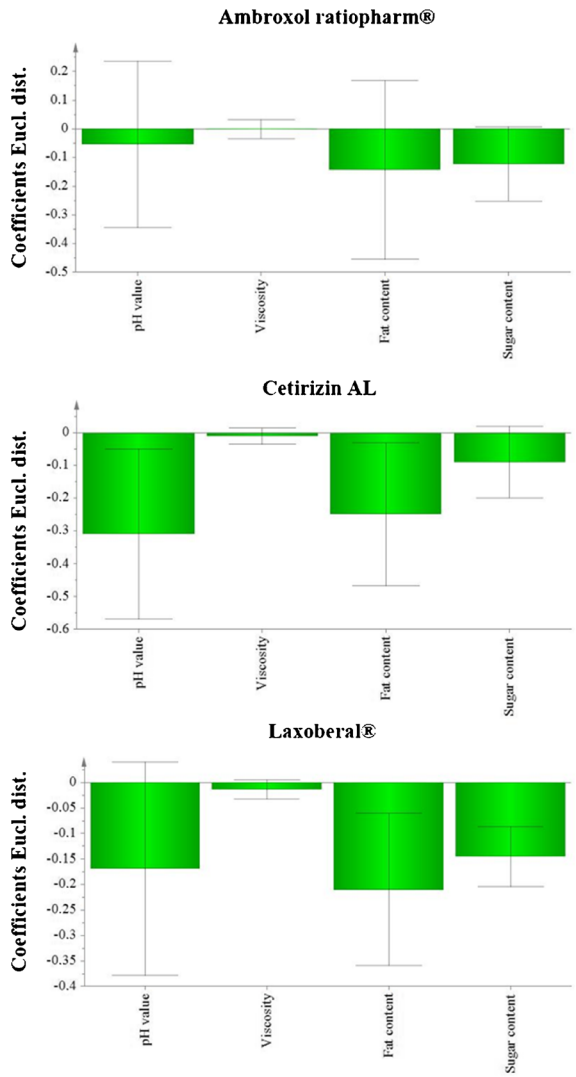

Fig. 5. Coefficient plots of the PLS models for Ambroxol-ratiopharm®, Cetirizin AL, and Laxoberal® showing the correlation of the X-variables pH value, viscosity, fat content and sugar content on the Eucidean distances, ctr scaled

As calculated, miLogP (method for logP prediction developed at Molinspiration (36)) values of ambroxol HCl were around 0 (−0.08) and lower compared to according values of cetirizine dihydrochloride (−0.14) and sodium picosulfat (−1.84), differing impact of the fat content is reasonable.

Remodeling the coefficient plot without the viscosity parameter, showing no significant correlation with the Euclidean distances, does not lead change the above mentioned findings.

Suitability of Electronic Tongue Sensors for Taste-Masking Assessment

Evaluating the taste-masking capability of several application media demonstrates the diverse applicability of electronic tongue sensors, in particular considering the different physico-chemical properties of the applied beverages. In the recent study, sensor membranes have been exposed to similar properties and conditions as the taste buds in the mouth. Based on their robustness on the one hand but sensitivity on the other hand, electronic tongue sensors are assessed as very suitable for taste-masking assessment considering physico-chemical properties of the applied beverages: one of the commercial sensors is dedicated to sourness (SB2AC0). Thus, one could have expected more significant impact of the pH value on the results—but the single sensor response is neglected due to the non-specificity of the sensor array (26). Although, sweeteners can to some extend be measured with electronic tongues (37–39), taste-masking is rather affected depending on molar amounts and ionic structure of sweetener than their sweetening potency (40,41). Fat dispersed in water compared to pure water also shows different sensor signals (42), while viscosity does not interfere with electronic tongue results (35). Considering our results, a higher fat content significantly influenced the results

of Laxoberal® and Cetirizin AL. The higher the sugar content, the higher the impact on taste-masking results—although this finding was only significant in case of Laxoberal®, a correlative trend could be seen for each of the three OTCs. According to the above-discussed results, this cannot be due to a resulting higher viscosity, since viscosity did not interfere with the obtained results. This finding might be of double interest for further e-tongue studies: one the one hand, it is so far recommended to avoid measurements in higher viscous media, but no issues (including shelf life issues) appeared. Moreover, if increased viscosity is not the explanation for the high impact of the sugar content on taste-masking, a co-sensitivity of e-tongue sensors for sugar in the presence of some drugs seems to exist and should be further evaluated. And as sweetness is the most convincing factor for children to take their medication, electronic tongue sensors have proven to be suitable for taste-masking assessment in the recent study.

CONCLUSION

The taste-masking efficiency of eight different beverages used as application liquids for the OTC pharmaceuticals Ambroxol-ratiopharm®, Cetirizin AL, and Laxoberal® was correlated to the physico-chemical properties of the liquids. As a quintessence, milk-based and sugar-containing media showed the best taste-masking efficiencies for all pediatric pharmaceuticals even if the impact of the pH value, the viscosity as well as the sugar and fat content of those media showed varying impacts on the taste-masking capability. The ability of the applied e-tongue sensors to point out the different correlations between the physico-chemical properties of the application media and their taste-masking efficiency demonstrate their suitability in taste-masking assessment.

REFERENCES

1. Strickley RG, Iwata Q, Wu S, Dahl TC. Pediatric drugs—review of commercially available oral formulations. J Pharm Sci. 2008;97(5):1731–74.
2. Akram G, Mullen AB. Paediatric nurses' knowledge and practice of mixing medication into foodstuff. Int J Pharm Pract. 2012;20(3):191–8. doi:10.1111/j.2042-7174.2011.00179.x.
3. Klingmann V, Spomer N, Lerch C, Stoltenberg I, Frömke C, Bosse HM, *et al*. Favorable acceptance of mini-tablets compared with syrup: a randomized controlled trial in infants and preschool children. J Peds. 2013;163(6):1728–32. doi:10.1016/j.jpeds.2013.07.014.
4. Sam T, Ernest TB, Walsh J, Williams JL. A benefit/risk approach towards selecting appropriate pharmaceutical dosage forms—an application for paediatric dosage form selection. Int J Pharm. 2012;435(2):115–23.
5. Milne CP, Bruss JB. The economics of pediatric formulation development for off-patent drugs. Clin Ther. 2008;30(11):2133–45. doi:10.1016/j.clinthera.2008.11.019.
6. Matsui D. Assessing the palatability of medications in children. Paediatr Perinat Drug Ther. 2007;8(2):55–60. doi:10.1185/146300907X178941.
7. Sohi H, Sultana Y, Khar RK. Taste masking technologies in oral pharmaceuticals: recent developments and approaches. Drug Dev Ind Pharm. 2004;30(5):429–48.
8. Cram A, Breitkreutz J, Desset-Brèthes S, Nunn T, Tuleu C. Challenges of developing palatable oral paediatric formulations. Int J Pharm. 2009;365(1–2):1–3. doi:10.1016/j.ijpharm.2008.09.015.
9. Davies EH, Tuleu C. Medicines for children: a matter of taste. J Ped. 2008;153(5):599–604. doi:10.1016/j.jpeds.2008.06.030.
10. Kozarewicz P. Regulatory perspectives on acceptability testing of dosage forms in children. Int J Pharm. 2014;469(2):245–8. doi:10.1016/j.ijpharm.2014.03.057.
11. Walsh J, Cram A, Woertz K, Breitkreutz J, Winzenburg G, Turner R, *et al*. Playing hide and seek with poorly tasting paediatric medicines: do not forget the excipients. Adv Drug Deliv Rev. 2014;73:14–33. doi:10.1016/j.addr.2014.02.012.
12. Anand V, Kataria M, Kukkar V, Saharan V, Choudhury PK. The latest trends in the taste assessment of pharmaceuticals. Drug Discov Today. 2007;12(5–6):257–65. doi:10.1016/j.drudis.2007.01.010.
13. Momin M. Taste masking techniques for bitter drugs-an overview. Int J Pharm Technol. 2012;4(2):2100–18.
14. Coupland JN, Hayes JE. Physical approaches to masking bitter taste: lessons from food and pharmaceuticals. Pharm Res. 2014;31(11):2921–39. doi:10.1007/s11095-014-1480-6.
15. Kaushik D, Dureja H. Recent patents and patented technology platforms for pharmaceutical taste masking. Recent Pat Drug Deliv Formul. 2014;8(1):37–45. doi:10.2174/1872211308666140206150840.
16. Zajicek A, Fossler MJ, Barrett JS, Worthington JH, Ternik R, Charkoftaki G, *et al*. A report from the pediatric formulations task force: perspectives on the state of child-friendly oral dosage forms. AAPS J. 2013;15(4):1072–81. doi:10.1208/s12248-013-9511-5.
17. KG BIPGC. Laxoberal® Abführ Tropfen. Gebrauchsinformation. 2013.
18. GmbH r. Ambroxol-ratiopharm® Hustentropfen. Gebrauchsinformation. 2014.
19. Thompson CA, Lombardi DP, Sjostedt P, Squires LA. Industry survey on current practices in the assessment of palatability and swallowability in the development of pediatric oral dosage forms. Ther Innov Regul Sci. 2013;47(5):542–9. doi:10.1177/2168479013500287.
20. Vlasov Y, Legin A, Rudnitskaya A, Di Natale C, D'Amico A. Nonspecific sensor arrays ("electronic tongue") for chemical analysis of liquids: (IUPAC technical report). Pure Appl Chem. 2005;77(11):1965–83. doi:10.1351/pac200577111965.
21. Ito M, Ikehama K, Yoshida K, Haraguchi T, Yoshida M, Wada K, *et al*. Bitterness prediction of H1-antihistamines and prediction of masking effects of artificial sweeteners using an electronic tongue. Int J Pharm. 2013;441(1–2):121–7. doi:10.1016/j.ijpharm.2012.11.047.
22. Maniruzzaman M, Douroumis D. An in-vitro-in-vivo taste assessment of bitter drug: comparative electronic tongues study. J Pharm Pharmacol. 2015;67(1):43–55. doi:10.1111/jphp.12319.
23. Nakamura H, Uchida S, Sugiura T, Namiki N. The prediction of the palatability of orally disintegrating tablets by an electronic gustatory system. Int J Pharm. 2015;493(1–2):305–12. doi:10.1016/j.ijpharm.2015.07.056.
24. Kobayashi Y, Habara M, Ikezazki H, Chen R, Naito Y, Toko K. Advanced taste sensors based on artificial lipids with global selectivity to basic taste qualities and high correlation to sensory scores. Sensors. 2010;10(4):3411–43. doi:10.3390/s100403411.
25. Preis M, Grother L, Axe P, Breitkreutz J. In-vitro and in-vivo evaluation of taste-masked cetirizine hydrochloride formulated in oral lyophilisates. Int J Pharm. 2015;491(1–2):8–16. doi:10.1016/j.ijpharm.2015.06.002.
26. Woertz K, Tissen C, Kleinebudde P, Breitkreutz J. Performance qualification of an electronic tongue based on ICH guideline Q2. J Pharm Biomed Anal. 2010;51(3):497–506. doi:10.1016/j.jpba.2009.09.029.
27. National Nutrient Database for Standard Reference Release 28 [Internet]. 2016. Available from: http://ndb.nal.usda.gov/ndb/search/list, accessed 27 Jan 2016.
28. Sadrieh N, Brower J, Yu L, Doub W, Straughn A, MacHado S, *et al*. Stability, dose uniformity, and palatability of three counterterrorism drugs—human subject and electronic tongue studies. Pharm Res. 2005;22(10):1747–56. doi:10.1007/s11095-005-6387-x.
29. Keast RSJ. Modification of the bitterness of caffeine. Food Qual Prefer. 2008;19(5):465–72. doi:10.1016/j.foodqual.2008.02.002.

30. Roberts IF, Roberts GJ. Relation between medicines sweetened with sucrose and dental disease. Br Med J. 1979;2(6181):14–6. doi:10.1136/bmj.2.6181.14.
31. Metcalf KL, Vickers ZM. Taste intensities of oil-in-water emulsions with varying fat content. J Sens Stud. 2002;17(5):379–90. doi:10.1111/j.1745-459X.2002.tb00354.x.
32. Mackey A. Discernment of taste substances as affected by solvent medium. J Food Sci. 1958;23(6):580–3. doi:10.1111/j.1365-2621.1958.tb17607.x.
33. Liem DG, Mennella JA. Heightened sour preferences during childhood. Chem Sens. 2003;28(2):173–80. doi:10.1093/chemse/28.2.173.
34. Paddock Laboratories L. ORA-BLEND®SF Flavored Sugar-Free Oral Suspending Vehicle. Available from: http://www.perrigo.com/files/rx/pdfs/pds172-Ora%20Blend%20SF%20Sell%20Sheet.pdf, accessed 27 Jan 2016.
35. Woertz K, Tissen C, Kleinebudde P, Breitkreutz J. Development of a taste-masked generic ibuprofen suspension: top-down approach guided by electronic tongue measurements. J Pharm Sci. 2011;100(10):4460–70. doi:10.1002/jps.22629.
36. Calculation of Molecular Properties and Bioactivity Score [Internet]. Molinspiration Cheminformatics. Available from: http://www.molinspiration.com/cgi-bin/properties, accessed 27 Jan 2016.
37. Yasuura M, Okazaki H, Tahara Y, Ikezaki H, Toko K. Development of sweetness sensor with selectivity to negatively charged high-potency sweeteners. Sens Actuator, B: Chem. 2014;201:329–35. doi:10.1016/j.snb.2014.04.087.
38. Yasuura M, Tahara Y, Ikezaki H, Toko K. Development of a sweetness sensor for aspartame, a positively charged high-potency sweetener. Sensors (Switzerland). 2014;14(4):7359–73. doi:10.3390/s140407359.
39. Toyota K, Cui H, Abe K, Habara M, Toko K, Ikezaki H. Sweetness sensor with lipid/polymer membranes: response to various sugars. Sensor Mater. 2011;23(8):475–82.
40. Choi DH, Kim NA, Nam TS, Lee S, Jeong SH. Evaluation of taste-masking effects of pharmaceutical sweeteners with an electronic tongue system. Drug Dev Ind Pharm. 2014;40(3):308–17. doi:10.3109/03639045.2012.758636.
41. Woertz K, Tissen C, Kleinebudde P, Breitkreutz J. Rational development of taste masked oral liquids guided by an electronic tongue. Int J Pharm. 2010;400(1–2):114–23. doi:10.1016/j.ijpharm.2010.08.042.
42. Eckert C, Pein M, Breitkreutz J. Lean production of taste improved lipidic sodium benzoate formulations. Eur J Pharm Biopharm. 2014;88(2):455–61. doi:10.1016/j.ejpb.2014.05.013.