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Quantitative Evaluation of Bitterness of H_1-Receptor Antagonists and Masking Effect of Acesulfame Potassium, an Artificial Sweetener, Using a Taste Sensor

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The objective of this study was to evaluate quantitatively the bitterness of eight H_1-receptor antagonists and to predict the bitterness-masking effect of adding acesulfame potassium, an artificial sweetener, to epinastine hydrochloride and cetirizine dihydrochloride, as representative H_1-receptor antagonists, using a taste sensor. The bitterness of eight H_1-receptor antagonists was evaluated using a highly sensitive sensor, BT0. On the basis of multiple regression analysis with three variables, relative value (*R*), change in membrane potential caused by adsorption (*CPA*), and adsorption ability (*CPA*/*R*), a good correlation was found between the estimated bitterness scores measured using the taste sensor and the actual bitterness scores obtained by human sensory testing with only one exception. The bitterness-masking effect of epinastine hydrochloride with acesulfame potassium could be predicted using a different taste sensor, C00, which is sensitive to acesulfame potassium. Good predictability was not observed for cetirizine dihydrochloride with the same sweetener. Using sensor CA0, which is sensitive to acidic taste, cetirizine dihydrochloride was predicted to have a sour taste, which may be derived from its dihydrochloride salt. Finally, principal component analysis using data from sensors BT0 and CA0 for all the drugs enabled the eight H_1-receptor antagonists to be classified into three groups on the basis of their taste characteristics. This grouping may be used to characterize basic bitter drugs and provide a useful guide for the selection of appropriate taste-masking approaches.

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1. Introduction

Taste sensors are composed of a number of functional sensors with artificial lipid membranes of different compositions.[1,2] Each sensor is capable of identifying a specific taste, i.e., saltiness, sourness, sweetness, bitterness, and umami, similarly to human gustatory sensation. The taste of various foods and beverages (*e.g.*, coffee, beer, mineral water, milk, rice, and vegetables) has been evaluated using taste sensors. In the pharmaceutical industry, bitterness evaluation using taste sensors is also attracting increasing attention.[3–5] Bitterness evaluation studies have been reported for various basic bitter drugs, such as quinine hydrochloride.[6–8] In addition, we have recently reported a quantitative analytical method of evaluating the bitterness of antibiotics such as clarithromycin,[9] Chinese medicines,[10] and bitterness-masked famotidine orally disintegrating tablets.[11] In many cases, it seemed to be advantageous to predict bitterness intensity using a particular type of taste sensor.

H_1-receptor antagonists are widely used in the treatment of histamine-mediated allergic conditions. Most H_1-receptor antagonists are bitter, which can hinder therapeutic management and lead to patient noncompliance. The quantitative and qualitative prediction of bitterness without conducting human sensory testing would be very valuable in the early stages of formulation development. We have recently reported a method of evaluating the bitterness of eight H_1-receptor antagonists using a new bitterness sensor, BT0, with high sensitivity, and this methodology may be promising for a more precise bitterness prediction for drug substances.[12] A method of quantitatively evaluating bitterness has not yet been established.

Since the palatability of drug products has become increasingly important recently, bitterness-masking is becoming an essential component of pharmaceutical development, particularly for orally disintegrating tablets or dry syrups containing a bitter drug substance. Bitterness-masking technologies have been developed using various methods, but can generally be classified into three approaches: physical masking, chemical masking, and masking using sweeteners or flavoring. Physical masking, such as pellet coating with polymers, is one of the most popular methods.[13,14] Chemical masking, by forming a complex between a cyclodextrin and the bitter substance is also widely used.[15,16] The addition of sweeteners is the most conventional approach to bitterness-masking, although the mechanism of bitterness suppression using this method has not yet been fully explained. Therefore, an objective method of predicting a bitterness-masking effect using sweeteners has not been established. The prediction of bitterness-masking using artificial supersweeteners, such as aspartame, acesulfame potassium, and sucralose, is a further challenge for technical reasons, as specific sensors have not yet been developed for the detection of these types of artificial sweetener. However, acesulfame potassium, for example, can be detected using certain sensors, such as C00 or AE1, which were not developed for the detection of sweetness.

In this study, the taste of eight H_1-receptor antagonists was evaluated using the sensor BT0, and the accuracy of bitterness prediction achieved was verified by human sensory testing. Furthermore, the bitterness-masking effect achieved by adding acesulfame potassium was evaluated using acesulfame potassium-sensitive sensors.

Epinastine hydrochloride and cetirizine dihydrochloride, representative H_1-receptor antagonists, were used for this study, because these two drugs were expected to have different bitterness characteristics. The acidity of cetirizine dihydrochloride was also evaluated using the sensor CA0, which is sensitive to the acidic taste. Finally, principal component analysis using data from sensors BT0 and CA0 for all the drugs enabled the classification of eight H_1-receptor antagonists into three groups on the basis of their taste characteristics.

2. Materials and Methods

2.1 *Chemicals*

Quinine hydrochloride and eight H_1-receptor antagonists, cetirizine dihydrochloride, diphenhydramine hydrochloride, chlorpheniramine maleate, epinastine hydrochloride, ketotifen fumarate, olopatadine hydrochloride, fexofenadine hydrochloride, and azelastine hydrochloride were purchased from Wako Pure Chemical Industries, Ltd., Osaka, Japan. Acesulfame potassium was purchased from Kirin Kyowa Foods Co., Ltd., Tokyo, Japan. All other reagents were of special reagent grade.

2.2 *Taste-sensing system*

The taste-sensing system, SA402B, of Intelligent Sensor Technology Inc. (Atsugi, Japan) was used to measure the electric potential of sample solutions. An overview of the taste-sensing system is shown in Fig. 1. The detector of the equipment, which is attached to a mechanically controlled robot arm, consists of a reference electrode and

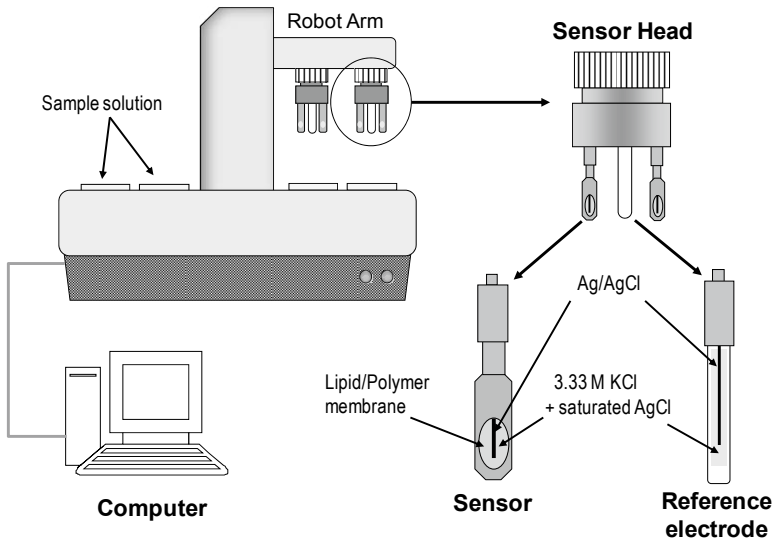


Fig. 1. Overview of the taste-sensing system (SA402B).

multiple sensors functioning as working electrodes. Four different types of sensor, BT0, AE1, CA0, and C00, were used in this study. The sensor BT0 is a new and improved bitterness sensor, developed especially to detect basic bitter materials. The sensor CA0 is typically used for sourness, which is derived from acidic materials. The sensors C00 and AE1 were used to detect the taste of acesulfame potassium in this study.

Each sensor is composed of a unique artificial lipid-based membrane. The lipid components of the sensors are listed in Table 1. A Ag/AgCl electrode and an inner solution containing 3.33 M KCl and saturated AgCl were used for the reference electrode and sensors. When the taste substances are adsorbed by the sensors, a change in potential occurs in the artificial lipid membrane, in the same manner as in the human tongue. The difference between the electric potential of the working electrode and that of the reference electrode was measured using a high-input impedance amplifier connected to a computer.

The procedure used to measure the sensor output values produced by the adsorption of the samples is summarized in Fig. 2. In the first step, a reference solution (corresponding to saliva) is measured and the electric potential obtained (mV) is defined as V_r. Then a sample solution is measured and the electric potential is defined as Vs. The relative sensor output is represented by the difference ($V_s \pm V_r$) between the potentials of the sample and the reference solution. The electrodes are subsequently rinsed with a fresh reference solution for 6 s. When the electrode is dipped into the reference solution again, the new potential of the reference solution is defined as V_{r0}. The difference ($V_{r0} \pm V_r$) between the potentials of the reference solution before and after sample measurement is the change in the membrane potential caused by adsorption (*CPA*) and corresponds to the so-called 'aftertaste'. The *CPA* value is used for the bitterness evaluation when using the sensor BT0. In this experiment, the measurement time was set at 30 s. After the measurement of each sample, the electrodes are rinsed first with 30% (v/v) ethanol for 90 s and then with a fresh reference solution for 240 s. The rinsing steps are intended to exclude cross-contamination between samples, and are performed after each set of measurements. The measurement of each sample is repeated four times and the average value of the last three measurements is used in the data analysis.

Table 1
Lipid components of the sensor membranes.

Sensor	Lipid	Plasticizer
BT0 (Bitterness, basic)	Phosphoric acid didodecyl ester	Bis (1-butylpentyl) adipate Tributyl o-acetylcitrate
CA0 (Sourness)	Phosphoric acid di(2-ethylhexyl) ester oleic acid Trioctylmethyl ammonium chloride	Dioctyl phenylphosphonate
C00 (Acesulfame K)	Tetradodecyl ammonium bromide	2-Nitrophenyl octyl ether
AE1 (Acesulfame K)	Tetradodecyl ammonium bromide	Di-*n*-octyl phenylphosphonate

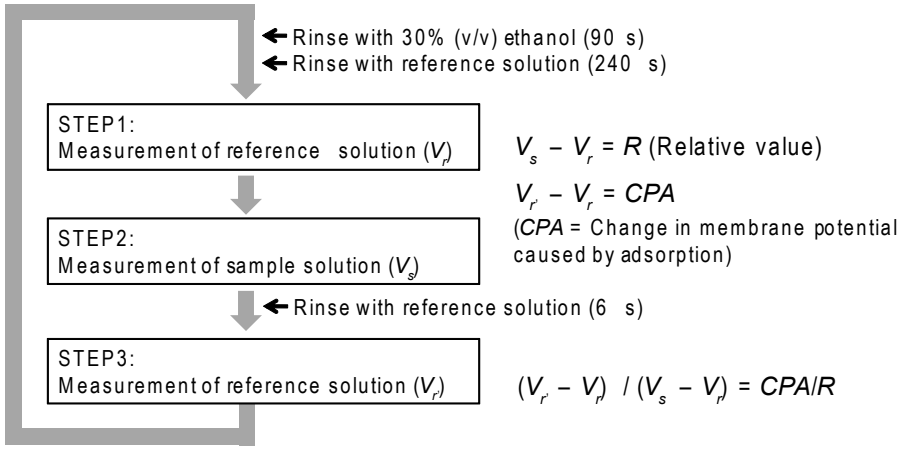


Fig. 2. Taste measurement procedure.

2.3 *Sensory evaluation of bitterness of H_1-receptor antagonists*

The sensory tests were performed by 11 well-trained volunteers according to the previously reported method.[17] Quinine hydrochloride was used as the standard for bitterness, using concentrations of 0.01, 0.03, 0.10, 0.30, and 1.00 mM with the bitterness scores of 0, 1, 2, 3, and 4, respectively. Before testing, the volunteers were instructed to keep 2 ml of the above-mentioned quinine hydrochloride solutions in their mouths and were told the bitterness scores. They were then asked to give bitterness scores for each of the test sample solutions. The test sample solutions were kept in the mouth for 15 s. After tasting each sample, the subjects gargled well and waited for at least 20 min before tasting the next sample. All the sensory tests were performed at Mukogawa Women's University. The protocol and experimental designs were approved by the ethical committee of the university.

2.4 *Sensory evaluation of bitterness suppression using acesulfame potassium*

The sensory tests were performed by 11 well-trained volunteers. Quinine hydrochloride was used as the standard for bitterness, and the concentrations were 0.013, 0.020, 0.030, 0.045, 0.067, and 0.100 mM with the bitterness scores of 1, 2, 3, 4, 5, and 6, respectively. The testing was then performed as described in § 2.3. All the sensory tests were performed at Mukogawa Women's University. The protocol and experimental designs were approved by the ethical committee of the university.

2.5 *Sample preparation*

For the taste-sensing system, the drug substances and sweeteners were completely dissolved in 10 mM KCl aqueous solution. The reference solution, corresponding to saliva, which is tasteless, was composed of 30 mM KCl and 0.3 mM tartaric acid.

For the sensory test, the concentrations of quinine hydrochloride and H_1-receptor antagonist solutions were fixed at 0.1 mM. The final concentration of acesulfame

potassium was fixed between 0.015–0.50 mg/ml.

2.6 *Method of simulating bitterness-masking effect*

The bitterness-masking effect with sweeteners was simulated using software developed and provided by Intelligent Sensor Technology Inc. (Atsugi, Japan). The software can be used to calculate bitterness scores of quinine hydrochloride solutions containing sweeteners, such as sucrose, aspartame, acesulfame potassium, and sucralose without human sensory testing. To simulate the bitterness scores of the test sample solutions containing acesulfame potassium, the bitterness intensities of the drugs were converted into bitterness intensities of quinine hydrochloride.

3. Results and Discussion

3.1 *Predictability of bitterness intensities of H_1-receptor antagonists using the taste sensor*

The bitterness of eight H_1-receptor antagonists was evaluated using the sensors BT0. Three variables, relative value (R), change in membrane potential caused by adsorption (CPA), and adsorption rate (CPA/R), were used in the data analysis. The bitterness evaluation results obtained from the taste sensors are summarized in Table 2. Multiple regression analysis was applied to the data to calculate estimated bitterness scores. The general model equation for bitterness can be represented as

$$Y = aX_1+bX_2+cX_3+\ldots+zX_z,$$

where Y is the estimated bitterness score and X_n is an explanatory variable.

Figure 3 shows the results of multiple regression analysis using R, CPA, and CPA/R as explanatory variables. As shown in Fig. 3(a), overall, no good relationship between the estimated and actual bitterness scores was found. This is because diphenhydramine

Table 2
Bitterness scores and taste sensor results for quinine hydrochloride and H_1-receptor antagonist solutions (0.1 mM).

Drug	Bitterness score by sensory test	Taste sensor output (Sensor BT0)		
		R	*CPA*	*CPA*/*R*
Quinine hydrochloride	2.00	50.43	31.98	0.63
Cetirizine dihydrochloride	0.36	76.62	24.82	0.32
Diphenhydramine hydrochloride	0.45	66.16	40.63	0.61
Chlorpheniramine maleate	1.00	68.29	30.22	0.44
Epinastine hydrochloride	1.82	58.19	29.14	0.50
Ketotifen fumarate	1.18	49.91	22.89	0.46
Olopatadine hydrochloride	0.73	38.08	15.74	0.41
Fexofenadine hydrochloride	1.18	73.90	41.56	0.56
Azelastine hydrochloride	3.27	73.22	58.56	0.80

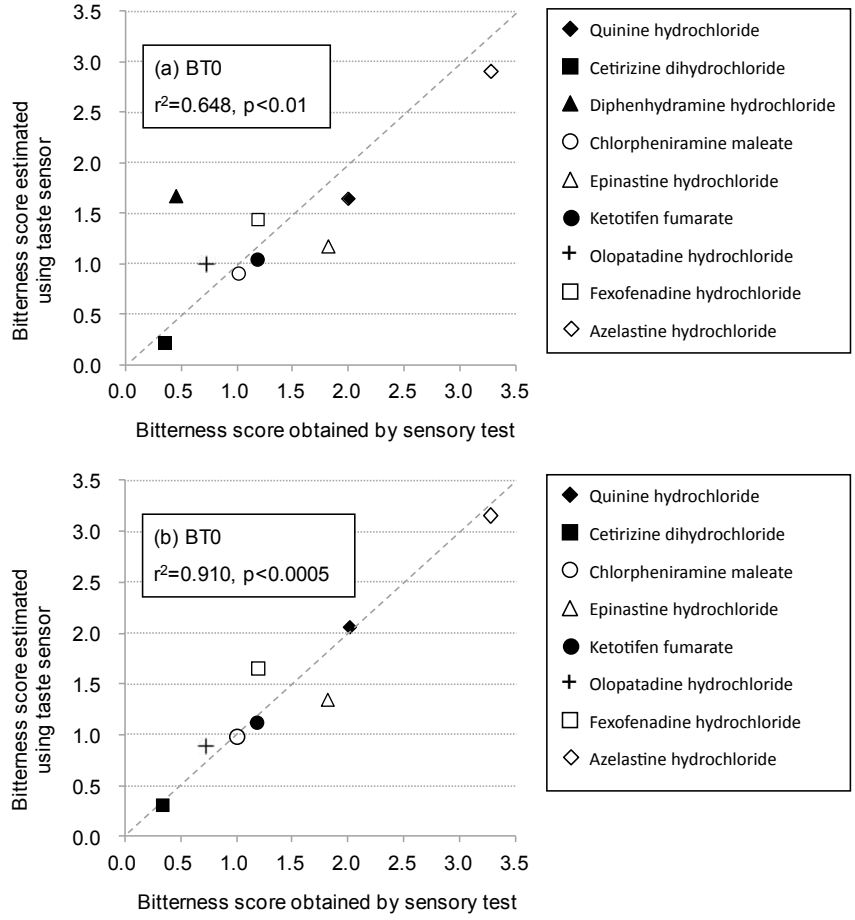


Fig. 3 Multiple regression analysis results using *R*, *CPA*, and *CPA*/*R* values measured with sensor BT0. (a) Test drug substances: quinine hydrochloride and eight H_1-receptor antagonists; (b) quinine hydrochloride and seven H_1-receptor antagonists, excluding diphenhydramine hydrochloride.

hydrochloride showed a relatively low bitterness score in human sensory testing, although a high sensor output was observed in the taste sensor. We have not yet determined the reason for this, although we suspect that a physicochemical characteristic of diphenhydramine hydrochloride, due to its structure, might be responsible. Figure 3(b) shows the multiple regression analysis results excluding those for diphenhydramine hydrochloride. A good correlation was observed between the estimated and actual bitterness scores. The predictability of bitterness intensity obtained using the taste sensor is considered to be acceptable for practical use with various types of H_1-receptor antagonist.

3.2 *Detection of acesulfame potassium using taste sensor*

To predict the bitterness-masking effect of sweeteners using the taste sensor, acesulfame potassium solutions were measured with three different types of sensor, C00, AE1, and BT0. The sensor outputs are summarized in Table 3. Acesulfame potassium was detected using sensors C00 and AE1. Sensor C00 showed good linearity, even at lower concentrations (0.015 mg/ml), whereas a decreased output was observed in sensor AE1. Based on these results, it was decided to use sensor C00 in further testing. Sensor BT0 was not affected by acesulfame potassium; this may be useful when a bitter substance is to be measured at the same time.

3.3 *Suppression of bitterness by sweetener*

Table 4 shows the bitterness scores of epinastine hydrochloride and cetirizine dihydrochloride solutions containing acesulfame potassium obtained by human sensory testing. Figure 4 shows the results of single regression analysis with the R value measured using sensor C00 as an explanatory variable. A good correlation was observed between the estimated bitterness scores and the actual bitterness scores obtained by human sensory testing. Since cetirizine dihydrochloride has a lower intensity of bitterness anyway, the evaluation of a suppression effect was less accurate, as the bitterness score obtained by human taste testing is already low. As 0.050 mg/ml of acesulfame potassium was already sufficient to mask bitterness, substances with bitterness scores below 1.5 were sweet enough to reduce bitterness scores. Nevertheless,

Table 3
Sensor outputs of acesulfame potassium.

Concentration of acesulfame potassium (mg/ml)	Sensor output of acesulfame potassium (mV)		
	C00 (R)	AE1 (R)	BT0 (R)
0.015	–61.09	–34.14	N.D.
0.050	–83.67	–89.24	N.D.
0.150	–106.95	–121.48	N.D.
0.500	–133.22	–151.45	N.D.

N.D.: not detected

Table 4
Bitterness scores of epinastine hydrochloride and cetirizine dihydrochloride solutions (0.1 mM) with acesulfame potassium obtained by human sensory testing.

Concentration of acesulfame potassium (mg/ml)	Bitterness score of epinastine hydrochloride	Bitterness score of cetirizine dihydrochloride
—	5.1	1.8
0.015	3.5	1.7
0.050	2.8	1.4
0.150	2.2	1.4
0.500	1.3	1.1

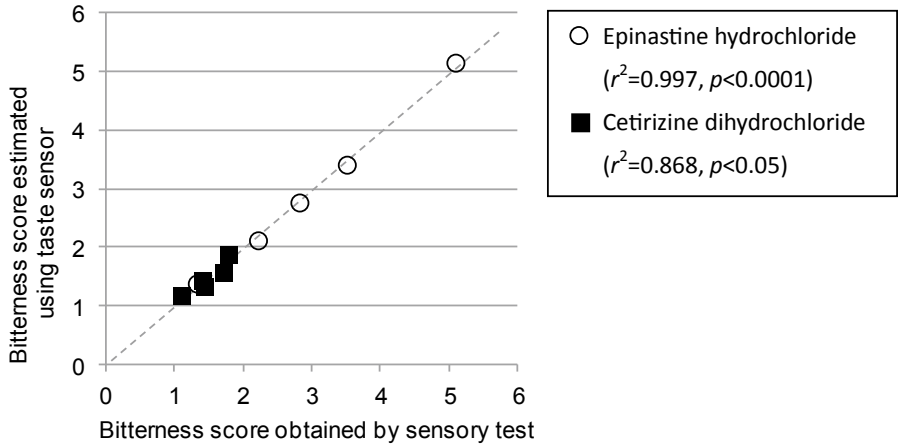


Fig. 4. Single regression analysis results using R value measured with sensor C00. Test drug substances: epinastine hydrochloride and cetirizine dihydrochloride.

the qualitative prediction of the bitterness-masking effect of acesulfame potassium on cetirizine dihydrochloride using the taste sensor is considered to be unreliable.

3.4 *Simulation of bitterness-masking effect of sweetener*

To simulate the bitterness scores of the test sample solutions containing acesulfame potassium using simulation software, the bitterness intensities of the drug substances were converted into the bitterness intensity equivalents of quinine hydrochloride. Figure 5 shows the relationship between concentrations (a: quinine hydrochloride, b: epinastine hydrochloride) and the CPA values measured with the sensor BT0.

Good correlations were found between these variables, and the following equations were derived.

$$Y = 56.2 \times \log C_q + 98.7, \quad (1)$$

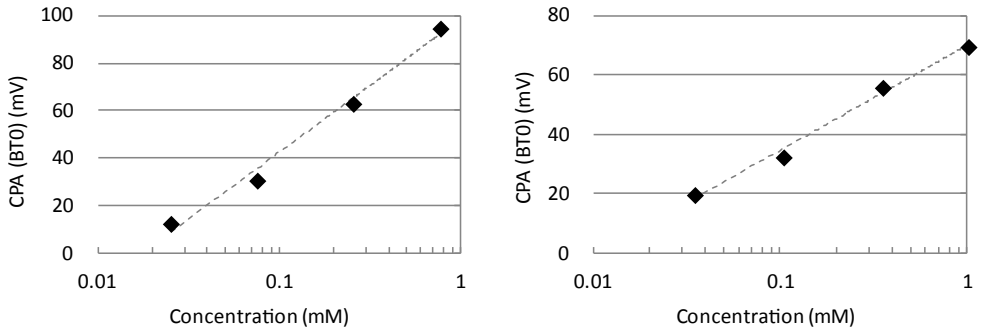
$$Y = 35.1 \times \log C_e + 69.5. \quad (2)$$

Here, Y = *CPA* value (BT0), C_q = quinine hydrochloride (mM), C_e = epinastine hydrochloride (mM)

According to eqs. (1) and (2), the concentration of epinastine hydrochloride can be converted into quinine hydrochloride equivalents using the following equation.

$$\log C_q = 0.62 \times \log C_e - 0.52 \quad (3)$$

Cetirizine dihydrochloride was also converted similarly. Table 5 shows the estimated bitterness scores of epinastine hydrochloride and cetirizine dihydrochloride solutions



(a) (b)

Fig. 5. Relationship between concentrations (a: Quinine hydrochloride, b: Epinastine hydrochloride) and *CPA* values measured with sensor BT0.

Table 5
Bitterness scores of epinastine hydrochloride and cetirizine dihydrochloride solutions (0.1 mM) with acesulfame potassium obtained using simulation software and human sensory testing.

Concentration of acesulfame potassium (mg/ml)	Bitterness score of epinastine hydrochloride		Bitterness score of cetirizine dihydrochloride	
	Simulated	Actual	Simulated	Actual
0.015	5.19	3.5	4.90	1.7
0.050	4.55	2.8	4.26	1.4
0.150	3.79	2.2	3.50	1.4
0.500	2.95	1.3	2.66	1.1

containing acesulfame potassium, calculated using the simulation software.

The relationship between the simulated and actual bitterness scores is shown in Fig. 6. A good correlation was observed for epinastine hydrochloride, and the efficacy of acesulfame potassium for bitterness-masking could be correctly predicted using the simulation software. On the other hand, for cetirizine dihydrochloride, the estimated bitterness scores did not reflect the actual bitterness. This seems to be due to the different taste characteristics of epinastine hydrochloride and cetirizine dihydrochloride.

3.5 *Sourness evaluation*

To investigate the taste characteristics of cetirizine dihydrochloride, the sourness intensities of the drugs were evaluated. The *R* value measured with the sensor CA0 represents sourness intensity. Epinastine hydrochloride and cetirizine dihydrochloride were therefore evaluated, with quinine hydrochloride and tartaric acid as references, using sensor CA0. Figure 7 shows the *R* values of the sample solutions. The sensor showed increased output depending on the tartaric acid concentration, but did not respond to bitter substances. Therefore, it is highly suitable for the evaluation of

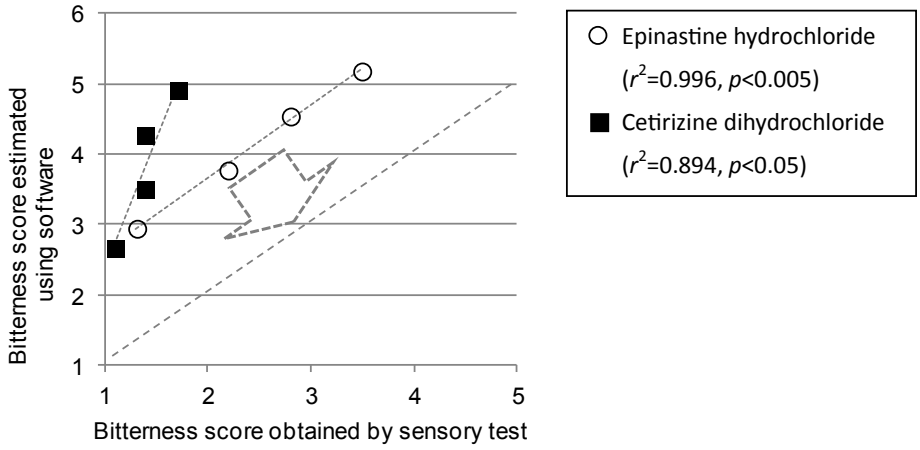


Fig. 6. Single regression analysis results: relationship between simulated and actual bitterness scores of epinastine hydrochloride (open circles) and cetirizine dihydrochloride (filled squares) containing acesulfame potassium.

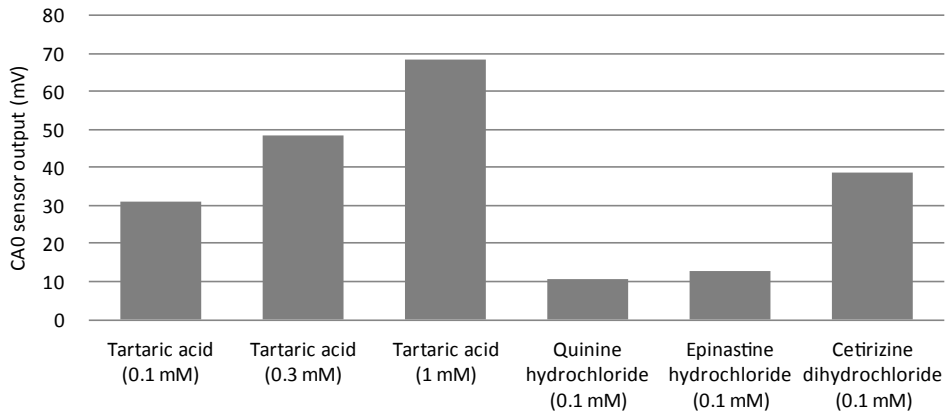


Fig. 7. *R* values of the various sample solutions measured with the sensor CA0.

sourness in bitter drug substances. Cetirizine dihydrochloride showed a higher sourness intensity, comparable to that of tartaric acid, while epinastine hydrochloride was not very sour. This sourness seems to be derived from the dihydrochloride salt form of cetirizine.

To evaluate the interaction between bitterness and sourness, the bitterness of the quinine hydrochloride solution containing tartaric acid was evaluated with sensor BT0. Figure 8 shows the *CPA* and *CPA*/*R* values of quinine hydrochloride solutions containing different amounts of tartaric acid. The data confirm that tartaric acid substantially

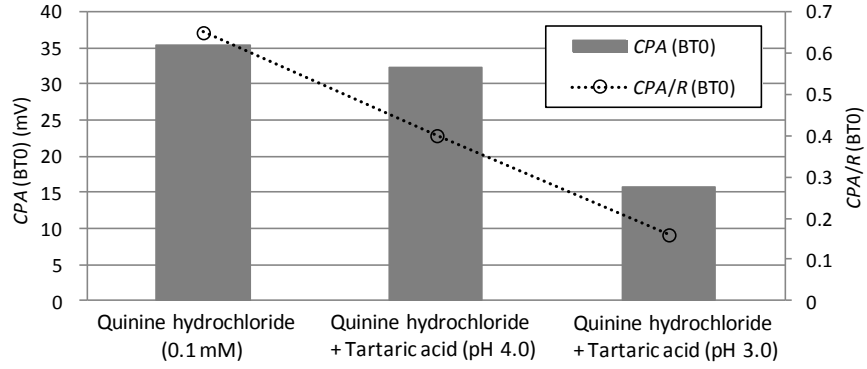


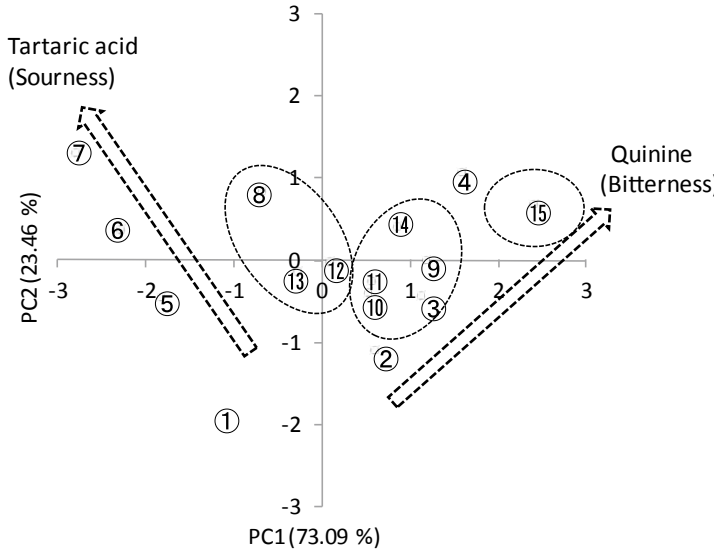
Fig. 8. *CPA* and *CPA*/*R* values of quinine hydrochloride solutions containing different amounts of tartaric acid measured with sensor BT0.

reduces the bitterness of quinine hydrochloride. Based on these results, it was concluded that the bitterness of cetirizine dihydrochloride is suppressed by the sourness of the salt. The ability to evaluate sourness is considered to be valuable, even in the bitterness evaluation of basic bitter substances.

3.6 *Principal component analysis for characterization of taste of H_1-receptor antagonists*

Principal component analysis (PCA) is a multivariate analytical method that reduces the dimensional space without losing any information. As reported in previous studies,[18,19] using PCA for the discrimination of the taste sensor output provides a better understanding of the obtained data. Three variables were used in the PCA, *CPA*, and *CPA*/*R* obtained from sensor BT0 and *R* obtained from sensor CA0 for all the eight H_1-receptor antagonists at 0.1 mM, plus three different concentrations of quinine hydrochloride and tartaric acid solutions as references of bitterness and sourness, respectively.

The PCA result is shown in Fig. 9. The relative contributions of PC1 and PC2 are described in the chart. Factors PC1 and PC2 can be assumed to represent the bitterness and sourness intensities, respectively. The bitterness of quinine hydrochloride, the standard for bitterness, moves to the upper right side with increasing concentration, while the sourness of tartaric acid, the standard for sourness, moves to the upper left side. The eight H_1-receptor antagonists can be divided into three groups: group A (diphenhydramine, chlorpheniramine, epinastine, and fexofenadine), group B (cetirizine, ketotifen, and olopatadine), and group C (azelastine). These groupings represent different combinations of the taste characteristics of bitterness and sourness. It can be interpreted as follows: group A, a moderately bitter drug group, has a similar taste to quinine hydrochloride; group B, a slightly bitter or sour drug group, and group C, a very bitter drug group, have



① 10 mM KCl (tasteless) ② Quinine (0.01 mg/ml) ③ Quinine (0.03 mg/ml) ④ Quinine (0.1 mg/ml)
⑤ Tartaric acid (0.01 mM) ⑥ Tartaric acid (0.03 mM) ⑦ Tartaric acid (0.1 mM)
⑧ Cetirizine ⑨ Diphenhydramine ⑩ Chlorpheniramine ⑪ Epinastine ⑫ Ketotifen
⑬ Olopatadine ⑭ Fexofenadine ⑮ Azelastine

Fig. 9. PCA result of the eight H_1-receptor antagonists using output values with sensors BT0 and C00.

different taste profiles from quinine hydrochloride. The bitterness of drugs in group A can be adequately predicted using the simulation software with the converted bitterness scores of quinine hydrochloride. For drugs in groups B and C, in contrast, other methods may be necessary for the prediction of the bitterness-masking effect, such as using the taste sensor. This grouping may provide a guide for the selection of an appropriate approach for taste-masking.

4. Conclusions

The following conclusions can be made on the basis of the data obtained in this study.

(1) Based on the multiple regression analysis with R, CPA, and CPA/R values obtained from the sensor BT0, a good correlation was found between bitterness scores estimated using the taste sensor and actual bitterness scores obtained by human sensory testing with only one exception. The predictability of bitterness intensity using the taste sensor is considered to be sufficiently precise to be used in pharmaceutical development.

(2) Acesulfame potassium, a typical artificial sweetener, was detectable using the taste

sensor. The qualitative prediction of the bitterness-masking effect of acesulfame potassium is considered to be feasible using the taste sensor. A good correlation was found between bitterness scores estimated using the taste sensor and actual bitterness scores obtained by human sensory testing.

(3) Simulation software can predict the efficacy of acesulfame potassium in masking the bitterness of epinastine hydrochloride. For cetirizine dihydrochloride, the estimated bitterness scores did not correspond to the actual bitterness scores owing to the different taste characteristics of cetirizine dihydrochloride.

(4) Based on data from sensor CA0, cetirizine dihydrochloride was demonstrated to have a pronounced sour taste, deriving from the dihydrochloride salt. The sourness seems to depress the intrinsic bitterness of cetirizine.

(5) PCA, using data obtained from sensors BT0 and CA0, enabled the eight H_1-receptor antagonists to be classified into three groups on the basis of their taste characteristics. This grouping may allow the characterization of basic bitter drugs and provide a guide to the selection of appropriate taste-masking approaches.

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