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Research paper

Application of an electronic nose system for evaluation of unpleasant odor in coated tablets

Shinji Ohmori*, Yasuo Ohno, Tadashi Makino, Toshio Kashihara

Healthcare Research Laboratories, Consumer Healthcare Company, Takeda Pharmaceutical Company Limited, Osaka, Japan

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Abstract

The purpose of this study was to apply an electronic nose system for evaluation of unpleasant odor in tablets containing L-cysteine, an unpleasant odor drug, and demonstrate the odor masking ability of thin-layer sugarless coated tablets, which we have newly developed, by both electronic nose system and sensory evaluations. We demonstrated the qualitative evaluation of the unpleasant odor using air as a reference indicator and the quantitative evaluation of the unpleasant odor using the distances between air and samples in the electronic nose system evaluation. The electronic nose system evaluation was positively and well-correlated with the sensory evaluation by volunteers. We suggest that the electronic nose system evaluation is appropriate as an alternative or a support method for sensory evaluation by volunteers. As the results of both electronic nose system and sensory evaluations, we demonstrated that the thin-layer sugarless coated tablets have excellent masking ability of the unpleasant odor, equivalent to that of sugar-coated tablets due to the dense coating layers.

Keywords: Electronic nose system; Odor; Sensory evaluation; L-cysteine; Air; Distance; Thin-layer sugarless coated tablets

1. Introduction

Formulations in the pharmaceutical field have three characteristics: physical characteristics such as size, hardness, friability, disintegration, and dissolution; chemical characteristics such as drug contents and stability of drugs; and sensory characteristics such as appearance, taste, and odor. Among these three characteristics, sensory characteristics are the characteristics which patients initially recognize, and of the sensory characteristics odor is one of the most important in patient acceptance, preference, and compliance for formulations. In other words, an unpleasant odor in a formulation reduces patient acceptance, preference, and compliance. Furthermore, an unpleasant odor in a formulation can reduce the manufacturing company's and sales company's image.

Since sensory characteristics have no unit, there are few useful evaluation methods for sensory characteristics. For appearance, there are three primary colors; red, green, and blue. We can evaluate colors in a formulation using a color computer. For taste, there are five primary tastes; sweet, bitter, sour, salt, and umami. Standard materials for sweet, bitter, sour, salt, and umami are sucrose, quinine sulfate, tartaric acid, sodium chloride, and monosodium glutamate, respectively. For bitterness evaluation in humans, the standard quinine sulfate concentrations used are 0.003, 0.006, 0.012, 0.020, 0.031, 0.050, 0.078, 0.126, 0.201, and 0.328 mM and the corresponding bitterness scores were defined as 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 [1]. Recently, some taste sensors have been developed and applied for bitterness evaluation in formulations. Toko et al. [2,3] developed a taste sensor and used it to evaluate bitterness. Uchida et al. [4–6] reported that this taste sensor could be useful in providing quantitative predictive data on bitterness of medicines. The taste of orally disintegrating tablets has been measured using the electronic tongue [7]. However, there are a few applications of the taste sensors in the pharmaceutical field. Further studies are necessary. Much research is currently in progress.

* Corresponding author. Healthcare Research Laboratories, Consumer Healthcare Company, Takeda Pharmaceutical Company Limited, 2-17-85, Jusohonmachi, Yodogawa-ku, Osaka 532-8686, Japan. Tel.: +81 6 6300 6530; fax: +81 6 6300 6788.
E-mail address: Ohmori_Shinji@takeda.co.jp (S. Ohmori).

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There are no primary odors, nor any standard odor materials. In the pharmaceutical field, sensory evaluation of odor is mainly carried out by volunteers. However, there is a limit on the performance of the sensory evaluation because of individual differences, acclimation, discomfort especially in the case of evaluation of an unpleasant odor, and safety. Evaluation of odors using instruments has thus been attempted. Electronic nose systems developed in 1990s have been applied in the food, beverage, and flavor industries [8–10]. However, few applications have been made in the pharmaceutical field [11].

In previous studies, we developed a novel coating termed thin-layer sugarless coating [12]. The coating formulation mainly consists of erythritol. We demonstrated that the masking ability of unpleasant odor in thin-layer sugarless coated tablets containing L-cysteine as an unpleasant odor drug was superior to that in film-coated tablets containing L-cysteine and the same as that in sugar-coated tablets containing L-cysteine [13]. However, this was a qualitative and not a quantitative evaluation. Further study was deemed necessary. Therefore, in this study, we applied an electronic nose system to the evaluation of unpleasant odor in the tablets and demonstrated the qualitative and quantitative evaluation of the odor by the electronic nose system. Using both the electronic nose system and sensory evaluations, we evaluated the masking ability of the unpleasant odor in the thin-layer sugarless coated tablets. In addition, we observed that patients sometimes placed the unpackaged tablets under high humidity conditions such as 25 °C/75% RH for their convenient usage, suggesting that companies should guarantee the quality of the tablets under high humidity conditions such as 25 °C /75% RH for certain periods. A number of reports have addressed the effects of moisture on physicochemical properties such as stability of drugs [14], compactibility of drugs and excipients [15,16], friability of tablets [17,18], and amorphous–crystalline transformation [19,20] in solid dosage forms. Therefore, evaluations of the stability of the drugs and the appearance stability under high humidity conditions have been performed in the development of solid dosage forms. However, evaluation of the degree of odor has rarely performed even though we empirically recognize that moisture affects the odor of the drugs and increases the degree of unpleasant odor of the drugs. Furthermore, very little is known about the effect of moisture on odor of tablets in the pharmaceutical field. The effect of moisture on the unpleasant odor in the tablets was thus investigated in this study.

2. Materials and methods

2.1. Materials

L-cysteine (Kyowa Hakko Kogyo Co.), thiamine hydrochloride (BASF Takeda Vitamins), thiamine nitrate (BASF Takeda Vitamins), fursultiamine hydrochloride (Takeda Chemical Industries), bisibuthiamine (Kongo Chemical), benfotiamine (Yonezawa Hamari Chemicals), prosultiamine (Takeda Chemical Industries), and sodium chondroitin sulfate (Maruha) were used as unpleasant odor drugs. Plain tablets containing L-cysteine (Kyowa Hakko Kogyo Co.), vitamin C (Takeda Chemical Ind.), vitamin E (Eisai Co.), vitamin B_2 (Takeda Chemical Ind.), and calcium pantothenate type S (BASF Takeda Vitamins) were used as core tablets. The weight, diameter, radius of curvature and thickness of the core tablets were 300 mg, 8.8, 7.0, 5.16 mm, respectively. Erythritol (Nikken Chemicals Co.), sucrose (Ensuiko Sugar Refining Co.), talc (Matsumura Sangyo Co.), titanium dioxide (TiO_2) (Ishihara Sangyo Co.), powdered acacia (San-ei Yakuhin Boeki Co.), microcrystalline cellulose (MCC) (Avicel PH-F20, Asahi Kasei Co.), polyethylene glycol 6000 (PEG 6000) (Sanyo Chemical Ind.), and hydroxypropylmethylcellulose (HPMC) (TC-5MW, Shin-Etsu Chemical Co.) were used as coatings.

2.2. Thin-layer sugarless coating

Thin-layer sugarless coating was performed by a continuous spray mist method, as often used for film coating. A coating machine (Dria Coater (DRC-500), Powrex Co.) was used as the thin-layer sugarless coating machine. Three thousand two hundred and forty grams of core tablets were loaded in the coating machine. The thin-layer sugarless coating can be divided into four steps: (1) under coating (UC), (2) build-up coating (BC), (3) syrup coating (SC), (4) polishing (PO). The thin-layer sugarless coating formulation was as follows: the UC formulation was HPMC 10.0% and purified water 90.0%, the BC formulation was erythritol 20.1%, talc 10.6%, TiO_2 0.8%, MCC 1.9%, powdered acacia 4.6% and purified water 62.0%, the SC formulation was erythritol 34.2%, PEG 6000 3.8% and purified water 62.0%. The coating conditions of UC were as follows: inlet air temperature 70 °C; outlet air temperature 45–49 °C; spray feed rate 10 g/min; spray air pressure 0.35 MPa; spray air volume 5000 Nl/h; pan revolution 10 rpm. Weight increase of UC was 6 mg per tablet. The coating conditions of BC were as follows: inlet air temperature 60 °C; outlet air temperature 42–46 °C; spray feed rate 20 g/min; spray air pressure 0.35 MPa; spray air volume 5000 Nl/h; pan revolution 10 rpm. Weight increase of BC was 9–114 mg per tablet. The coating conditions of SC were as follows: inlet air temperature 55 °C; outlet air temperature 37–40 °C; spray feed rate 10 g/min; spray air pressure 0.35 MPa; spray air volume 5000 Nl/h; pan revolution 10 rpm. Weight increase of SC was 15 mg per tablet. PO was achieved by applying a mixture of waxes (carnauba wax and white beeswax) to the tablets in a polishing pan.

2.3. Film coating

A coating machine (HCT-MINI, Freund Ind. Co.) was used as the film-coating machine. Three hundred grams of core tablets were loaded in the coating machine. The film-coating suspension formulation was HPMC 6.5%, TiO_2 2.0%, PEG 6000 1.5%, purified water 90.0%. The coating conditions were as follows: inlet air temperature 75 °C; outlet air temperature 38–45 °C; spray feed rate 1 g/min; spray air pressure 0.15 MPa; pan revolution 30 rpm. Weight increase of film coating was 12 mg per tablet.

2.4. Sugar coating

Sugar coating was performed manually in a 12 in. onion pan (Kikusui Seisakusyo). Nine hundred grams of core tablets were loaded in the pan. A sugar-coating suspension (sucrose 41.8%, talc 30.4%, TiO_2 1.7%, powdered acacia 4.9%, purified water 21.2%), dusting powder (talc 78%, powdered acacia 2%, MCC 20%), and syrup (sucrose 66.6%, purified water 33.4%) were used for sugar coating. The dusting method was carried out. The dusting method can be divided into four steps: (1) subcoating, (2) smoothing, (3) syrup coating, (4) polishing. The subcoating was applied to round the edges and build up the tablet size. The subcoating step consisted of alternately applying the sugar-coating suspension to the tablets followed by dusting with the powders and then drying at 55 °C. Weight increase of subcoating was 180 mg per tablet. The smoothing step was to smooth out the tablet surface further prior to application of the syrup coating. The smoothing step consisted of alternately applying the sugar coating suspension to the tablets and then drying at 55 °C. Weight increase of smoothing was 75 mg per tablet. The syrup coating step was to impart an elegant appearance to the tablets. The syrup coating consisted of alternately applying the syrup to the tablets and then drying at 50 °C. The drying temperature in the syrup coating step was gradually reduced to 25 °C. Weight increase of syrup coating was 45 mg per tablet. Polishing was achieved by applying a mixture of waxes (carnauba wax and white beeswax) to the tablets in a polishing pan.

2.5. Moisturizing and drying of the tablets

Four kinds of tablets, the plain tablets, the film-coated tablets, the sugar-coated tablets, and the thin-layer sugarless coated tablets were used for this experiment. The tablets were stored at 25 °C/75% RH under open conditions for 10 days as moisturizing. Drying of the tablets in a vacuum dryer (VS-40, Irie Seisakusho) at 25 °C for 1 day was performed as vacuum drying. We used equilibrium relative humidity (ERH) as a measure of moisture content in tablets [21]. ERH of tablets was measured using a water activity analyzer (Hygroskop DT, Rotronic). Six roughly crushed tablets were used for the measurements.

2.6. Sensory evaluation

Sensory evaluations were performed in order to determine the degree of unpleasant odor. The unpleasant odor drugs, the thin-layer sugarless coated tablets, the sugar-coated tablets, the film-coated tablets, and the plain tablets were used for this experiment. Wetted drugs, in which 1 g of purified water was added for each 3 g of the drug, were also used for this experiment in order to investigate the effect of moisture on the degree of unpleasant odor of the drugs. Ten volunteers were participated in the sensory evaluation. The drugs or the tablets were placed into a glass bottle. The glass bottle was capped with a metal cap. The volunteers opened the glass bottle containing the drugs or the tablets and smelled the odor. Then, the volunteers awarded scores as one of five ranks: 0, no unpleasant odor; 1, slight unpleasant odor; 2, unpleasant odor; 3, strong unpleasant odor; 4, remarkably strong unpleasant odor. From 0 to 1, the unpleasant odor was sufficiently masked. From 2 to 4, the unpleasant odor was insufficiently masked.

2.7. Electronic nose system evaluation

Evaluations using an electronic nose system (αPrometheus, Alpha M.O.S.) were performed in order to determine the degree of unpleasant odor in the tablets. Fig. 1 shows a schematic diagram of the electronic nose system. The electronic nose system (αPrometheus, Alpha M.O.S.) is composed of three main elements; a sensor array system (αFox2000, Alpha M.O.S.), a fingerprint mass spectrometer (αKronos, Alpha M.O.S.), and a headspace autosampler (HS100, Alpha M.O.S.). The sensor array contains six metal

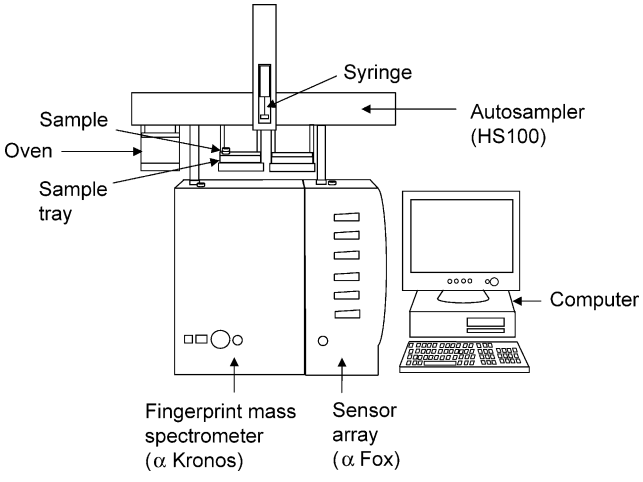

Fig. 1. Schematic diagram of the electronic nose system.

oxide gas sensors (T30/1, P10/1, P10/2, P40/1, T70/2, PA2). The principle of the detection on the sensor array is based on conductivity measurements. The sensors have sensitivities in the ppm range to a very broad range of chemical compounds. Due to their relatively low selectivity, only the use of arrays leads to a specific selectivity, i.e. a pattern or fingerprint of several sensors. The sensor performance was validated based on the sensor responses to the chemical kit 2 (propanol 0.1% in water, acetone 0.1% in water, and isopropanol 0.05% in water) (Alpha M.O.S.) before the measurements. The lifetime of the sensors is from 18 to 24 months. The fingerprint mass spectrometer is based on an electron impact quadrupole mass spectrometer and allows direct headspace injection in a mass spectrometric detector. The fingerprint mass spectrometer was calibrated using perfluorotributylamine (PFTBA) (Aldrich) before the measurements. The minimum molecular weight detectable in the fingerprint mass spectrometer in this study is 45. The molecular weight less than 45 is unused in this study because we cannot separate between the gas originated from the sample and the gas in the atmosphere such as oxygen and carbon dioxide. The headspace autosampler allows automation of the headspace generation, extraction, and injection in both the sensor array and the fingerprint mass spectrometer.

The thin-layer sugarless coated tablets, the sugar-coated tablets, the film-coated tablets, and the plain tablets were used for this experiment. Air was measured as a reference indicator. The evaluation using the electronic nose system was performed in triplicate for each sample. The measurement conditions were as follows: sample 3 tablets; vial volume 10 ml; incubation temperature on headspace generation 100 °C; incubation time on headspace generation 15 min; agitation speed of a vial on headspace generation 500 rpm; injection volume 500 μl (αFox2000), 4500 μl (αKronos). In this study, the sensors (T30/1, P10/1, P10/2, P40/1, T70/2, PA2) and *m/z* (48, 53, 64) were used for the evaluation of the degree of unpleasant odor. The data were analyzed with Alpha Soft Version 8.0 software. Principal component analysis (PCA) was used to remove the redundancy of variables and to give a representative map of the different olfactive areas. Moreover, Euclidean distances between air and samples were calculated for quantitative evaluation for the degree of unpleasant odor with Alpha Soft Version 8.0 software. The Euclidean distance of two points $A=(A_1,\ldots,A_n)$ and $B=(B_1,\ldots,B_n)$ in Euclidean n-space was calculated using the following equation

$$\text{Distance} = \sqrt{\sum_{i=1}^{n}(A_i - B_i)^2} \quad (1)$$

where A_i is a centroid of the sample and B_i is a centroid of the air. Furthermore, the relationships between the electronic nose system and the sensory evaluations were analyzed with Microsoft Excel software.

3. Results and discussion

3.1. Relationship between the coating level and the degree of unpleasant odor in thin-layer sugarless coated tablets

We investigated the relationship between the coating level and the degree of unpleasant odor in thin-layer sugarless coated tablets. Fig. 2 shows a schematic diagram of the thin-layer sugarless coated tablets. The thin sugarless coating layers consist of an under coating (UC) layer, build-up coating (BC) layer and syrup coating (SC) layer. We evaluated the odors in the thin-layer sugarless coated tablets with various coating levels by electronic nose system evaluation and the data were analyzed by a principal component analysis (PCA). The results are shown in Fig. 3. *C1* is the first principal component and *C2* is the second principal component by the principal component analysis. The solid lines mean the three measurements for each sample. We discriminated the odor among the coated tablets in Fig. 3. The proportion of *C1* was remarkably larger than the one of *C2*. The discrimination of samples can be done in the *C1* axis, the abscissa axis. The UC tablets were located near the plain tablets compared with other coated tablets. The BC 40% tablets were located near the SC tablets. With increasing coating level, the location of the coated tablets moved from the right (plus) side of the map to the left (minus) side of the map. Although *C1* and *C2* axes can discriminate the samples with different odors, *C1* and *C2* axes cannot represent the characteristics of odors. Furthermore, we could not evaluate the degree of unpleasant odor in Fig. 3 because there were no indicators in the map. We needed a reference indicator, which shows no unpleasant odor. Therefore, we proposed the measurement of air as the reference indicator and used these data in the map. The results are shown in Fig. 4. Air was located in the left (minus) side of the map. The plain tablets were located far from the air. The SC tablets, which are the highest coating level, were located close to the air. The coated tablets with increasing coating levels became gradually closer to the air. The degree of unpleasant odor in the coated tablets located

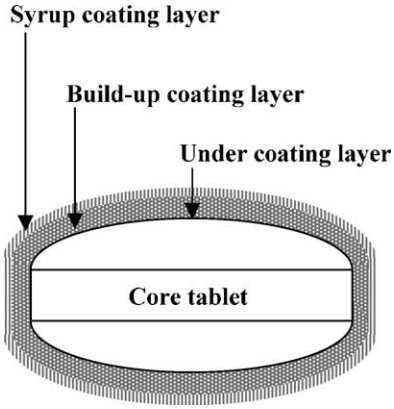

Fig. 2. Schematic diagram of the thin-layer sugarless coated tablet.

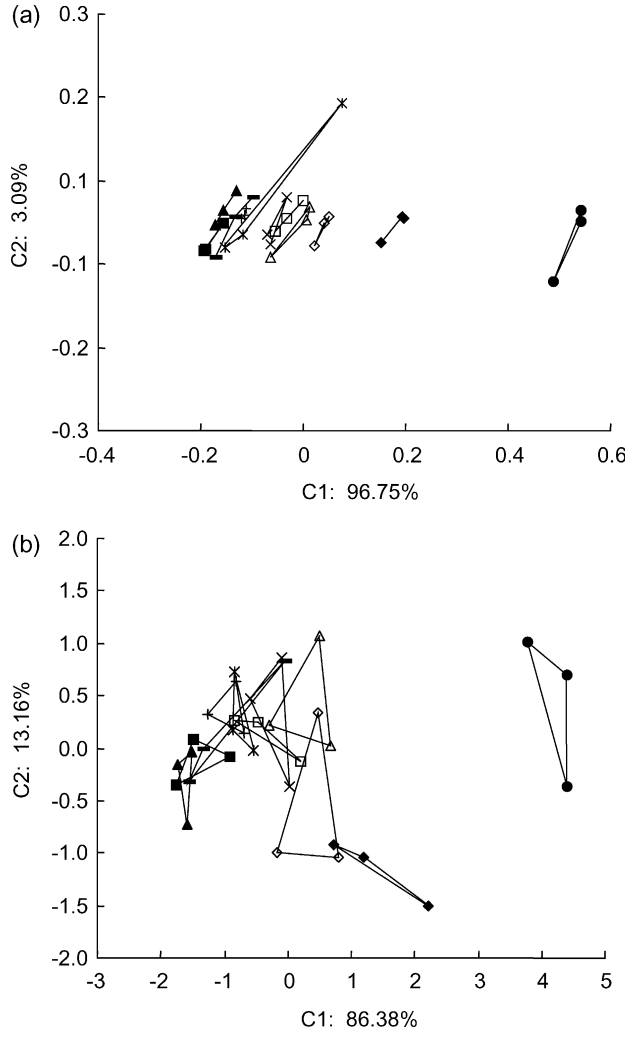

Fig. 3. Effect of coating level on the odor in thin-layer sugarless coated tablets evaluated by electronic nose system evaluation. Principal component analysis (PCA) map of the tablets. (a) Sensor array ($n=3$), (b) fingerprint mass spectrometry ($n=3$). Key: (●) plain; (♦) UC; (◇) BC5%; (△) BC10%; (□) BC15%; (×) BC20%; (✱) BC25%; (−) BC30%; (+) BC35%; (■) BC40%; (▲) SC tablets.

near the air would be lower. We thereby demonstrated the qualitative evaluation of unpleasant odor in the tablets using air as a reference indicator in the electronic nose system evaluation.

In order to quantify the degree of unpleasant odor in the tablets, the distances between the air and the samples were calculated. The results are shown in Fig. 5. Increasing coating levels resulted in reduced the distances and the distances nearly leveled off beyond the 10% BC level. It is thus suggested that a 15% BC layer would sufficiently mask the unpleasant odor in the tablets.

Fig. 6 shows the sensory evaluation. The plain tablets showed a high score, indicating a strong unpleasant odor. The UC tablets showed a lower score than the plain tablets. However, the score of the UC tablets was relatively high. The SC tablets showed a low score, which indicates that the tablets have no unpleasant odor. Increasing coating levels resulted in lower the scores. From the results in Fig. 6, we confirmed that a 15% BC layer sufficiently masked the unpleasant odor in the tablets. Although this coating level is sufficient for the masking of the unpleasant odor, we determined in a previous study that a coating level of BC 40% is required for sufficient impact toughness and SC is necessary for the elegant appearance and low hygroscopicity of thin-layer sugarless coated tablets [13].

We investigated the relationship between the electronic nose system and the sensory evaluations. The results are shown in Fig. 7. In Fig. 7(a), the straight line is drawn using linearization, shown by

$$S = 5.8582D_s - 3.2144 \quad (2)$$

where S is the score in the sensory evaluation and D_s the distance in the sensor array. The R^2 value was 0.8941. In Fig. 7(b), the straight line is drawn using linearization, shown by

$$S = 0.9272D_m + 0.1912 \quad (3)$$

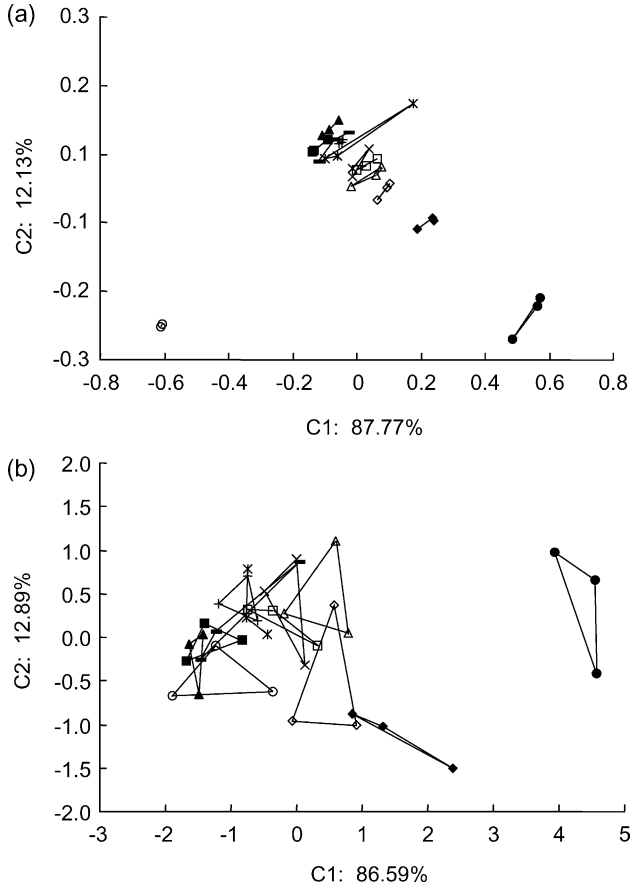

Fig. 4. Effect of coating level on the odor in thin-layer sugarless coated tablets evaluated by electronic nose system evaluation using air as the reference indicator. Principal component analysis (PCA) map of the tablets. (a) Sensor array ($n=3$), (b) fingerprint mass spectrometry ($n=3$). Key: (○) air; (●) plain; (♦) UC; (◇) BC5%; (△) BC10%; (□) BC15%; (×) BC20%; (✱) BC25%; (−) BC30%; (+) BC35%; (■) BC40%; (▲) SC tablets.

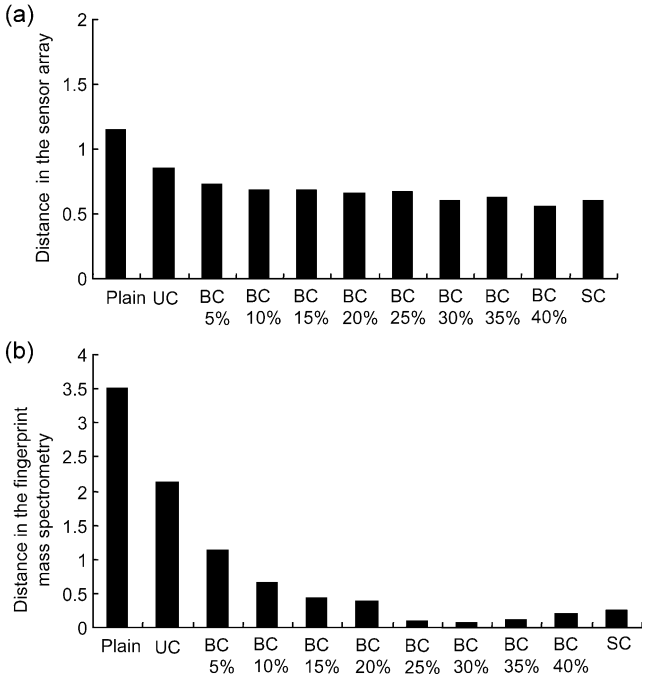

Fig. 5. Effect of coating level on the degree of unpleasant odor in thin-layer sugarless coated tablets evaluated by distance calculated from electronic nose system evaluation. (a) Sensor array, (b) fingerprint mass spectrometry.

where S is the score in the sensory evaluation and D_m the distance in the fingerprint mass spectrometry. The R^2 value was 0.9500. The electronic nose system evaluation was positively and highly correlated with the sensory evaluation in both Fig. 7(a) and (b). These findings suggested that the electronic nose system evaluation is suitable as an alternative or a support method for sensory evaluation of the unpleasant odor in the tablets.

We compared the results of the sensor array with those of the fingerprint mass spectrometry. The R^2 value in Fig. 7(b), the fingerprint mass spectrometry, was larger than that in Fig. 7(a), the sensor array. In the sensor array, a certain distance existed even for coated tablets with the high coating levels. It suggested that the sensor array recognized the difference between the air and the odor of the coated tablets whose unpleasant odor was sufficiently masked.

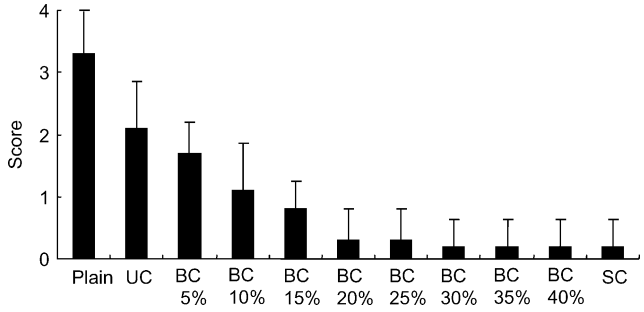

Fig. 6. Effect of coating level on the degree of unpleasant odor in thin-layer sugarless coated tablets evaluated by sensory evaluation (mean ± SD; $n = 10$). Score: 0, no unpleasant odor; 1, slight unpleasant odor; 2, unpleasant odor; 3, strong unpleasant odor; 4, remarkably strong unpleasant odor.

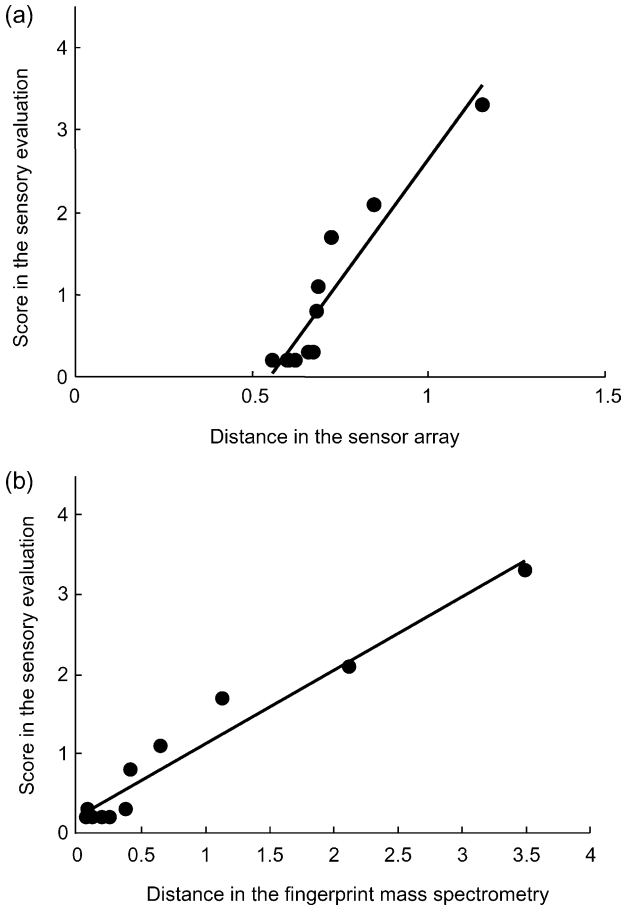

Fig. 7. Relationship between the electronic nose system and the sensory evaluations. (a) Sensor array, (b) fingerprint mass spectrometry.

In the fingerprint mass spectrometry, the distance was short when a high coating level was applied. It suggested that the fingerprint mass spectrometry only recognized the unpleasant odor of the tablets. We confirmed that the fingerprint mass spectrometry is more useful than sensor array for evaluation of the degree of unpleasant odor in the coated tablets because of its selectivity. In addition, we also confirmed that the sensor array is useful for discrimination of the odor in the tablets.

3.2. Effect of moisture on the degree of unpleasant odor in the tablets

We investigated the degree of unpleasant odor of the drugs, which consist of a sulfur element, and the effect of moisture on the degree of unpleasant odor using sensory evaluation by volunteers. The results are shown in Fig. 8. We confirmed that L-cysteine has a strong unpleasant odor besides the cases of prosultiamine and sodium chondroitin sulfate. We also confirmed that moisture enhanced the degree of unpleasant odor in the case of L-cysteine besides the cases of thiamine hydrochloride, thiamine nitrate, fursultiamine hydrochloride, bisibuthiamine, prosultiamine, and sodium chondroitin sulfate. We further investigated

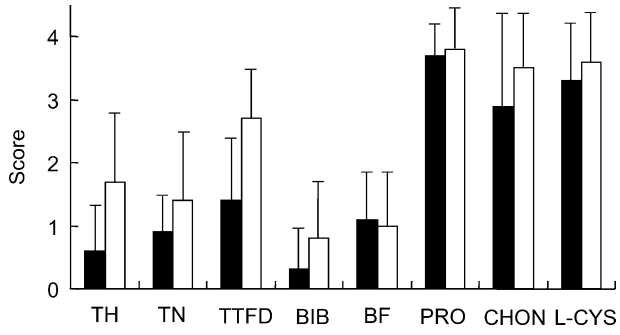

Fig. 8. The degree of unpleasant odor in drugs evaluated by sensory evaluation (mean ± SD; $n = 10$). Score: 0, no unpleasant odor; 1, slight unpleasant odor; 2, unpleasant odor; 3, strong unpleasant odor; 4, remarkably strong unpleasant odor. Key: (■) initial; (□) wetted; TH, thiamine hydrochloride; TN, thiamine nitrate; TTFD, furusultiamine hydrochloride; BIB, bisibuthiamine; BF, benfotiamine; PRO, prosultiamine; CHON, sodium chondoroitin sulfate; L-CYS, L-cysteine.

the degree of unpleasant odor in tablets stored at 25 °C/75% RH under open conditions for 10 days or dried for 1 day in a vacuum dryer. Fig. 9 shows distances calculated from the electronic nose system evaluation. In Fig. 9(b), the distances between the plain and the film-coated tablets after storage at 25 °C/75% RH and air were longer than those at the initial conditions and air. The distances

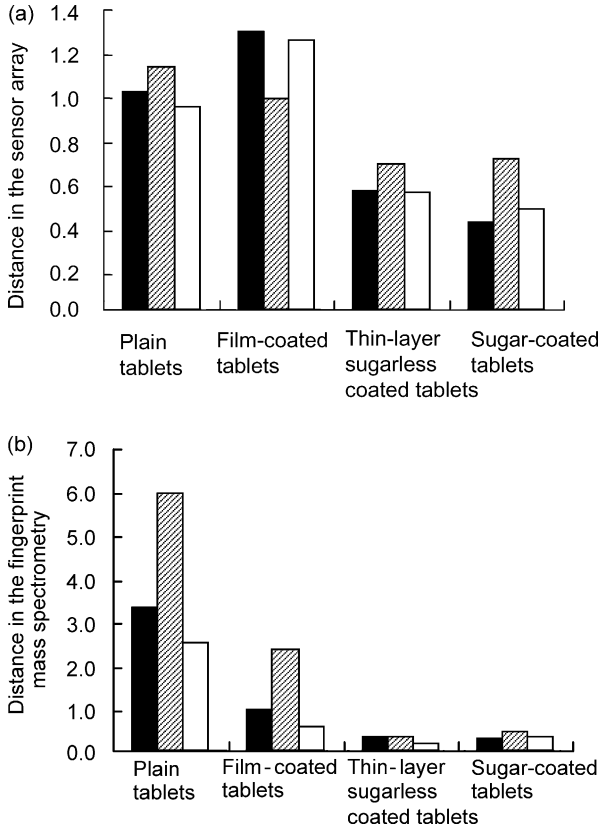

Fig. 9. Effect of moisturizing or drying on the degree of unpleasant odor in the tablets evaluated by distance calculated from electronic nose system evaluation. (a) Sensor array, (b) fingerprint mass spectrometry. Key: (■) initial; (▨) 25 °C/75% RH under open conditions for 10 days; (□) 25 °C vacuum dried for 1 day.

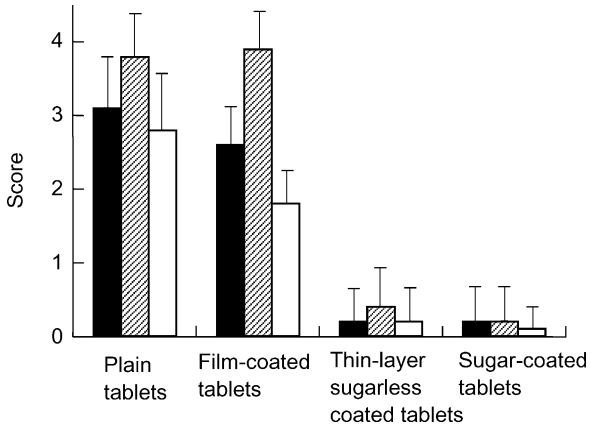

Fig. 10. Effect of moisturizing or drying on the degree of unpleasant odor in the tablets evaluated by sensory evaluation (mean ± SD; $n = 10$). Score: 0, no unpleasant odor; 1, slight unpleasant odor; 2, unpleasant odor; 3, strong unpleasant odor; 4, remarkably strong unpleasant odor. Key: (■) initial; (▨) 25 °C/75% RH under open conditions for 10 days; (□) 25 °C vacuum dried for 1 day.

between the plain and the film-coated tablets after vacuum drying and air were shorter than those at the initial conditions and air. The distances between the thin-layer sugarless coated and the sugar-coated tablets after storage at 25 °C/75% RH and air were similar to those at the initial conditions and air. Furthermore, the distances between the thin-layer sugarless coated and the sugar-coated tablets after vacuum drying and air were also similar to those at the initial conditions and air. These findings suggested that the degree of unpleasant odor in the thin-layer sugarless coated and the sugar-coated tablets would be almost the same even after storage at 25 °C/75% RH under open conditions or after vacuum drying. Moreover, these findings suggested that the degree of unpleasant odor in the plain and the film-coated tablets would increase after storage at 25 °C/75% RH under open conditions and would decrease after vacuum drying.

Fig. 10 shows the sensory evaluation. The results indicated that the degree of unpleasant odor in the thin-layer sugarless coated and the sugar-coated tablets remained almost the same even after storage at 25 °C/75% RH under open conditions or after vacuum drying. In contrast, the degree of unpleasant odor in the plain and the film-coated tablets increased after storage at 25 °C/75% RH under open conditions and decreased after vacuum drying.

We investigated the relationship between the electronic nose system and the sensory evaluations. The results are shown in Fig. 11. In Fig. 11(a), the straight line is drawn using linearization, shown by

$$S = 3.9715D_s - 1.7019 \quad (4)$$

where S is the score in the sensory evaluation and D_s the distance in the sensor array. The R^2 value was 0.6421. In Fig. 11(b), the straight line is drawn using linearization,

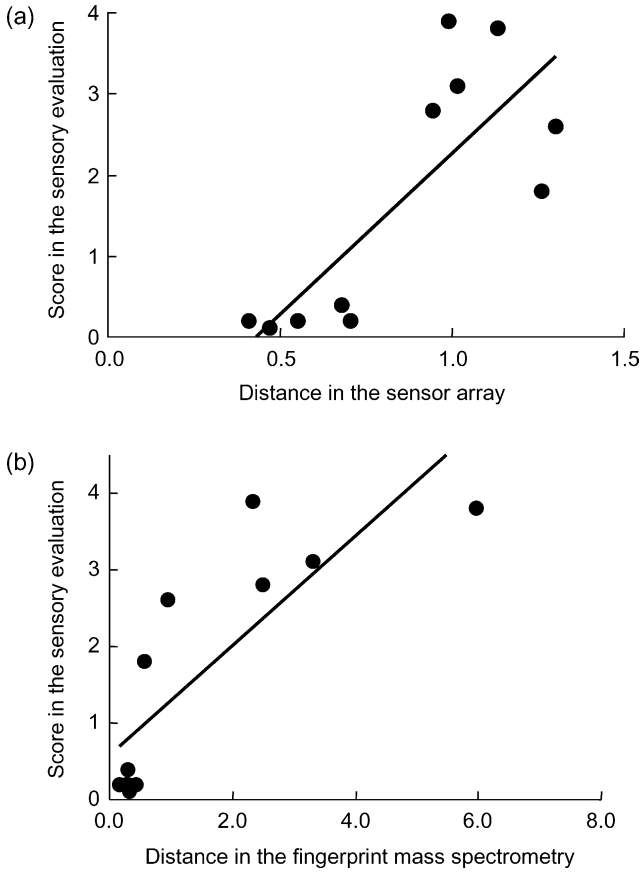

Fig. 11. Relationship between the electronic nose system and the sensory evaluations. (a) Sensor array, (b) fingerprint mass spectrometry.

shown by

$$S = 0.7147D_m + 0.5717 \quad (5)$$

where S is the score in the sensory evaluation and D_m the distance in the fingerprint mass spectrometry. The R^2 value was 0.6748.

In Fig. 11(a) and (b), the electronic nose system evaluation was positively and moderately correlated with the sensory evaluation. The R^2 value in Fig. 11(b), the fingerprint mass spectrometry, was larger than that in Fig. 11(a), the sensor array. This also suggested that the sensor array recognized the difference between the air and the odor of the coated tablets whose unpleasant odor is sufficiently masked while the fingerprint mass spectrometry only recognized the unpleasant odor of the tablets, as in the discussion for Fig. 7.

The thin-layer sugarless coated and the sugar-coated tablets have low hygroscopicity compared with the film-coated and the plain tablets [13]. Hygroscopicity could have an impact on the effect of moisture on the degree of unpleasant odor. However, the moisture content of the sugar-coated tablets is high. In order to clarify the mechanism of the masking ability, we investigated the relationship between ERH of tablets and distances calculated from the electronic nose system evaluation (fingerprint mass spectrometry). The results are shown in Fig. 12. The degrees of unpleasant odor in the plain and the film-coated tablets increased with increasing ERH of the tablets and were well correlated with ERH of the tablets. In contrast, the thin-layer sugarless coated and the sugar-coated tablets showed low degrees of unpleasant odor despite the ERH of the tablets. We found no general correlations between ERH of the tablets and the degree of unpleasant odor in the tablets. We confirmed that the masking abilities of the unpleasant odor in the thin-layer sugarless coated and the sugar-coated tablets are not susceptible to moisture whereas the masking abilities of the unpleasant odor in the plain and the film-coated tablets are susceptible to moisture. The difference between the film-coated and the thin-layer sugarless coated or the sugar-coated tablets is the coating layer structure. In the previous study, we demonstrated that the thin-layer sugarless coating layer is dense, like the sugar-coating layer [13]. We revealed that the masking ability of the coated tablets is related to the dense coating layer structure, but not related to the hygroscopicity of the coating layer.

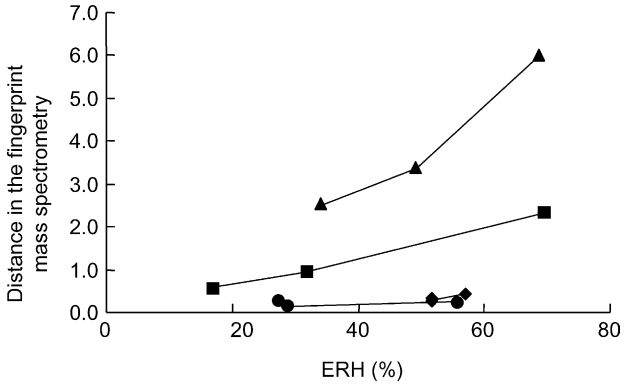

Fig. 12. Relationship between ERH of tablets and the degree of unpleasant odor in the tablets evaluated by distance calculated from electronic nose system evaluation (fingerprint mass spectrometry). Key: (●) thin-layer sugarless coated tablets; (♦) sugar-coated tablets; (■) film-coated tablets; (▲) plain tablets.

4. Conclusions

Using air as a reference indicator, and calculation of the distances between air and samples are useful for the qualitative and quantitative evaluation of unpleasant odors in the electronic nose system evaluation. We suggest that the electronic nose system is very promising and useful for evaluation of unpleasant odors in formulations, as an alternative to or a support method for sensory evaluation. We demonstrated that the masking ability of the thin-layer sugarless coating is excellent from the viewpoint of subjective (sensory evaluation) and objective (electronic nose system evaluation) evaluations. We suggest that the thin-layer sugarless coating is a useful method for masking

of the unpleasant odor, equivalent to sugar coating because of its dense coating layers.

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