Famotidine Orally Disintegrating Tablets: Bitterness Comparison of Original and Generic Products

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The purpose of the present study was to compare the palatability of the original and eight generic versions of famotidine orally disintegrating tablets by means of human gustatory sensation tests, a comparison of the release profiles, and using an automated taste sensor, the α-Astree Electronic Tongue. In the gustatory sensation test, the original product (Gaster®D, 10 mg) showed the lowest bitterness intensity. Among the eight generic products tested, the variance in the sweetness intensity was not great, but there were large variances in the intensity of bitterness, some of the generic products being significantly more bitter than that of the original product. On the other hand, some generic products show similar bitterness level as the original product. In a study of release profiles, the original product had the lowest release rates of both famotidine and aspartame; in comparison, some of the generic products had high release rates of famotidine and aspartame, even in the initial stages. Whereas some generic products had low release rates of famotidine and aspartame. Finally, sample solutions were analysed using the taste sensor. There was a good correlation between the taste predicted by principal component analysis and the Euclidean distance obtained by the taste sensor, and bitterness intensities obtained in the human gustatory tests.

Key words famotidine orally disintegrating tablet; taste sensor; generic product; Euclidean distance; bitterness

Orally disintegrating tablets (ODTs) are often prescribed for older people and children whose swallowing abilities are poor, as they disintegrate easily in saliva in the mouth without the need for additional water.[1)] Recently, ODT formulations have been developed for various medicines, and many generic products are now available on the market.[2)] When ODTs disintegrate in the mouth, the concentration of dissolved drug in the mouth is greater than that which is found when conventional tablets are kept in the mouth. Thus, taste masking is an important issue for ODTs.

Famotidine orally disintegrating tablet (FODT) was the first ODT on the Japanese market and currently, after expiry of the patent, there are eight generic forms of this product on the market. Although some characterization of generic FODT products has been reported previously,[3—5)] the article which compares the palatability of the original and generic products are quite few.[6)] Tachiki *et al.* evaluated 20 mg-famotidine containing orally disintegrating tablet using multichannel taste sensor SA402B (Intelligent Sensor Technology and Co., Ltd.) in the previous article.[6)] In the article, they evaluated FODT using one sensor (AN0) showing the largest sensor output value for famotidine. The sensor output using AN0 shows comparatively good correlationship with the bitterness evaluated by six-stage image score, for 7 products. Neverthelss, the masking effect of sweeteners or other additives for each product was not demonstrated on the article. The reason for different bitterness or palatability was not also mentioned in the article.

In the present study, therefore, we focused on differences of taste between the original 10 mg-famotidine containing orally disintegrating tablet and eight generic versions of FODTs. Taste was evaluated using human gustatory sensation tests, in a study of release profiles, and using a quantitative taste sensor, the α-Astree Electronic Tongue (Alpha MOS, France); the taste sensor output of the sensor was used to calculate the Euclidean distance, a variable used to quantify the taste of the sample medium.[7)] The taste sensor α-ASTREE is able to evaluate the overall taste of product by using the output value from all sensors (α-ASTREE consists of seven sensors) for the analysis. In the present study, we try to compare not only the bitterness of famotidine but also the overall taste of 10 mg-famotidine containing drug product.

In the human gustatory sensation tests, not only bitterness intensity but also sweetness intensity (aspartame is the main sweetener used) were evaluated, as described in a previous study,[8)] since sweetness and bitterness are the critical factors determining palatability. The release rates of famotidine and aspartame from FODTs were also quantified using HPLC, as the release rates seem to be directly correlated with bitterness or sweetness (although the quantities of released famotidine and aspartame did not reflect the extent of disintegration of the FODTs).

As for the sweetener, we focused the release profile of aspartame, not other additives since the aspartame seems to be the most sweetest constituent among additives involved in FODTs. The sweet intensity of other additives such as D-mannitol, seems considerably small compared with the aspartame, as amount of other sweeteners in the product was kept so low level. The sweet intensity of D-mannitol is smaller compared with that of the sucrose whereas the aspartame is 200 times as sweet as same concentration of sucrose. We focused on the aspartame as a sweetener since the sweetness of other additives such as D-mannitol, lactose and maltose were reported to be almost about 1/300—1/1000 of that of the aspartame and neglectable.[9)]

The correlation between the Euclidean distances, obtained

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from principal component analysis of the taste sensor measurements, and the palatability of the various FODTs, was also examined.

Experimental

Materials Nine different 10-mg FODTs were used in the present study: the original product, Gaster®D (Astellas Pharma Inc., Tokyo, Japan), and the following eight generic products: Climagen®-ES (Merck Seiyaku Ltd., Tokyo, Japan), Famogast®D (Shiono Chemical Co., Ltd., Tokyo, Japan), Famotidine D [KOBA] (Kobayashi Pharmaceutical Industries, Co., Ltd., Toyama, Japan), Famotidine D [SAWAI] (Sawai Pharmaceutical Co., Ltd., Osaka, Japan), Famostagine®-D (Towa Pharmaceutical Co., Ltd., Osaka, Japan), Gamofa®D (Ohara Pharmaceutical Co., Ltd., Shiga, Japan), Gasport-D (Taiyo Yakuhin Co., Ltd., Aichi, Japan), Gasrick®D (Nissin Yakuhin Co., Ltd., Miyagi, Japan). Eight generic products were randomly named products A to H.

Quinine sulfate was purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.), and sucrose from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All other reagents were of special reagent grade.

The sample solutions of FODT used in the HPLC study and taste sensor measurements were prepared as follows: 10 tablets of each product (corresponding to 100 mg famotidine) were placed in a stainless-steel mesh basket. The baskets were placed in a 100-ml beaker which was put into a thermostatically controlled shaking water bath (37±0.5 °C at 25 rpm) containing 100 ml of distilled water. After 10, 20, 30 and 60 s, the suspensions were filtered under reduced pressure. These solutions (from all four time points) were used for taste sensor measurement and, after filtration through a membrane with 0.45-μm pore size, for examination of the release profile by HPLC.

Gustatory Sensation Tests The gustatory sensation tests were performed with 11 well-trained volunteers according to a previously described method,[10,11] using quinine sulfate at concentrations of 0.0029, 0.012, 0.031, 0.078 and 0.20 mM as a standard for bitterness, and sucrose at concentrations of 29.24, 87.72, 187.1, 409.4 and 994.1 mM as a standard for sweetness. Scores of 1, 2, 3, 4 and 5 were allocated to the increasing concentrations of the standard solutions.

Before testing, the volunteers were asked to keep the abovementioned standard quinine and sucrose solutions in their mouths, and were told the concentration and bitterness or sweetness score of each solution. They were then asked to give each of the samples bitterness and sweetness scores. Each sample was from one FODT, and all samples were kept in the mouth for 30 s. After tasting each sample, subjects gargled well and waited for at least 20 min before tasting the next sample. The differences between the bitterness or sweetness scores of the various samples were analyzed using the Dunnett's multiple comparison tests, a non-parametric method. The protocol and experimental design for all gustatory sensation tests was approved in advance by the ethical committee of Mukogawa Women's University.

Release Profile The famotidine and aspartame (as a sweetener) concentration in the sample solutions were determined by HPLC. The measurement was under the following conditions: 10 μl of the prepared sample was injected onto a chromatograph (Shimadzu LC-10AT, Kyoto, Japan) equipped with an ultraviolet absorption photometer detector (Shimadzu SPD-10AV, Kyoto, Japan), an integrator (Shimadzu C-R6A, Kyoto, Japan) and a reversed-phase column (Capcell Pak C18 UG120, 4.6 mm i.d.×15 cm, Shiseido Co., Ltd., Tokyo, Japan). As mobile phase, 0.2% 1-heptanesulfonic acid sodium salt (pH 3.0) : acetonitrile : methanol (25 : 6 : 1) was used for famotidine, and 40 mM sodium acetate buffer (pH 4.0) : methanol (3 : 1) for aspartame. The flow rate was 1.0 ml/min and the wavelength was set at 254 nm (famotidine) or 250 nm (aspartame). The column temperature was set at 25 °C (famotidine), or 40 °C (aspartame).

Taste Sensor Measurements and Data Analysis The taste sensor system, 'α-ASTREE' Liquid and Taste Analyzer[12] of Alpha MOS, Toulouse, France, was used to measure the electronic potential of the FODT solution. This taste sensor consists of an array of seven liquid cross-sensitive electrodes or sensors (ZZ, BA, BB, CA, GA, HA, and JB), a 16-position autosampler, and associated interface electronic module. Each sensor consists of a silicon transistor with an organic coating that determines the sensitivity and selectivity of the sensor. This system was found to permit good characterization and to allow differentiation between the majority of food groups and pharmaceutical products. A measurement consists of the electric potential difference between each sensor and the Ag/AgCl reference electrode in the equilibrium state at room temperature. Thus an integral signal for each sample comprised a vector with seven individual sensor determinations. Four measurements were performed for every sample and the mean and standard deviation were calculated.

The distance between each sample group and the original product (the Euclidean distance) was calculated using the taste sensor output values. The Euclidean distance (d_{PQ}) of sample $P=(P_1, P_2, \ldots, P_k)$ and sample $Q=(Q_1, Q_2, \ldots, Q_k)$ can be shown by expression (1).

$$d_{PQ}=\sqrt{\sum_{k=1}^{7}(P_k-Q_k)^2} \quad (1)$$

d_{PQ}: Euclidean distance of sample P and sample Q

P_k: Sensor output value of sensor k in sample P

k: sensors (ZZ, BA, BB, CA, GA, HA, and JB)

It has previously been shown that the smaller the Euclidean distance between two samples, the more similar their taste.[7] Accordingly, the difference between the taste of each generic product and that of the original product was evaluated by calculating the Euclidean distances between them.

Results

Gustatory Sensation Tests on FODTs Figure 1 shows the gustatory sensation data for the nine FODTs. The bitterness score of the original product was 1.0, the lowest of all the FODTs used in the present study. The bitterness intensities of the generic products A, E and F showed significantly stronger bitterness compared with the original product, while no significant differences in sweetness scores were found between the original and the generic products, which was significantly less sweet than the original product.

Table 1 shows the comparison of product name, its company name, and evaluated bitterness in the present and the

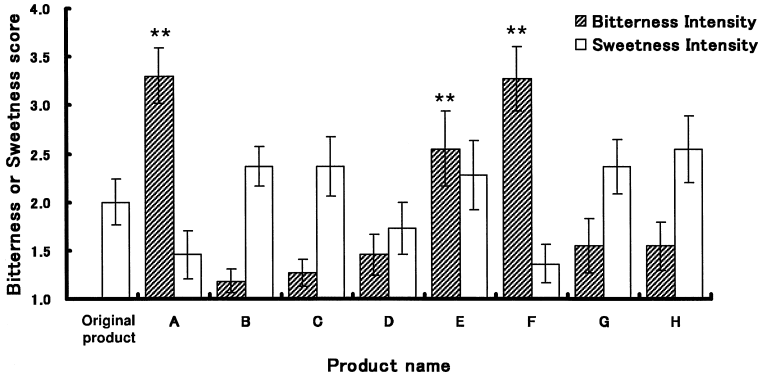

Fig. 1. Bitterness and Sweetness Intensity Obtained in Gustatory Sensation Test for Various FODT

Error bars represent the mean plus or minus standard error ($n=11$). ** $p<0.01$ compared with original drug.

Table 1. Comparison of Product Name, Its Company Name, and Evaluated Bitterness in the Present (Left) and the Previous (Right) Study

Product name, its company name and evaluated bitterness in the present study (All products contain 10 mg of famotidine)			Product name, its company name and evaluated bitterness in the previous study (ref. 6) (All products contain 20 mg of famotidine)		
Product name	Company name	Evaluated bitterness score[a)]	Product name	Campany name	Evaluated btterness score[b)]
A	1	3.3	*A** (B in the present study)[c)]	2	0
B	2	1.2	*B** (original in the present study)	9	0
C	3	1.3	*C** (C in the present study)	3	3
D	4	1.5	*D*	10	3
E	5	2.6	*E** (F in the present study)	6	4
F	6	3.3	*F*	11	4
G	7	1.6	*G** (G in the present study)	1	5
H	8	1.6			
Original product	9	1			

In both case, the product name was represented by alphabet. Company name was represented by number 1 to 11. *a*) In the present study, quinine sulfate at determined concentrated solution as a standard for bitterness was employed, and bitterness intensity was determined. *b*) In the previous study (ref. 6), famotidine standard solutions was employed to evaluate the bitterness. *c*) *A** (B in the present study) means that the product *A** was the same name FODT as used in this study, but famotidine loading was just twice as that used in this study.

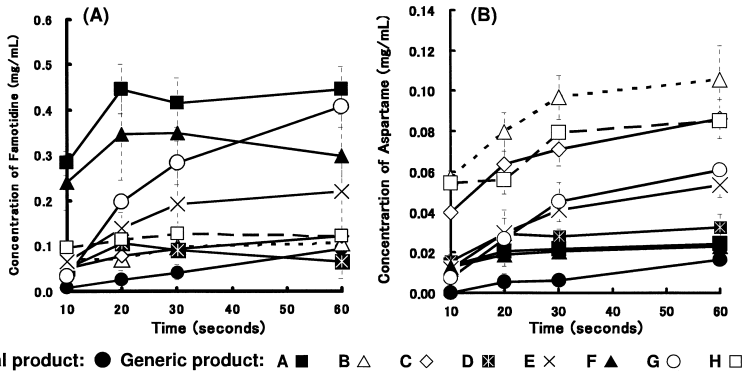

Fig. 2. Content of Famotidine (A) or Aspartame (B) Eluted from the Original Product Gaster®D and Eight Generic FODTs

previous study demonstrated by Tachiki *et al.*[6)] In the left-hand side of the table, the bitterness intensity demonstrated in Fig. 1 was represented as an average score. Whereas in the right-hand side of the table, the bitterness intensity score evaluated by six-stage evaluation in the previous article[6)] was shown. Even though the previous study was performed for 20 mg-famotidine loaded original and 6 generic ODTs, the present study was done for 10 mg-famotidine loaded original and 8 generic ODTs, and their gustatory sensation methods were also different, the bitterness intensity for 6 generic ODTs in the previous study varied so much as in the present study. As shown in the right hand of the Table 1, the original product and product *A* in the previous article,[6)] shows similar low bitterness level. But other products seem to show moderate or severe bitterness. The word "*A** (B in the present study)" in the Table 1 means that the product *A** was the same name FODT as used in this study, but famotidine loading was just twice as that used in this study. Even though it might be difficult to compare the bitterness of two different loading ODT with same product name (and company) and the bitterness was estimated by different methods, the bitterness of 10 mg- and 20 mg-loading original ODT produced brand company, and the bitterness of generic ODTs (B in the present study and *A* in the previous study) produced by company 2 were almost at the same level, respectively, and their bitterness were restricted to low level. Whereas ODT A in the present study and ODT *G* in the previous study those produced by company 1, and ODT F in the present study and ODT *E* in the previous study those produced company 6, all show stronger bitterness. Thus there seems to be no differences between results of two studies for bitterness evaluation.

Release Profiles of FODT Sample Solutions Figure 2 shows the cumulative release profile of famotidine and aspartame (incorporated into the tablets as sweetener) from the nine FODTs, as determined by HPLC. There was a considerable difference in the famotidine and aspartame contents between the FODTs. The concentration of famotidine eluted from the original FODT was the lowest. The products B, C, D and H show low release rate of famotidine. Whereas the concentrations released from the generic products A, G and F were at least 10 times higher. In products A and F, the large amount of famotidine was released immediately at initial phase. In product G, the fast drug release was observed for 60 s, whereas the gradual release was observed in Product E (Fig. 2A).

In related to aspartame release profile, the concentration of aspartame released from the original product was also lower than those from the generic products, although the difference was far less than with famotidine (Fig. 2B). Some products such as B, C and H show the comparatively fast release rate at initial phase, whereas in products E and G, the aspartame was gradually released. In other products, the released

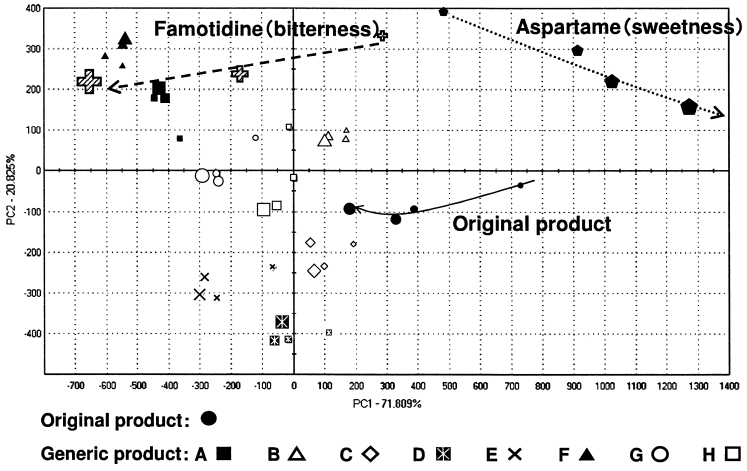

Fig. 3. Principal Component Analysis of FODT Solutions Using the Output Value of the Taste Sensor

The symbol of famotidine and aspartame standard solutions were enlarged as increasing their concentrations. The plot of FODTs was enlarged the symbol as increasing shaking time.

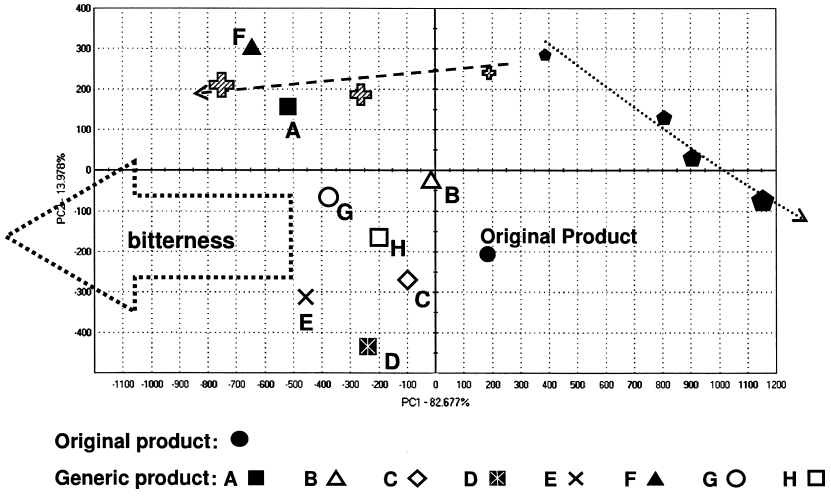

Fig. 4. Principal Component Analysis of FODT Solutions Using the Output Value of the Taste Sensor after Shaking for 30 s

The symbol of famotidine and aspartame standard solutions were enlarged as increasing their concentrations.

amount of aspartame was small even after shaking for 1 min.

Principal Component Analysis and Calculation of Euclidean Distance Using Taste Sensor Data A principal component analysis (PCA) was carried out on the taste sensor data obtained from the FODT solutions. PCA is a multivariate analytical method which reduces the dimensional space without losing any information. PCA was used to estimate the largest and second largest relative contribution factors (PC1 and PC2) using all sensor data. The results are shown in Figs. 3 and 4. The relative contributions of PC1 and PC2 were 71.8 and 20.8%, respectively. In Fig. 3, for famotidine, the index of bitterness moved to the left of the plot with increasing concentrations, while for aspartame, the index of sweetness moved to the right with increasing concentrations (the symbols become larger with the increase of concentration). The original product was located on the right-hand side of the PCA plot, at some distance from the generic products. All products moved to the left on the plot as the shaking time became longer (the symbols become larger as the shaking time increases). Figure 4 shows the PCA of the taste sensor data obtained from FODT sample solutions shaken for 30 s.

The Euclidean distances calculated for the generic products by comparison with the original product on the basis of taste sensor output values, were summarized in the middle column in Table 2. The Euclidean distance of the generic products decreases in the order of F>A>E>G>D>H>B>C. Firstly, it was confirmed that Euclidean distances increased logarithmically with increasing of bitterness intensity of famotidine standard solution (1.00 for 0.01 mg/ml, 1.38 for 0.1 mg/ml, 4.25 for 1 mg/ml famotidine solution, respectively). The good relationship between Euclidean distances and the logarithm of bitterness scores by gustatory sensation for all products including the original product, was also obtained as shown in Fig. 5 ($y=1377.8x+184.95$, $R^2=0.8578$).

Discussion

Comparison of Bitterness and Sweetness Intensity of Generic FODTs In gustatory sensation tests of generic products B and C, bitterness masking can be seen to have been largely successful, as their bitterness scores were about at the same level as the original product. However, the bitterness of products A, E and F was not adequately masked by

Table 2. Comparison between Euclidean Distances, Bitterness Score Obtained in Gustatory Sensation Test and Released Rate of Famotidine by HPLC

Bitterness score by gustatory sensation test	F**	A**	E**	G	H	D	C	B	Original drug
	3.3±0.3	3.3±0.3	2.6±0.4	1.6±0.3	1.6±0.3	1.5±0.2	1.3±0.1	1.2±0.1	1.0±0.0
Euclidean distances by taste sensor	F	A	E	G	D	H	B	C	Original drug
	977	796	663	577	523	421	348	331	0
Released famotidine (%) from FODT by HPLC (30 s)	A	F	G	E	H	B	C	D	Original drug
	41.6	35.0	28.3	19.4	12.6	9.9	9.3	9.2	4.1

** $p<0.01$ compared with original drug.

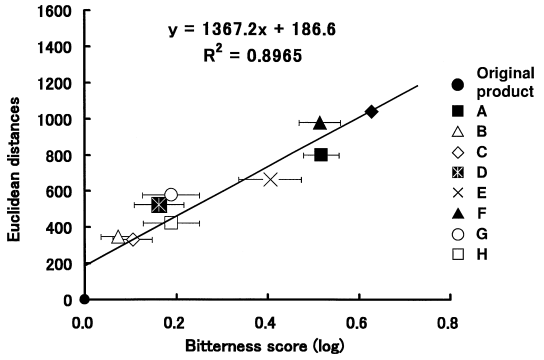

Fig. 5. The Relationship between Euclidean Distances and Bitterness Scores Obtained in Gustatory Sensation Tests

Error bars represent the mean plus or minus standard error ($n=11$).

sweeteners and the products were still quite strongly bitter. Kataoka *et al.* reported that overall palatability is negatively correlated with bitterness.[8] It is assumed that differences in the bitterness scores of each product best reflect the overall taste of the product, since there were no significant differences in the sweetness scores. Therefore, the bitterness intensity scores obtained in human gustatory sensation tests were used in the comparison with taste sensor data.

Comparison of Famotidine and Aspartame Release from FODTs The sweetness scores obtained in gustatory sensation tests were all comparatively high (Fig. 1), although the quantities of aspartame released from the FODTs were low, especially from the original product. Moreover, the differences in bitterness scores in the gustatory sensation tests between original and generic products, did not reflect the magnitudes of the differences in the amount of famotidine released. The bitterness rank derived from the results of the gustatory sensation test was F=A>E>G=H>D>C>B> original product as shown in the upper column in Table 2. While, the bitterness of product predicted from the concentration of famotidine measured with HPLC becomes A>F>G>E>H>B=C=D>original as shown in bottom column in Table 2. The famotidine release from product G was 10 times greater than that of the original product. Similarly, the bitterness score of product E was higher than that of product G, although famotidine release was more extensive from product G (the levels of aspartame released from products E and G were similar). It is thought that the palatability of substances in which bitterness is masked with sweeteners is not predictable from consideration of the release profile alone, presumably because the products contain various additives as well as famotidine and aspartame. Therefore, as taste prediction of FODTs could not be achieved on the basis of the release profile alone, the FODTs were also evaluated using the taste sensor.

Prediction of Taste of FODTs Using the Taste Sensor In Figs. 3 and 4, the precise meaning of the horizontal axis in the graph is unclear. It can be said that the sweetness is enhanced as the value of horizontal axis increases, while bitterness is enhanced as the value of horizontal axis decreases. The plot of famotidine moves to the left of the graph with increasing concentrations, while the plot of aspartame moves to the right. The original product started toward the right-hand side of the graph, but moved to the left as the shaking time increased. Similarly, the plots of the generic products moved to the left of the graph as the shaking time increased. This confirms that the amount of famotidine released from the FODTs increased with increased shaking time; the associated increase of bitterness was reflected in the PCA of the taste sensor data. The bitterness of the generic products was more intense than that of the original product; this is evident from the fact that all the generic products were located to the left of the original product on the graph.

The Euclidean distances between the original and generic products were calculated from taste sensor data obtained from FODT sample solutions shaken for 30 s to evaluate the similarity of the taste including bitterness and sweetness. The larger the Euclidean distance, the greater the difference of taste between original and generic product. In the present study, it is confirmed that bitterness intensity of the original product is 1.0, and does not have bitterness. Therefore, in this thesis, the obtained Euclidean distance between original and each generic product seemed to reflect difference of the bitterness between original and generic product. The larger the Euclidean distance, the more bitter the product. The Euclidean distance data are summarized in the table.

In this way, the relative bitterness of the generic products was determined as F>A>E>G>D>H>B>C>original product. This compares quite well with the bitterness ranking derived from the results of the gustatory sensation test: F=A>E>G=H>D>C>B>original product (Table 2). There were some minor differences in the ranking obtained using the two different techniques, *e.g.* between products D and H, but the differences in bitterness concerned are quite small and it may be caused by difference of dissolved additives. The bitterness of product E with strong bitterness was not able to predict from the result of HPLC, but the bitterness intensity of the product could be predicted fairly well

when we use the Euclidean distance. This was confirmed by the fact that a good correlation was found between the bitterness scores predicted by Euclidean distances and the bitterness obtained in the human gustatory tests: ($y=1367.2x+186.6$, $R^2=0.8965$).

If a bitterness score of 2.0 (corresponding to the bitterness of a 0.012 mM quinine sulfate solution) is adopted as the threshold of bitterness based on previous paper,[12] and this value is substituted to the regression equation $y=1367.2x+186.6$, a Euclidean distance of 598.13 corresponding to the threshold of bitterness, was obtained. In the present study, therefore, we concluded that the product A, E, and F of which Euclidean distance over 600 were judged to be bitter and give unpleasant taste to patients. These results suggested that Euclidean distances calculated based on the taste sensor output value may be useful for the taste evaluation of generic FODT products.

For drug products with a low release of sweeteners and high release of famotidine, such as products A and F, prediction of bitterness may be possible by determination of the release rate, however, bitterness prediction by this method is more difficult in products in which bitterness is masked by sweeteners to a greater degree. For example, the bitterness intensity of product G is not intense by the gustatory sensation test, even though it was predicted to have greater bitterness intensity on the basis of only the amount of famotidine released from FODT in the dissolution test (Fig. 2). In such cases the taste sensor may be more useful for taste evaluation than the release profile alone, because the taste sensor is able to evaluate the overall taste of the sample solution. Determination of the concentrations of base component and sweeteners by HPLC alone is not capable of evaluating the bitterness of solutions in which the bitterness is masked by sweeteners.

Conclusions

In the gustatory sensation test, the bitterness intensities of generic FODT products A, E and F showed significantly larger than that of the original product. Whereas FODT product B and C shows the same bitterness level as original product. Among the generic products it was confirmed that there were considerable differences in the amount of famotidine (base component) and aspartame (sweeteners) eluted from the tablets during examination of the release profile, as measured by HPLC. The overall taste of each FODT could be predicted from the result of a principal component analysis of taste sensor data, and differences in the taste of the products could be predicted from consideration of their Euclidean distances compared with that of the original product, Gaster®D.

Prediction of the overall taste of FODTs on the basis of release profile data alone was not accurate, although the content of the base components and sweeteners could be determined. However, using the taste sensor it was possible to compare the overall tastes of all the drug products in a single PC analysis if seven sensors, each with a different response pattern, are used. In this case it was possible to compare directly the taste of the original product and generic copies using Euclidean distances calculated from the taste sensor data. The development of the method to discriminate products with considerable bitterness, which is uncomfortable for patients without gustatory sensation test, seems important. Euclidean distances we proposed in the present study has the potential for discrimination of bitter product among original or generic products even though further study has to be done for designing more useful usage of the distance.

In this study, the bitterness-suppressing effect of aspartame on famotidine was mainly evaluated. It was suggested that taste sensor was able to predict the bitterness. However, menthol aroma is included in the products as a flavor. The influence of flavor on palatability such as pleasant cooling sensation of menthol or grittiness was not clearly evaluated yet. The combinatory usage of taste and nose sensor might give more useful information on evaluation of palatability for all products containing famotidine.

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