INTRODUCTION
The isosorbide dinitrate or mononitrate are used chiefly to treat angina pectoris, and used as the osmotic diuretics in Japan. Additionally, it is used as a treatment of the intracranial hypertension, the ocular hypertension, and Meniere’s disease. ISOBIDE® was approved and put on the market in Japan in 1968. ISOBIDE® is raising plasma osmolality and shows a brain pressure descent action, an intraocular pressure descent action, an inner lymph pressure descent action of an ear, and a diuretic effect. Moreover, a brain tumor patient may be administered for the purpose of brain pressure descent. However, the taste of ISOBIDE® is unpalatable in the one that sweetness, acidity, and bitterness existed together. Generally, a bad taste drug may resist taking medicine, the possibility that the effect of the drug therapy is not achieved is thought, and there is a possibility that a satisfactory therapeutic effect is not obtained. In a package insert, it is important to consider the taste to complete the drug therapy though the method to take by the dilution with water is adopted to secure the adherence of ISOBIDE®. In
Japan, the value added generic drugs to which the taste is improved is marketed in the generic of ISOBIDE®.

Generic drug use has increased gradually in Japan and is an accepted part of health care. A generic drug is usually considerably less expensive than the brand name original. A key element for a generic drug is establishing bio-equivalency. Bio-equivalency means that the product to be evaluated produces essentially the same biological availability of the active substance in the body when given in the same quantity as the original. Value added generic drugs are usually developed using innovative pharmaceutical technologies and such products achieve the goal of being more patient friendly. However, there is no report of having proved scientifically about the taste of the value added generic drugs.

In the present study, we measured objective taste of brand and value added generic drugs of the isosorbide liquid formulations using electronic taste system α-ASTREE®. The taste sensor is used in various fields such as food and drink, pharmaceutical products, packaging container, the environment 2, 3. A high correlation is understood between the taste predicted by the taste sensor and the human gustatory sensation tests 4-7. Moreover, since it turns out that it will become easy to take a medicine if the isosorbide liquid formulation is diluted with juice 8, mineral water and the restraint effect of the taste by apple juice dilution were scientifically proved using the taste sensor. The judgment of the taste was evaluated with Euclidean distances.

MATERIALS and METHODS

1. Electronic Taste System

The objective taste of brand and value added generic drugs of the isosorbide measured it with the taste sensor system “α-ASTREE®” Liquid and Taste Analyzer (Alpha M.O.S., France). The sensor part of the taste sensor consists of seven electrodes or sensors, a 16-position auto sampler, and an associated interface electronic module 9. We measured each four times of samples after sensor conditioning and performed data analysis. Seven taste sensors which we used were ZZ, AB, BA, BB, CA, DA and JE. Each sensor consists of a silicon transistor with an organic coating that determines the sensitivity and selectivity of the sensor (Fig. 1).

![Figure 1: System of α-ASTREE Electronic Tongue](image)
2. Measurement Principles
The taste recognition by the person and the taste recognition by \(\alpha\)-ASTREE\textsuperscript{\textregistered} were shown in Fig. 2. \(\alpha\)-ASTREE\textsuperscript{\textregistered} performs taste recognition by three steps of the detection of the solution ingredient with the taste sensor, analysis by the software and the data analysis. The taste sensor is equivalent to the gustatory cell of the person, and the analysis by the software is equivalent to the cerebrum of the person. And it can perform a comparison of qualitative taste or quantitative taste and a classification. In other words, it may be said that these three steps resemble a recognition principle of the taste of the person closely very much.

3. Evaluation of restraint effect of the taste by Euclidean distance
Euclidean distance is expressed by the square root of square sum of difference of each parameter shown in Fig. 3. The Euclidean distance calculates the distance between a center of gravity of placebo sample (P) and centers of gravity of drug sample (D). The taste is similar so that distance is near. If the difference of the sensor output value between two samples is small, the taste shows that it resembles the placebo sample\textsuperscript{10}.

4. Materials and Preparation of the Sample Solutions
Prepared sample solution was shown in Table 1. Label S1\textasciitilde3 is ISOBIDE\textsuperscript{\textregistered} of brand-name drug (Kowa Company, Ltd., Aichi, Japan), label A1\textasciitilde3 is ISOSORBIDE ORAL SOLUTION 70% of generic drug (ASKA Pharmaceutical Co., Ltd., Tokyo, Japan), label T1\textasciitilde3 is ISOSORBIDE of generic drug (TAIYO Pharmaceutical Industry Co., Ltd., Aichi, Japan). Mineral water (CG) for the dilution is CRYSTAL GEYSER (Otsuka Foods Co., Ltd., Osaka, Japan) on the market.

Label S1, A1, and T1 of the sample

Fig. 2  Recognition process of the taste by the person and \(\alpha\)-ASTREE

\[
d_{PD} = \sqrt{\sum_{k=1}^{n} (P_k - D_k)^2}
\]

Fig. 3  Formula for computation of Euclidean distance
\(d_{PD}\): Euclidean distance of sample P and sample D  
\(P_k\): Sensor output value of sensor k in sample P  
k: Sensors(ZZ, AB, BA, BB, CA, DA and JE)
solution are each drugs stock solution. Label S2, A2, and T2 diluted each drugs stock solution with CG by the twice and label S3, A3, and T3 diluted each drugs stock solution with apple juice (ASAHI SOFT DRINKS Co., Ltd., Tokyo, Japan) on the market by the twice. In addition, the comparison sample solution that diluted the apple juice with CG by the twice (AJ1CG1) was prepared. The measurement of the taste by α-ASTREE® prepared the thing which diluted all samples 5 times with CG and made the quantity of sample 80mL. Additionally, the measurement condition was shown in Table 2.

RESULTS
As a result of chief ingredient analysis, the identification index was 95. The taste of each sample was able to be classified excellently. In a word, it could be judged that α-ASTREE® was able to evaluate the difference of the taste. The result of the chief ingredient analysis measured with the taste sensor is summarized to two-dimension map (Fig. 4). In other words, the taste sensor was

<table>
<thead>
<tr>
<th>Table 1 Preparation of the Sample Solutions</th>
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<tbody>
<tr>
<td><strong>Label</strong></td>
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<tr>
<td>---------</td>
</tr>
<tr>
<td>CG</td>
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<tr>
<td>AJ1CG1</td>
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<tr>
<td>S1</td>
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<td>S2</td>
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<td>S3</td>
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<td>T3</td>
</tr>
</tbody>
</table>

Table 2 Measurement Condition
<table>
<thead>
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<th>Preparation of the sample solutions</th>
<th>All samples except the CG were diluted five times with CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quantity of the sample</td>
<td>Sample dilution, 80 ml</td>
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<tr>
<td>Measurement temperature</td>
<td>Room temperature</td>
</tr>
<tr>
<td>Time of the data acquisition</td>
<td>120 seconds</td>
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<tr>
<td>Interval of the data acquisition</td>
<td>One second</td>
</tr>
<tr>
<td>Cleaning solution</td>
<td>Sample CG (Mineral Water : CRYSTAL GEYSER)</td>
</tr>
<tr>
<td>Cleaning time</td>
<td>10 seconds</td>
</tr>
</tbody>
</table>

**Fig. 4** The classification of the sample by the chief ingredient analysis
This is the result of evaluating the degree of identification. Identification index because there is no overlap between groups is a positive value. If there is overlap between each group, then identification index is negative. A positive, maximum value of the identification index is 100. The identification index height shows that there is a discrimination capacity. It can be said that the discrimination capacity of each sample solution with the taste sensor is enough if the identification index is 80 or more.
able to predict the overall palatability of isosorbide solution formulations with high accuracy.

The comparison of the tastes of brand drug (S1) by the calculation result of Euclidean distance and the value added generic drug (A1 and T1) was shown in Fig. 5. A1 restrained the taste a little compared with S1. However, T1 has understood there was no restraint effect of the taste.

In addition, the taste restraint effects of brand drug stock solution (S1) and mineral water dilution (S2) and apple juice dilution (S3) were compared, and the calculation result of the Euclidean distance was shown in Fig. 6. The taste of brand drug is not restrained by the mineral water dilution (S2), but it is largely restrained by the apple juice dilution (S3).

Euclidean distance of each stock solution (S1, A1, and T1) was adjusted to 100%, and the taste restraint effects by mineral water dilution (S2, A2, and T2) and apple juice dilution (S3, A3, and T3) were compared (Fig. 7). Taste of both brand drug and value added generic formulations were restrained slightly by dilution with a mineral water, and taste was restrained largely by dilution with apple juice.

**DISCUSSION**

There is no report of having proved scientifically about the taste of the value added generic drugs. In this study, when the taste of brand and value added generic drugs of isosorbide liquid formulation was measured using a taste sensor, identification index of all the sample was 95. This indicates that there is no problem to detect the taste of α-ASTREE®. The restraint effect of brand and value added generic drugs of isosorbide liquid formulation was compared using Euclidean distances. Although ISOSORBIDE ORAL SOLUTION 70%®

![Fig. 5 The comparison of the taste of the brand and the generic formulations.](image)

![Fig. 6 The comparison of the taste of brand by the dilution of Mineral Water and Apple Juice.](image)

![Fig. 7 The comparison of the taste restraint effect of mineral water and the apple juice.](image)
had restrained the taste more slightly than brand, it became clear that ISOSORBIDE® had not restrained the taste. ISOSORBIDE ORAL SOLUTION 70%® is value added generic drugs of the isosorbide liquid formulations put on the market now, and is considered to be pharmaceutical preparation by which the taste has been improved. ISOSORBIDE ORAL SOLUTION 70%® is mitigating sweetness and bitterness peculiar to isosorbide by adding 180 times as many sweeteners as sucrose. Furthermore, it is the pharmaceutical preparation which added "umami" ingredient and mitigated bitterness. Moreover, mellow acidity has been obtained by addition of lactic acid and acidulant. ISOSORBIDE ORAL SOLUTION 70%® is the value added generic drugs to which the taste was improved with these additives.

The package insert for each of the brand and generic isosorbide solution formulations are "take from it 2-fold dilution with cold water if necessary" because it is described, we examined a restraint effect of taste when each stock solutions were diluted to 2-fold with the mineral water. However, the taste of each stock solution was only slightly restrained, there is no much change. In other words, dilution with water had been shown that it couldn't restrain the taste. However, the taste of each stock solution was significantly restrained by the 2-fold dilution of apple juice. The significant restraint of taste was shown like 71.5% in ISOBIDE®, 81.5% in ISOSORBIDE ORAL SOLUTION 70%®, and 74.3% in ISOSORBIDE® when Euclidean distances of each stock solution were compared as 100%, and restraint was especially large in ISOSORBIDE ORAL SOLUTION 70%®. The restraint degree of the taste of generic drug goods is higher than that of the brand drug though the restraint effect of the taste grows when each stock solution is diluted with the apple juice, and it is a little. The taste improvement of value added generic drugs may be applied for the rational therapy by increasing adherence of some patients. It was proven that it was one method of rising of the possibility that an effective drug therapy could be done by diluting it with the apple juice from these by the patient of the medication nonadherence of the isosorbide solution formulations by this research.

Generally, maintaining adherence is necessary to perform a smooth treatment. However the taste of isosorbide is undesirable making the adherence of this medication lower. Moreover, in the result of having investigated the package insert in 2006, the pharmaceutical preparations of 50 or more is indicated to be "The taste is bitter" in the item of description of package insert. When we investigated package insert in 2011, the pharmaceutical preparations of 73 was indicated to be "The taste is bitter" in the item of description. Since the bitter taste of active ingredient is masked by tablet technology, such as film-coated tablet, sugar-coated tablet, and capsules, adherence is not affected. However, liquid formulation like isosorbide influences adherence easily in order to be directly subject to the influence of the taste. Moreover, because the function evaluation of the taste is generally influenced according to the individual difference, the physical condition, mood, and the fatigue, it is difficult to get reappearance and objectivity. In development phase of pharmaceutical preparation, the taste of the medicine with indistinct safety such as anticancer drug and poisonous drug cannot be confirmed. However, α-ASTREE® has been reported to be possible to predict the taste of medicines safely and objectively. Moreover, electronic taste sensor is prediction of the taste which people have not experienced is also possible.
The method of the taste evaluation by α-ASTREE® excels in objectivity, and is considered to become a good index that forecasts the taste of the medicine as a means not to resort on person's sensory test. It is thought that it can predict the taste of the value added generic drug to use α-ASTREE® for a method of the taste evaluation. Moreover, the method described in the present study seems to offer good predictability for the evaluation of taste of value added generic drugs. We have demonstrated in this study that the taste improvement of value added generic drugs may be applied for the rational therapy by increasing adherence of some patients. And it was proven that it was one method of rising of the possibility that an effective drug therapy was able to be done by diluting it with the apple juice from these by the patient of the medication nonadherence of the isosorbide solution formulations by this research.

REFERENCES


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