Orally disintegrating tablets (ODTs) are formulated to disintegrate upon contact with saliva, allowing administration without water. Olopatadine hydrochloride, a second-generation antihistamine, is widely used for treating allergic rhinitis. However, it has a bitter taste; therefore, the development of taste-masked olopatadine ODTs is essential. Some studies have suggested that citric acid could suppress the bitterness of drugs. However, these experiments were performed using solutions, and the taste-masking effect of citric acid on ODTs has not been evaluated using human gustatory sensation tests. Thus, this study evaluated citric acid’s taste-masking effect on olopatadine ODTs. Six types of olopatadine ODTs containing 0–10% citric acid were prepared and subjected to gustatory sensation tests that were scored using the visual analog scale. The bitterness and overall palatability of olopatadine ODTs during disintegration in the mouth and after spitting out were evaluated in 11 healthy volunteers (age: 22.8±2.2 years). The hardness of the ODTs was >50N. Disintegration time and dissolution did not differ among the different ODTs. The results of the gustatory sensation tests suggest that citric acid could suppress the bitterness of olopatadine ODTs in a dose-dependent manner. Olopatadine ODTs with a high content of citric acid (5–10%) showed poorer overall palatability than that of without citric acid despite the bitterness suppression. ODTs containing 2.5% citric acid, yogurt flavoring, and aspartame were the most suitable formulations since they showed low bitterness and good overall palatability. Thus, citric acid is an effective bitterness-masking option for ODTs.

Key words citric acid; orally disintegrating tablet; organoleptic masking; human gustatory sensation test; olopatadine

Orally disintegrating tablets (ODTs) are easy to swallow for patients with dysphagia and easy to administer to elderly and pediatric patients. ODTs are designed to disintegrate upon contact with saliva and in the absence of water, allowing patients to take medication anywhere and at any time, such as in school or workplace. ODTs are highly convenient; hence, these formulations improve patient adherence and increase the effectiveness of pharmacotherapy. In addition, ODTs reduce the amount of water required compared to that required with conventional tablets. Ingestion of ODTs without water may improve QOL of patients with an overactive bladder because an ODT reduces the amount of fluid intake when taking medications.

Many drugs have unpleasant tastes, including ODTs containing drugs, which may reduce patient’s adherence. Taste and palatability of drugs are the greatest barriers to treatment not only in children but also in adults. To improve a drug’s palatability, unpleasant tastes are masked using various methods such as physical masking, organoleptic masking, and chemical masking. Taste-masking agents such as flavorings, sweeteners, and acids are often used in organoleptic masking. Some studies reported that flavorings and sweeteners suppressed the bitterness and improved the palatability of ODTs. Acids are widely used in many food products, beverages, and drugs to improve their taste, adjust pH, and maintain their stability. Adding acids to ODTs may mask their bitterness and improve palatability because sourness has been reported to be liked by patients, particularly pediatric patients.

Citric acid, which is found in high levels in citrus fruits such as lemon, is an odorless carboxylic acid and one of the most popular acid ingredients. It is often added to food and beverages for its sourness and to adjust the pH. Similarly, citric acid is used in drug formulations such as “gummy” formulations. Some studies, by using an electronic tongue and calcium imaging analysis of human bitter taste receptor hTAS2R, demonstrated that citric acid can suppress the bitterness of drugs. However, these studies were performed using solutions and not ODTs. Further, the taste-masking effect of citric acid in ODTs has not been evaluated using human gustatory sensation tests. The efficacy of citric acid as a taste-masking agent remains unknown.

Recently, the prevalence of allergic rhinitis has increased in Japan, not only in adults but also in children. The three cardinal symptoms in allergy are sneezing, nasal obstruction, and rhinorrhea, which may lead to a loss of concentration and disturb study, work, and daily life. They also deeply affect the QOL. Treatment of allergic rhinitis is important since by controlling the symptoms it improves work productivity and QOL. The international guideline for allergic rhinitis “Allergic Rhinitis and its Impact on Asthma (ARIA)” recommends second-generation antihistamines as therapeutic agents for allergic rhinitis. Olopatadine hydrochloride, a second-generation antihistamine, is widely used for the treatment of allergy in
both pediatric and adult patients worldwide. However, olopa
tadine hydrochloride has a bitter taste; thus, effective taste
masking of olopatadine ODTs is necessary in the develop-
ment of ODTs. Olopatadine hydrochloride ODTs could reduce
problems with administration and also enhance patient adher-
ence, since patients are usually required to follow a long-term
course of treatment. In addition, long-term medication is often
associated with a decreased QOL.

The aim of our study was to clarify the effect of citric acid in
masking the bitter taste and improving the overall palatabil-
ity of olopatadine ODTs. Six types of olopatadine ODTs con-
taining 0–10% citric acid were prepared and the taste-masking
effect of citric acid was evaluated using human gustatory
sensation tests.

MATERIALS AND METHODS

Materials All samples were commercially obtained as fol-

follows: olopatadine hydrochloride from Sumitomo Chemi-
cal Co., Ltd. (Tokyo, Japan); α-mannitol (Mannit P) from
Mitsubishi Shoji Foodtech Co., Ltd. (Tokyo, Japan); low-
substituted hydroxypropyl cellulose (L-HPC LH-20) from
Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan); methacrylate
copolymer (Eudragit® L 30 D-55) from Evonik Japan Co., Ltd.
(Tokyo, Japan); methacrylate copolymer (Eudragit® L 30 D-55) from Evonik Japan Co., Ltd. (Tokyo, Japan); low-
substituted hydroxypropyl cellulose (L-HPC LH-20) from
Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan); methacrylate
copolymer (Eudragit® L 30 D-55) from Evonik Japan Co., Ltd.
(Tokyo, Japan); methacrylate copolymer (Eudragit® L 30 D-55) from Evonik Japan Co., Ltd. (Tokyo, Japan); yellow ferric oxide from Kishi Kasei Co., Ltd. (Tokyo, Japan); and aspartame from Ajinomoto Co., Inc.
(Yokohama, Japan); talc (CROWN TALC) from Matsumura
Seiki Co., Ltd., Kyoto, Japan). All raw materials used in the formulations
were Japanese Pharmacopeia (JP)-compliant products, and
the reagents used were either JP listed or commercial special
ity chemicals.

Preparation of ODTs The core particles containing
oloapatadine hydrochloride were granulated by using a mixer
granulator (VG-01, Powrex Corp., Hyogo, Japan), composed
oloapatadine hydrochloride, α-mannitol, L-HPC, yellow ferric
oxide, and Eudragit L 30 D-55. The core particles were coated
with a coating solution comprising of α-mannitol, triethyl
citrate, Eudragit L 30 D-55, and talc using a fluidized-bed
granulator (MP-01, Powrex Corp.).

The ODTs were prepared by a direct powder compression
method using a tablet compressor (HANDTAB-100, Ichihashi
Seiki Co., Ltd., Kyoto, Japan). The ODTs formulations are
shown in Table 1. The ODTs contained 5mg olopatadine hy-
drochloride, and the diameter and weight of the ODTs were
9mm and 250mg, respectively. Citric acid was added to the
ODTs at concentrations of 0, 0.1, 1.0, 2.5, 5.0, and 10% (C0-
C10, C1-, C2.5-, C5-, and C10-ODTs, respectively).

In addition, to further improve the palatability of the ODTs,
ODTs containing other taste-masking agents, a flavoring and
a sweetener, were prepared with 2.5% citric acid. ODTs; CF-
ODT contained 2.5% citric acid and 0.1% yogurtt flavoring,
and CFS-ODT contained 2.5% citric acid, 0.1% yogurtt flavor-
ing, and 0.3% aspartame.

Table 1. Formulations of the Orally Disintegrating Tablets Containing Citric Acid

| Ingredients                      | ODTs          |
|----------------------------------|---------------|
|                                  | C0  | C0.1 | C1   | C2.5 | C5   | C10  |
| Olopatadine granules (mg)         | 37.71| 37.71| 37.71| 37.71| 37.71| 37.71|
| Ludiflash (mg)                    | 188.54| 198.29| 196.04| 192.29| 186.04| 173.54|
| Kollidon CL-SF (mg)               | 12.50| 12.50| 12.50| 12.50| 12.50| 12.50|
| Citric acid (mg)                  | —   | 0.25 | 2.50 | 6.25 | 12.50| 25.00|
| Sodium stearyl fumalate (mg)      | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 | 1.25 |
| Total (mg)                        | 250.00| 250.00| 250.00| 250.00| 250.00| 250.00|

The hardness of the tablets was mea-
sured using a load-cell-type hardness tester (PC-30, Okada
Seiko Co., Ltd., Tokyo, Japan). Five tablets of each type of
ODTs were evaluated and the mean hardness was calculated.

Tablet Hardness The hardness of the tablets was mea-
sured using a load-cell-type hardness tester (PC-30, Okada
Seiko Co., Ltd.) as described previously.12) Artificial saliva
(NaCl, 1.44 g/L; KCl, 1.47 g/L; Tween 80, 0.3%) warmed to
37°C was used as the test solution, and was dripped from a
height of 80 mm at a flow rate of 6.0 mL/min. Five tablets of
each type of ODTs were evaluated and the mean disintegra-
tion time was calculated.

Dissolution The dissolution test was performed in accor-
dance with the JP Dissolution Test Method 2 (paddle method)
at 50 rpm using a JP dissolution tester (PI-6S, Miyamoto
Riken Ind. Co., Ltd., Osaka, Japan). One tablet was placed in
900 mL of purified water that was kept at 37±0.5°C. Samples of
the dissolved solutions were taken at 15 min, and the con-
centration of olopatadine hydrochloride was determined using
HPLC.

Dissolution in a Small Volume of Solution To evalu-
ate the dissolution of olopatadine hydrochloride ODTs in the
mouth, the dissolution test was performed with small volumes
of solution. One tablet of each ODTs was dissolved for 45 s
under magnetic stirring in 10 mL of purified water. The so-
lution was filtered through a 0.45-μm disposable membrane
filter (Toyo Roshi Kaisya, Ltd., Tokyo, Japan) and the con-
centration of olopatadine hydrochloride was determined using
HPLC.

HPLC Condition The concentration of olopatadine hy-
drochloride was determined using a HPLC system (Promi-
enance UFLC, Shimadzu Corporation, Kyoto, Japan) compris-
ing of a pump (LC-20AD, Shimadzu Corporation), an online
degassing unit (DGU-20A3, Shimadzu Corporation), a column
oven (CTO-20AC, Shimadzu Corporation), an autosampler
(SIL-20AC, Shimadzu Corporation), and a photodiode array
detector (SPD-M20A, Shimadzu Corporation), and was inte-
grated using a system controller (CBM-20A, Shimadzu Corpor-
ation). HPLC was performed using an analytical column
(L-column ODS, 4.6×250 mm, Chemicals Evaluation and
Research Institute, Tokyo, Japan) with a mobile phase (0.05 M phosphate buffer (pH 3.5)/acetonitrile (1:9, v/v) containing 8 mM sodium lauryl sulfate) delivered at a flow rate of 1 mL/min. The column temperature was kept at 40°C. Detection was based on UV absorbance at 299 nm.

**Human Gustatory Sensation and Clinical Disintegration Time** First, the taste-masking effect of citric acid was assessed. Eleven healthy volunteers (2 male and 9 female volunteers; age, 22.8±2.2 years, mean±standard deviation (S.D.)) participated in this study after providing written informed consent. The study protocol was approved by the Ethics Committee of Hamamatsu University School of Medicine, Japan. The study was registered at the UMIN Clinical Trials Registry (UMIN0000022590). The subjects placed each ODT in their mouth and allowed the ODT to disintegrate. Thereafter, the bitterness and overall palatability of the ODTs were evaluated using a visual analog scale (VAS) (1st evaluation). All subjects were asked to place a mark along the VAS line. The strongest sensation for each parameter was marked at 100 mm. VAS bitterness scores of 0 and 100 indicate “none” and “very bitter,” respectively, whereas VAS overall palatability scores of 0 and 100 indicate “bad” and “good,” respectively. Parallel with the VAS evaluation, the clinical disintegration time was measured using stopwatches. After the disintegrated tablet was removed, the subjects were immediately subjected to the VAS evaluation again (2nd evaluation). Thereafter, the subjects rinsed their oral cavity with 120 mL of water and were given a 15-min interval before the testing of the next tablets.

Further tests were performed to clarify the effect of combining the taste-masking agents. The ODTs (C2.5-, CF-, and CFS-ODTs) were evaluated in 13 healthy volunteers (3 males and 10 females; age, 23.3±2.5 years, mean±S.D.) as described above.

**Electronic Gustatory Test** The Astree e-tongue system electronic gustatory system (Alpha M.O.S. Japan K.K., Tokyo, Japan) was used for the taste evaluation of the sample solutions. The solutions were prepared as follows: one tablet of each ODTs was dissolved for 30 min under magnetic stirring in 100 mL of purified water. The solution was then filtered through a 0.45-µm disposable membrane filter and subjected to the electronic gustatory tests. Each ODT was analyzed in triplicate. For the analysis, we prepared the placebo ODTs corresponding to C0-, C0.1-, C1-, C2.5-, C5-, and C10-ODTs by replacing olopatadine hydrochloride with Ludiflash.

The data obtained from the Astree sensors were analyzed using AlphaSoft V14 (Alpha M.O.S. Japan K.K.). In this study, principal component analysis (PCA) was employed. PCA can reduce the dimension of data and visualize the differences between the samples on a two-dimensional graph, PCA map. On the PCA map, data points of the sample were compared using the calculated distance between them. The Euclidean distance (the distance between the center of gravity of the placebo and that of the drug samples) was calculated. The Euclidean distance was calculated according to equation below, where $d_{PQ}$, $n$, $P$, and $Q$ represent the Euclidean distance, the number of sensors, the value measured by sensor of ODT, and the value measured by sensor of placebo, respectively. If the Euclidean distance between two samples is small, then the taste of the drug sample is similar to that of the placebo.

$$d_{PQ} = \sqrt{\sum_{i=1}^{n} (P_i - Q_i)^2}$$

**Statistical Analysis** All data are expressed as the mean±S.D. Statistical analysis was performed by using paired t-test with Bonferroni correction by using GraphPad Prism ver.5.02 (GraphPad Software, Inc., San Diego, U.S.A.).

**RESULTS**

**Tablet Characteristics** Table 2 shows the hardness, in vivo and clinical disintegration time, and dissolution at 45 s and 15 min of C0-, C0.1-, C1-, C2.5-, C5-, and C10-ODTs.

The hardness of the ODTs was >50 N. The in vitro and clinical disintegration times were 10.5–13.5 and 14.4–15.7 s for all tablets, respectively. The disintegration times of the ODTs containing citric acid (C0.1-, C1-, C2.5-, C5-, and C10-ODTs) were similar to that of C0-ODT. The dissolution of C0, C0.1, C1, C2.5, and C5-ODTs in water at 45 s was 50.2–55.9%, whereas that of C10-ODT in water at 45 s was higher than that of the other tablets. The dissolution of C0, C0.1, C1, C2.5, C5, and C10-ODTs in water at 15 min was 82.9–88.4%.

**Taste Evaluation of ODTs in Human Gustatory Sensation Test** To evaluate the taste-masking effect of citric acid, gustatory sensation tests were performed. The bitterness and overall palatability of the ODTs were evaluated with 11 volunteers using the VAS. Bitterness VAS scores of ODTs in the 1st and 2nd evaluations are shown in Figs. 1a and b, respectively. Bitterness scores of C0-ODT were the highest in the 1st and 2nd evaluations (47 and 40) in all the tablets tested. Bitterness scores of ODTs decreased with increasing concentration of citric acid in the 1st evaluation (Fig. 1a). In the 2nd evaluation, the bitterness scores of the ODTs containing citric acid (C0.1-,...
C1-, C2.5-, C5-, and C10-ODTs) were lower than that of C0-ODT; C2.5-ODT showed the lowest score (Fig. 1b).

Overall palatability scores of ODTs in the 1st and 2nd evaluations are shown in Figs. 1c and d, respectively. Overall palatability scores of C0-, C0.1-, C1-, and C2.5-ODTs in the 1st evaluation were similar (38–46), but those of C5-ODT and C10-ODT were lower (26 and 20, respectively) than those of C0-, C0.1-, C1-, and C2.5-ODTs (Fig. 1c). In the 2nd evaluation, the overall palatability scores of C0.1-ODT and C2.5-ODT (54 and 55) were higher than that of C0-ODT (44) (Fig. 1d).

C1-, C2.5-, C5-, and C10-ODTs) were lower than that of C0-ODT; C2.5-ODT showed the lowest score (Fig. 1b).

Overall palatability scores of ODTs in the 1st and 2nd evaluations are shown in Figs. 1c and d, respectively. Overall palatability scores of C0-, C0.1-, C1-, and C2.5-ODTs in the 1st evaluation were similar (38–46), but those of C5-ODT and C10-ODT were lower (26 and 20, respectively) than those of C0-, C0.1-, C1-, and C2.5-ODTs (Fig. 1c). In the 2nd evaluation, the overall palatability scores of C0.1-ODT and C2.5-ODT (54 and 55) were higher than that of C0-ODT (44) (Fig. 1d).

Each column presents the mean±S.D. (n=11). Paired t-test with Bonferroni correction was used to detect any significant differences among the orally disintegrating tablets for each test compared with C0-ODT. p<0.01 was considered significant.

Fig. 1. Bitterness VAS Score in 1st Evaluation (during Disintegration) (a) and 2nd Evaluation (after Spitting) (b), and the Overall Palatability VAS Score of C0-, C0.1-, C1-, C2.5-, C5-, and C10-ODTs in 1st Evaluation (c) and 2nd Evaluation (d) Using the Gustatory Sensation Test

(a) Each column represents the mean±S.D. (n=11). Paired t-test with Bonferroni correction was used to detect any significant differences among the orally disintegrating tablets for each test compared with C0-ODT. p<0.01 was considered significant.

Fig. 2. Euclidean Distances of C0-, C0.1-, C1-, C2.5-, C5-, and C10-ODTs (a), and the Relationship between the Euclidean Distance and Bitterness VAS Score in the 1st Evaluation (b)

(a) Each column represents the data from one experiment. (b) Bitterness VAS scores in the 1st evaluation as shown Fig. 1a were plotted on the y-axis, and the Euclidean distances shown in Fig. 2a were plotted on the x-axis.
Electronic Gustatory Test

The sensor data obtained from the sample solutions were analyzed using PCA, and the Euclidean distances were calculated. The Euclidean distance is the distance between each drug-containing ODT and its corresponding placebo. The Euclidean distances are shown in Fig. 2a. The Euclidean distances decreased with increasing content of citric acid, from C0-ODT (373) to C10-ODT (33.8). The relationship between the Euclidean distances and the bitterness VAS scores in the 1st evaluation of each ODT obtained by the human gustatory sensation test is shown in Fig. 2b. A good correlation was observed between these 2 parameters (correlation coefficient \( r^2 = 0.982; p<0.001 \)).

Effect of Combining Taste-Masking Agents

To evaluate the effect of combining the taste-masking agents (flavoring and sweetener) with C2.5-ODT, which showed a low bitterness VAS score and a high overall palatability VAS score, we prepared 2 types of ODTs (CF- and CFS-ODT). Flavoring and flavoring plus sweetener were added to C2.5-ODT to obtain the preparations CF- and CFS-ODTs, respectively. The hardness of CF- and CFS-ODTs was 59±4.5 and 54±3.1 N, respectively. The in vitro disintegration times of CF- and CFS-ODTs were 12.4±0.38 and 13.2±1.7 s, and the clinical disintegration times of CF- and CFS-ODTs were 19.7±4.2 and 15.9±3.0 s, respectively. The dissolution of CF- and CFS-ODTs was 48.0±24 and 42.2±21% at 45 s, and 88.3±2.5 and 89.6±1.0% at 15 min, respectively.

In the human gustatory sensation tests, the bitterness VAS scores in the 1st and 2nd evaluations were decreased by the addition of flavoring and sweetener compared to those of C2.5-ODT (Figs. 3a, b). The overall palatability VAS scores were increased following the addition of flavoring and sweetener in both the 1st and 2nd evaluations (Figs. 3c, d). Overall palatability VAS score in the 2nd evaluation of CFS-ODT was significantly higher than that of C2.5-ODT.

DISCUSSION

The aim of this study was to clarify the taste-masking effect of citric acid on ODTs. Six types of olopatadine ODTs containing citric acid were evaluated for their bitterness and overall palatability in human gustatory sensation tests. The results suggested that citric acid effectively suppresses the bitterness of olopatadine ODTs.

In the human gustatory tests, the bitterness VAS score of the ODT without citric acid (C0-ODT) was the highest among the tested ODTs in both the 1st and 2nd evaluations, indicating that C0-ODT has the strongest bitter taste during disintegration in the mouth and after administration. We previously showed that the palatability of several ODTs could be quantitatively evaluated using the VAS in human gustatory sensation tests.\(^2\)\(^5\)\(^13\) VAS is widely used to assess the levels of
pain or palatability in humans and is regarded as a reproducible approach that provides a good representation of subjective measurements.\textsuperscript{14–16}

The bitterness VAS scores of the ODTs containing citric acid decreased with an increasing amount of citric acid. Furthermore, the ODTs without citric acid (C0-ODT) showed the longest Euclidean distance as measured by the electronic gustatory system (Astree e-tongue system) among the tested ODTs, and the distance decreased with an increasing amount of citric acid. In addition, VAS score and Euclidean distance of the ODTs showed the plateau over 5% of citric acid. These results strongly suggest that citric acid can suppress the bitterness of olopatadine ODTs in a dose-dependent manner, at least under 5% of citric acid. In vitro and clinical disintegration times and dissolution at 45 s and 15 min of the ODTs containing citric acid did not differ among the ODTs tested. Thus, the suppressive effect of citric acid on the bitterness of olopatadine ODTs was not caused by changes in tablet characteristics from the content of citric acid. The results of the in vitro evaluations demonstrated the suppressive effects of citric acid on bitterness. Rachid \textit{et al.} showed that citric acid suppressed the bitterness of epinephrine by using the taste evaluation using an e-tongue.\textsuperscript{9} Calcium imaging analysis also indicated that citric acid inhibited the response of hTAS2R16, one of the human bitter taste receptors, to salicin.\textsuperscript{10} In addition, Lawless \textit{et al.} demonstrated that citric acid suppressed the bitterness of calcium chloride by using human gustatory sensation tests.\textsuperscript{17} Our results were consistent to these findings, and demonstrated the suppressive effect of citric acid on the bitterness of ODTs. In these previous studies, however, the effects were observed with citric acid solutions instead of tablet formulations. In this study, we demonstrated the role of citric acid as a taste-masking ingredient in ODTs.

Interestingly, the overall palatability of the olopatadine ODTs with a high content of citric acid (5–10%) were poorer than that of C0-ODT, despite its bitterness. In addition, the bitterness VAS scores of ODTs with a high content of citric acid did not differ to that of ODTs containing 2.5% citric acid. Rousmans \textit{et al.} reported a confusion in taste between sour and bitter in 12% of the subjects.\textsuperscript{18} Therefore, it is likely that the ODTs with a high content of citric acid could be recognized as bitter by some of the subjects because of a confusion in taste. In this context, the addition of high-content citric acid should be avoided, and C2.5-ODTs were the most suitable formulation since it is associated with low bitterness and high overall palatability.

In this study, a good correlation was observed between the bitterness VAS score determined using human gustatory test and the Euclidean distance measured using electric gustatory test. Previously, Nakamura \textit{et al.} evaluated the palatability of famotidine- and amloidipine-containing ODT by using human gustatory sensation test and e-tongue, and reported a good correlation between the Euclidean distance and the VAS score.\textsuperscript{19} Thus, it was suggested that the electric gustatory test of Astree e-tongue could evaluate the effects of organoleptic taste-masking ingredients including citric acid.

Various organoleptic methods have been reported to improve the palatability of ODTs.\textsuperscript{5,13} Accordingly, to further improve the palatability of ODTs, ODTs containing 2.5% citric acid, yogurt flavoring, and aspartame were prepared. The ODTs containing 2.5% citric acid was thought as a basic formulation because this was the most suitable olopatadine ODTs preparation. The overall palatability VAS score of the ODT containing citric acid, yogurt flavoring, and aspartame was the highest compared to those of other ODTs in the 1st and 2nd evaluations. This result suggests that this combination of taste-masking agents is effective in improving palatability, and we could formulate olopatadine ODTs with good palatability by using a combination of citric acid, yogurt flavoring, and aspartame.

CONCLUSION

Olopatadine hydrochloride ODTs were prepared and subjected to bitterness and overall palatability evaluations using the VAS scale in human gustatory sensation tests. Our results suggested that citric acid could suppress the bitterness of olopatadine ODTs dose-dependently. Olopatadine ODT containing 2.5% citric acid was the most suitable formulation. As expected, citric acid is an effective bitterness-masking option for ODTs and could help improve patient’s adherence.

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Conflict of Interest SU and NN received a Research Grant from Kissei Pharmaceutical Co., Ltd. (Tokyo, Japan), Kyowa Hakko Kirin Co., Ltd. (Tokyo, Japan), Towa Pharmaceutical Co., Ltd. (Osaka, Japan), and Otsuka Pharmaceutical Co., Ltd. (Tokyo, Japan). NN serves as a consultant to Kissei Pharmaceutical Co., Ltd., Otsuka Pharmaceutical Co., Ltd., and Shiseido Japan Co., Ltd. (Tokyo, Japan). KO received research funding from Japan Research Foundation for Clinical Pharmacology. The other authors declare no conflict of interest.

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