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Development of oral acetaminophen chewable tablets with inhibited bitter taste

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Abstract

Various formulations with some matrix bases and corrigents were examined for development of oral chewable tablets which suppressed the bitter taste of acetaminophen, often used as an antipyretic for infants. Corn starch/lactose, cacao butter and hard fat (Witepsol H-15) were used for matrix bases, and sucrose, cocoa powder and commercial bitter-masking powder mixture made from lecithin (Benecoat BMI-40) were used for corrigents against bitter taste. The bitter taste intensity was evaluated using volunteers by comparison of test samples with standard solutions containing quinine at various concentrations. For the tablets made of matrix base and drug, Witepsol H-15 best inhibited the bitter taste of the drug, and the bitter strength tended to be suppressed with increase in the Witepsol H-15 amount. When the inhibitory effect on the bitter taste of acetaminophen solution was compared among the corrigents, each tended to suppress the bitter taste; especially, Benecoat BMI-40 exhibited a more inhibitory effect. Further, chewable tablets were made of one matrix base and one corrigent, and of one matrix base and two kinds of corrigents, their bitter taste intensities after chewing were compared. As a result, the tablets made of Witepsol H-15/Benecoat BMI-40/sucrose, of Witepsol H-15/cocoa powder/sucrose and of Witepsol H-15/sucrose best masked the bitter taste so that they were tolerable enough to chew and swallow. The dosage forms best masking bitter taste showed good release of the drug, indicating little change in bioavailability by masking.

Keywords: Oral acetaminophen chewable tablet; Bitter taste intensity; Masking; Matrix base; Corrigent

1. Introduction

Many drugs including alkaloids such as quinine or berberine and antibiotics such as sparfloxacin or clarithromycin exhibit bitter taste when orally administered (Shirai et al., 1993, 1994; Katsuragi et al., 1995, 1997; Yajima et al., 1999). As oral dosage forms are easily available due to their simple method of administration way, they have also been developed for the drugs with bitter taste. However, for patients, such drugs are not necessarily easy to swallow, resulting in non-compliance

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and subsequent decrease in efficacy. Therefore, various techniques have been examined for improving the problems of the bitter taste. Use of capsules, coating with polymers, microencapsulation, complexation, and chemical modification have been reported. These methods are very useful for masking the drug taste, but preparation of these dosage forms is not necessarily easy. The dosage forms will be bulky or large when a large amount of drug is required in one dose. It is important for infants or elderly people to be able to have medications easily. Powders, solutions and chewable dosage forms will be adequate for such people. In such dosage forms, use of some additives may be available for masking the bitter taste. Actually, recently, additives altering taste are examined extensively (Katsuragi and Kurihara, 1993; Katsuragi et al., 1996, 1995, 1997), and methods to evaluate bitterness of drugs have been developed (Uchida et al., 2000, 2001). Syrup is known as a traditional dosage form often used for infants and children, which masks the unpleasant taste of drugs.

Acetaminophen, an antipyretic, has a bitter taste, and suppository and syrup dosage forms are commonly used to infants and children (Autret et al., 1994; Van Esch et al., 1995; Coulthard et al., 1998; Hansen et al., 1999). For this medicine, a considerably large amount (some hundreds of mg—nearly 1 g) is required in one dose. Therefore, for acetaminophen, the dosage form easy to swallow with inhibited bitter taste is necessary to achieve good compliance and simple administration way; powders, solutions, suspensions and chewable dosage forms are considered adequate for easy swallow. Although the syrup dosage form of acetaminophen is already in the market, it will not always be available for clinical use because drinking a fairly large volume of its dosage form may be a burden on some patients or syrup taste may be hated by some patients. Chewable dosage form may be useful for improving such problems. Thus, in the present study, chewable dosage forms to mask bitter taste of acetaminophen were investigated in efforts to obtain oral acetaminophen dosage forms which could be taken more easily. The physical mixture of corn starch and lactose, cacao butter and hard fat (Witepsol H-15) (Choi et al., 1996) were used as a matrix base for the tablet because they can be used safely as additives for oral dosage forms. Sucrose, cocoa powder (Koyama and Kurihara, 1972; Pickenhagen and Dietrich, 1975; Aremu et al., 1995) and commercial bitter-masking powder mixture made from lecithin (Benecoat BMI-40) (Katsuragi et al., 1997) were used as corrigents against bitter taste because each corrigent is often utilized for masking of bitter taste and appears to mask the bitter taste in its own manner. Sucrose is often utilized as a sweetening agent against drugs with unpleasant tastes or stimuli (Yin et al., 1996). Cocoa has been shown possibly useful for suppression of bitter taste of drugs (Popova, 1969; Takano, 2002). Benecoat BMI-40 is known as a corrigent against bitter taste. In the present study, the inhibitory effects of these bases and corrigents against bitter taste of acetaminophen were examined by a bitter taste intensity test using volunteers. At the same time, a drug release test was performed to investigate the expected bioavailability.

2. Materials and methods

2.1. Materials

Acetaminophen was purchased from Sigma Chemical Co. (USA). Quinine sulfate and sucrose were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Corn starch and lactose were supplied by Kosakai Pharmaceutical Co. (Japan) and Miyazawa Pharmaceutical Co. (Japan), respectively. Cacao butter was obtained from Hayashi Ichiji Co. (Japan). Hard fat (Witepsol H-15) was purchased from Mitsuba Trading Co. (Japan). Commercial bitter-masking powder mixture made from lecithin (Benecoat BMI-40) was supplied by Kao Corporation (Japan). A commercial product was used for cocoa powder. All other chemicals were of reagent grade.

2.2. Preparation of tablets

The tablets (600, 800, 1000 and 1200 mg), having disk shape with the diameter of 1.5 cm and acetaminophen content of 100 mg per tablet,

were made using the mixture of corn starch and lactose (1:2, w/w) as additives, when magnesium stearate was added to be 3% (w/w) of the total amount. After mixing the powder mixture, tabletting was performed with a Shimadzu Hand Press HP-10 under the conditions of 80 kg/cm^2 and pressing time of 30 s. The other tablets were prepared as follows. A certain amount of Witepsol H-15 or cacao butter was melted at 40 °C. Then, actoaminophen was added at 1/5, 1/7, 1/9 and 1/11 ratios (w/w) to the melted base, and the resultant mixture was sufficiently mixed. The mixture was put into a disk-shaped frame (2 cm diameter) to yield tablets containing 100 mg acetaminophen per tablet and cooled at 7–8 °C to solidify. Each disk-shaped tablet obtained was taken out from the frame and used in the experiments.

Furthermore, when Witepsol H-15 and cacao butter were used as matrix bases, the tablets made of acetaminophen, matrix base and corrigent(s) were prepared. Namely, each tablet was prepared using 100 mg acetaminophen and 900 mg matrix base containing one corrigent (1 or 5%, w/w) or two corrigents (each 1 or 5%, w/w). The preparation of the tablet was performed in the same manner as above.

2.3. Standard solution for evaluation of bitter taste intensity

The bitter taste strength was evaluated based on human bitter taste recognized by volunteers. For determination of the bitter taste intensity, a series of quinine sulfate solutions were prepared at different concentrations as standard solutions based on the reports by Indow (1966, 1969) and Katsuragi et al. (1997). A series of scores of the bitter taste intensity are ranged from 0 to 10 as shown in Table 1.

2.4. Effect of corrigent on bitter taste of acetaminophen in aqueous solution

Acetaminphen solutions of 0.2, 0.3 and 0.6% (w/v) were tested for bitter taste intensities. Sucrose, cocoa powder and Benecoat BMI-40 were used as corrigents for masking of bitter taste. Firstly, the masking effect of corrigents was investigated by adding those at 1.0% (w/v) and to acetaminophen aqueous solution with bitter taste of 8.4. Next, each corrigent was added at 0.1, 0.3, 0.5 and 1.0% (w/v) to acetaminophen aqueous solution of each concentration, and the resultant solutions were tested for bitter taste intensities.

Table 1
Relationship between defined bitter taste intensity and concentration of quinine sulfate aqueous solution (standard solution)

Defined bitter taste intensity	Concentration of quinine sulfate (%, w/v)
0	0.00000
1	0.00023
2	0.00050
3	0.00094
4	0.00157
5	0.00241
6	0.00388
7	0.00608
8	0.00985
9	0.01572
10	0.02568

The bitter taste intensity was evaluated as follows. One ml of each standard solution was dropped on the center of the tongue, the solution was retained in the mouth for 10 s, and then the mouth was thoroughly rinsed with deionized water. Next, 1 ml of the test solution was put in the mouth and tasted in the same manner. Subjects compared the bitter taste intensity of the test solution with that of the standard solution, and selected the standard solution having a bitter taste intensity equivalent to that of the test solution.

2.5. Effect of matrix base or the mixture of matrix base and corrigent(s) on bitter taste of acetaminophen in chewable tablets

The acetaminophen (100 mg)-containing tablets made using matrix base alone as an additive were investigated for bitter taste intensities. Next, the acetaminophen (100 mg) containing tablets (1 g) with matrix base and one corrigent (1 or 5% concentration to total weight) as additives were examined for bitter taste intensities. Further, the acetaminophen (100 mg) containing tablets (1 g) with matrix base and two kinds of corrigents (each

1 or 5% concentration to total weight) were evaluated for bitter taste intensities.

The bitter taste intensity was evaluated as follows. About 1 ml of each standard solution was dropped on the center of the tongue, the solution was retained in the mouth for 10 s, and then the mouth was thoroughly rinsed with deionized water. Next, one tablet was put in the mouth, chewed normally at ten times and retained on the center of the tongue in the mouth for 10 s. Then, subjects compared the bitter taste intensity of the chewed tablet with that of the standard solution, and selected the standard solution having a taste intensity equivalent to that of the tested chewed tablet.

2.6. Drug release studies

This experiment was examined for the tablets and crushed tablets according to the first method (rotation basket method) in the Pharmacopoeia of Japan (JP) 14. For crushed tablets, a tablet was mechanically broken into nearly ten pieces with similar fragment size, which simulated chewing a tablet.

The first fluid, aqueous HCl solution containing NaCl at 0.2% (w/v) (pH 1.2), and the second fluid, 50 mM phosphate buffer (KH_2PO_4–NaOH) (pH 6.8), were used as dissolution media. One tablet or all the fragments obtained by crushing one tablet as described above were put in a basket, set in 900 ml of the dissolution medium pre-warmed at 37 °C, and rotated at 60 rpm at 37 °C. At appropriate time points, 1 ml of the tested medium was taken and filtered with a membrane filter (0.45 μm pore size). Immediately after each sampling, 1 ml of fresh medium was complemented. The filtered sample was diluted to 10-fold volume with fresh medium, and measured spectrophotometrically at 244 nm to determine the amount of released drug.

2.7. Statistical analysis

Statistical analyses were performed using the unpaired t-test. Significant difference was set at $P < 0.05$.

3. Results and discussion

3.1. Effect of corrigent on bitter taste of acetaminophen solution

As shown in Table 1, the standard solutions for matching the bitter taste intensity of tested samples were prepared by referring to the reports by Indow (1966, 1969) and Katsuragi et al. (1997); though it is possible to express the bitter taste intensities in other score manners (Takano, 2002). The present standard solutions of a series of quinine concentrations gave a continuity of bitter taste intensities and allowed subtle discrimination between the bitter taste intensities by humans. Namely, all the volunteers recognized that the bitter taste intensity was not or slight at the score of less than 3 and that it reached the highest level at the scores of more than 8. Further, they could discriminate well the bitter taste intensities of the scores of 3–7.

It was recognized that aqueous solution of acetaminophen elicited various strengths of bitter taste sensation in humans at the concentration range of 0.0–0.6% (w/v) (Fig. 1). The bitter taste intensities were not related linearly to the concentration, and increase in bitter taste intensity was slower at higher concentration. In the solution form, the bitter taste intensity of acetaminophen was found lower around one order for concentration (w/v) than that of alkaloids such as quinine and berberine, and near that of propranolol or

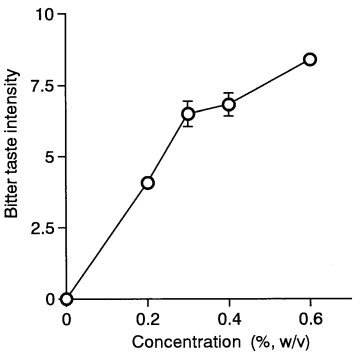

Fig. 1. Bitter taste intensities of acetaminophen solution at various concentrations. Each point represents the mean ± S.E. ($n = 5$–6).

thiamine. The bitter taste strength appears to be different among drugs (Katsuragi et al., 1997).

It was confirmed that each corrigent inhibited the bitter strength of quinine solution (Fig. 2A). Especially, Benecoat BMI-40 showed the strongest inhibition of bitter taste of quinine solution, indicating corrigents related to masking of bitter taste receptors would act effectively on the inhibition of the bitter taste intensity. When the corrigents were added at 1% (w/v), their inhibitory effect against the bitter taste was compared between acetaminophen aqueous solution and quinine aqueous solution, which showed bitter taste intensity scores of 8.4 and 9, respectively, with no corrigent. The results are shown in Fig. 2. Quinine aqueous solution underwent significantly marked inhibition of bitter taste by each corrigent. The decrease in the bitter taste intensity of acetaminophen solution was smaller, but the bitter taste was significantly lowered by addition of each corrigent.

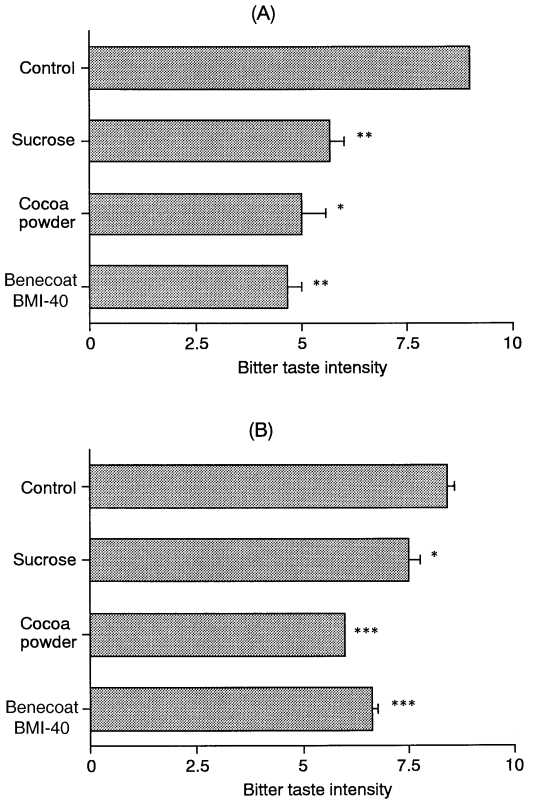

Fig. 2. Inhibitory effect of corrigent against bitter taste of quinine aqueous solution (A) and acetaminophen aqueous solution (B). Quinine and acetaminophen solutions showed bitter taste intensities of 9 and 8.4, respectively, under the absence of corrigents. Corrigents were added at 1% (w/v). Each column represents the mean ± S.E. ($n = 3$ for A; $n = 4$–5 for B). * $P < 0.05$ vs. control; ** $P < 0.01$ vs. control; *** $P < 0.001$ vs. control.

When each corrigent was added to aqueous acetaminophen solution of 0.2, 0.3 and 0.6% (w/v) at different concentrations, change in the bitter taste was examined. Each corrigent tended to suppress the bitter taste to some extent with increase in the concentration; especially, inhibitory effect of corrigent was observed more greatly in acetaminophen solution of higher concentration (Fig. 3). For 0.2% (w/v) acetaminophen solution, each corrigent scarcely inhibited the bitter taste even at higher concentration. Benecoat BMI-40 and cocoa powder suppressed bitter taste with increase in the concentration, and both exhibited the greatest inhibition at the highest concentration, 1.0% (w/v), for aqueous acetaminophen solution of 0.3 and 0.6% (w/v). On the other hand, sucrose was less inhibitory against bitter taste at the highest concentration, 1.0% (w/v). As sucrose is a sweetening agent but does not directly affect the bitter taste receptor, inhibitory effect of sucrose against bitter taste was considered to be weak even if the concentration was increased. A similar tendency was recognized to some extent in masking of the quinine bitter taste (Fig. 2); though the decreasing degrees of bitter taste intensities were different between acetaminophen and quinine. Since Benecoat BMI-40 masks bitter taste receptors, it was considered to show more suppression of bitter taste at the higher concentration. Cocoa powder suppressed bitter taste to the similar extent to Benecoat BMI-40. Cocoa powder itself shows a small bitter taste, which is considered related to the component, theobromine, which is a xanthine derivative and one of alkaloids (Koyama and Kurihara, 1972; Pickenhagen and Dietrich, 1975; Aremu et al., 1995). Therefore, it was proposed that theobromine might affect the bitter taste receptors and cause masking of bitter taste of acetaminophen; though other components might be related to the masking of acetaminophen bitter taste in addition to theobromine.

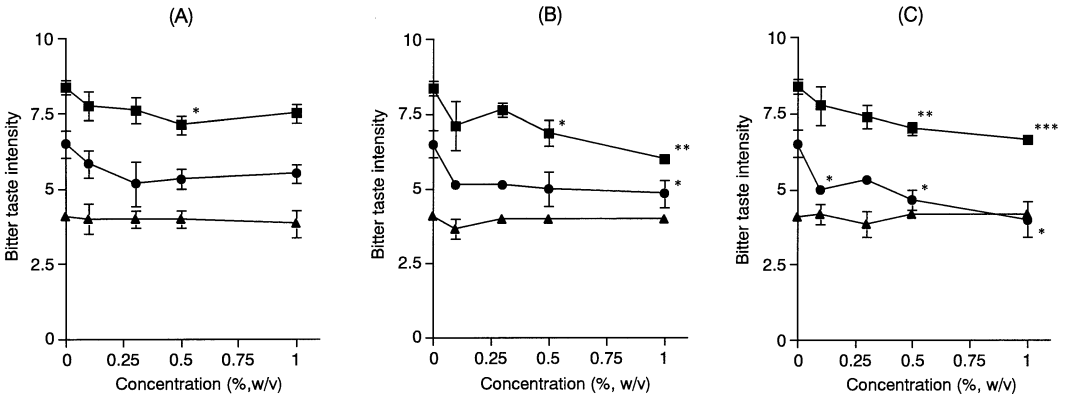

Fig. 3. Bitter taste intensity profiles of acetaminophen aqueous solution at various concentrations of sucrose (A), cocoa powder (B) and Benecoat BMI-40 (C). ▲, 0.2% (w/v) acetaminophen; ●, 0.3% (w/v) acetaminophen; ■, 0.6% (w/v) acetaminophen. Each point represents the mean ± S.E. ($n = 3$–6). * $P < 0.05$ vs. without corrigent; ** $P < 0.01$ vs. without corrigent; *** $P < 0.001$ vs. without corrigent.

3.2. Effect of matrix base on bitter taste of acetaminophen in chewable tablets

After chewing each tablet, the bitter taste intensity was evaluated by comparison with quinine standard solution. The results are shown in Fig. 4. The mixture of corn starch and lactose (1:2, w/w) did not mask the bitter taste of acetaminophen. Cacao butter and Witepsol H-15 suppressed the bitter taste at higher amounts. Especially, Witepsol H-15 inhibited bitter taste most greatly.

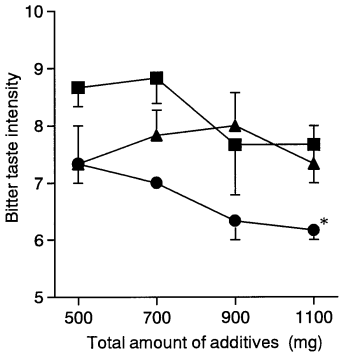

Fig. 4. Effect of additives on bitter taste of chewable tablets containing 100 mg acetaminophen. ▲, Corn starch/lactose (1:2, w/w) mixture; ●, Witepsol H-15; ■, cacao butter. In the corn starch/lactose tablets, magnesium stearate was contained at 3% (w/w). Each point represents the mean ± S.E. ($n = 3$). * $P < 0.05$ vs. total amount of additives, 500 mg.

It is reported that bitter taste receptors are located in hydrophobic regions. Cacao butter and Witepsol H-15 were considered to be able to mask the hydrophobic regions because of their lipophilicity, resulting in inhibitory effect of bitter taste. For cacao butter and Witepsol H-15, the difference in the bitter taste intensity was not found between 1000 and 1200 mg tablets.

3.3. Effect of the mixture of matrix base and corrigent(s) on bitter taste of acetaminophen in chewable tablets

In this examination, cacao butter and Witepsol H-15 were used as matrix bases. The 1 g tablets containing 100 mg acetaminophen were chosen because effect of the matrix base was found almost best in the tested region. The tablets (1 g) containing one or two corrigents were made, and the bitter taste intensities were investigated. Addition of large amount of the corrigent must be avoided to suppress the taste of the corrigent itself and change of the property of the matrix base. Referring to the corrigent concentration and corrigent/acetaminophen ratio in the bitter taste examination in solution, the corrigent was added at 1 and 5% (w/w) of the tablet weight. The bitter taste intensity profiles for tested tablet formulations are shown in Fig. 5. Overall, the bitter taste

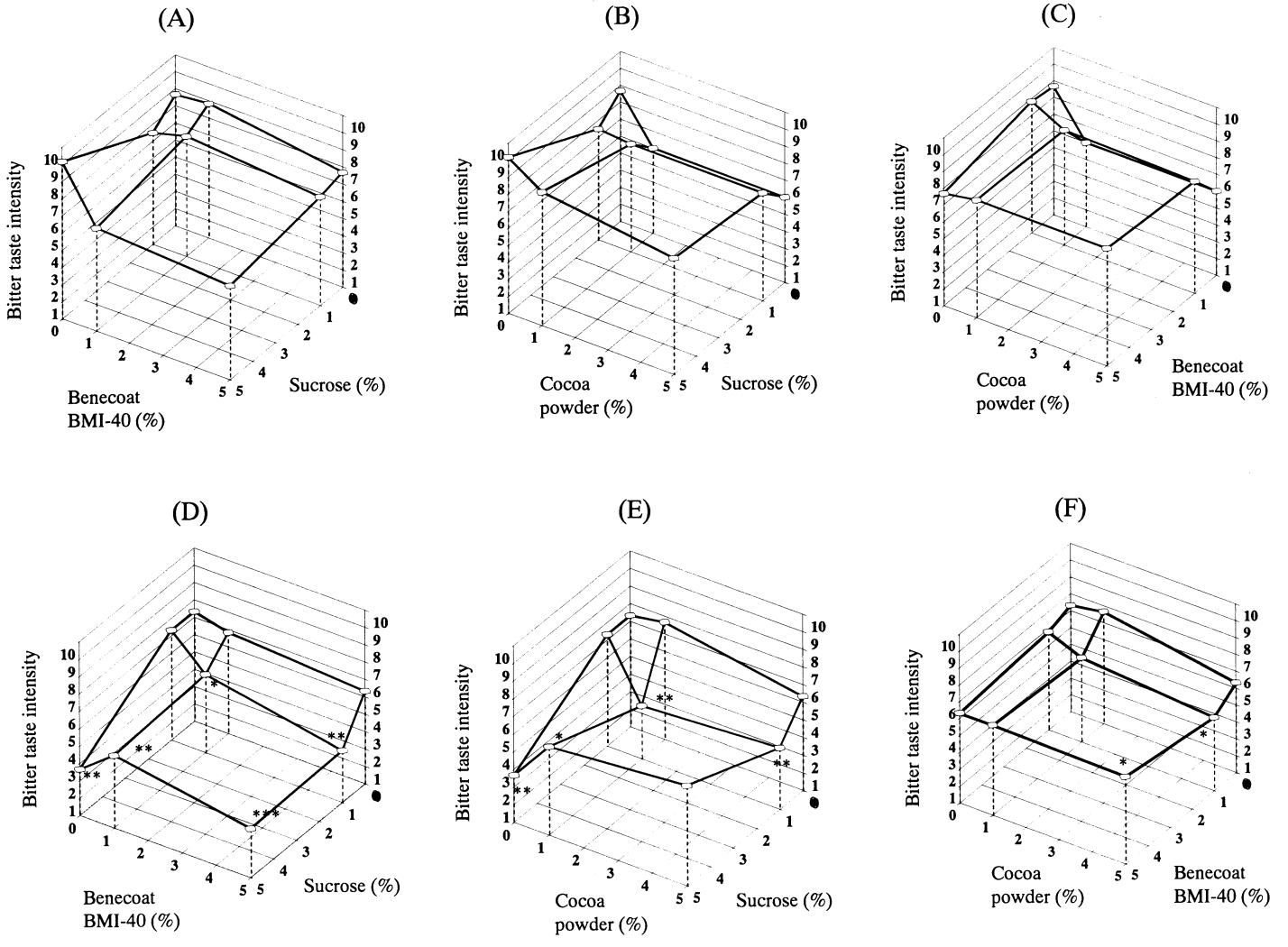

Fig. 5. Effect of matrix base/corrigent mixture on bitter taste of chewable tablets (1 g) containing 100 mg acetaminophen. A, B, C, cacao butter base; D, E, F, Witepsol H-15 base. Each point represents the mean ($n = 3$). * $P < 0.05$ vs. without corrigent; ** $P < 0.01$ vs. without corrigent; *** $P < 0.001$ vs. without corrigent.

intensities tended to be suppressed more greatly using Witepsol H-15 than cacao butter, even in addition to corrigent(s). In a series of tablets of cacao butter base, cocoa powder alone tended to inhibit the bitter taste. Sucrose slightly affected the bitter taste intensity and tended to show cooperative inhibitory effect along with Benecoat BMI-40. However, in the tablets of cacao butter base, the bitter taste intensity was not significantly lowered with addition of corrigents. On the other hand, in the tablets of Witepsol H-15 base, addition of Benecoat BMI-40 and sucrose, each at 5 and 5% (w/w), or sucrose alone at 5% (w/w) inhibited bitter taste greatly and significantly. The combination of Benecoat BMI-40 and sucrose appeared to suppress bitter taste well. Furthermore, the combination of cocoa powder and sucrose well inhibited bitter taste with addition of 1% (w/w) sucrose.

Throughout the corrigent combinations, Witepsol H-15 base tablets showed less bitter taste intensities by 2–3 scores than cacao butter base tablets. As a result, the Witepsol H-15-based tablets with 5% (w/w) Benecoat BMI-40—5% (w/w) sucrose, with 5% (w/w) Benecoat BMI-40—1% (w/w) sucrose, with 1% (w/w) cocoa powder—1% (w/w) sucrose and with 5% sucrose (w/w) showed the lowest bitter taste intensities. The bitter taste intensities of these tablets were less than 3 and significantly lower than the bitter taste intensity (6.3) of the tablet without corrigent. Those tablets were easy enough for humans to chew and swallow, while the tablet without corrigent was too bitter to chew and swallow. Sucrose, cocoa powder and Benecoat BMI-40 are considered to suppress the bitter taste with different mechanisms. The latter two corrigents are considered related to masking the receptor sites. The combination of cocoa powder and Benecoat BMI-40 appeared not to work cooperatively (Fig. 5). On the other hand, in the tablets with Benecoat BMI-40/sucrose or cocoa powder/sucrose, masking effect appeared to act cooperatively. In these tablets, masking mechanisms of the corrigents included were quite different. This suggested that combination of corrigents with different mechanism of masking bitter taste might be important for the cooperative inhibition of bitter taste. The masking abilities of corrigent(s) and lipophilicity of Witepsol H-15 were considered to lead to the greatest inhibition of bitter taste.

3.4. Drug release profiles from chewable tablets

The four chewable tablets with the lowest bitter taste intensities described above (3.3) were investigated for release profiles of acetaminophen in order to evaluate the bioavailability in vitro. As described in Fig. 6, the release profiles from the tablets were not much varied even after crushing. They all showed a drug release of more than 50% in the second fluid within 1 h after start of the release test; though the drug was not released completely during the observation period. Since the concentration calculated for 100% release was much lower than the solubility in both release media, the incomplete or slow release was not due to the drug solubility in the release media. Therefore, the drug was considered trapped by the matrix, which would be related to the properties of dissolution and diffusion of the drug in the matrix, partition between the matrix and release medium, etc. The detailed mechanism causing such incomplete release will have to be elucidated. As a result, these tablets were considered to be highly bioavailable irrespective of chewing, demonstrating that these bases were adequate for preparation of acetaminophen chewable tablets. Since Witepsol H-15 is used as a suppository base, it is safe enough to use for oral administration. Thus, these chewable tablets used in the release studies were recognized to show good inhibition of bitter taste of acetaminophen and available drug release.

The chewable dosage form of acetaminophen was developed so that the drug could be taken more easily. Although a fairly large volume of liquid must be drunk in taking the syrup dosage form, the chewable dosage form does not require such drinking. Syrup taste may not always be acceptable. Chewable tablets may improve such drawbacks of the syrup dosage form. The present results suggested that the chewable tablets prepared by several combinations of matrix base and corrigents should be possibly useful as oral dosage forms which could be taken easily.

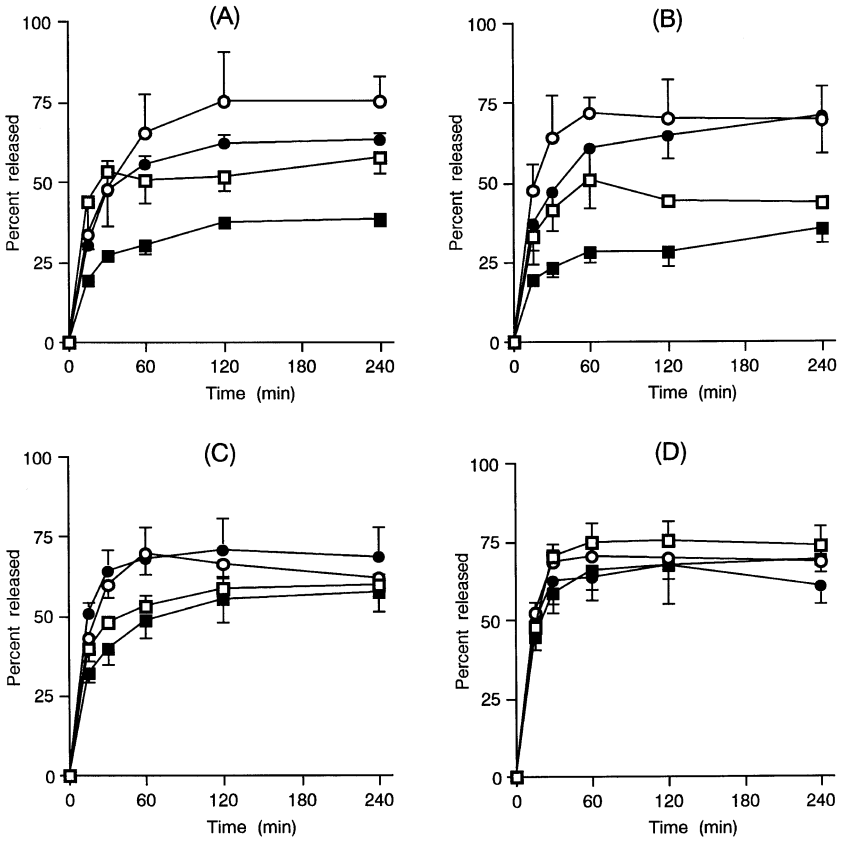

Fig. 6. Release profiles of actaminophen in the first and second fluids in JP 14 from intact and crushed tablets prepared using Witepsol H-15 as tablet base. A, 5% (w/w) sucrose/5% (w/w) Benecoat BMI-40; B, 1% (w/w) sucrose/5% (w/w) Benecoat BMI-40; C, 1% (w/w) sucrose/1% (w/w) cocoa powder; D, 5% (w/w) sucrose. □, intact tablet in the first fluid; ○, intact tablet in the second fluid; ■, crushed tablet in the first fluid; ●, crushed tablet in the second fluid. Each point represents the mean mean ± S.D. ($n = 3$) except for the first fluid in intact tablet in B each point represents the mean ± difference/$\sqrt{2}$ ($n = 2$) for intact tablet in the first fluid in B.

4. Conclusion

The present studies revealed that when the acetaminophen chewable tablets are made of various formulations, Witepsol H-15 containing Benecoat BMI-40 (5%)/sucrose (1 or 5%), or cocoa powder (1%)/sucrose (1%), or sucrose (5%) alone could mask bitter taste of the drug most excellently. Such masking effect appeared to be fairly related to lipophilic characteristics of the additives. Further, the tablets obtained with the above formulations showed a good drug release in vitro irrespective of chewing. Thus, these tablets are proposed to be available as chewable acetaminophen tablets with inhibited bitter taste. However, Witepsol H-15 can cause an unpleasant feeling in the oral cavity because of its melting characteristics in the mouth, as expressed by volunteers. Improvement of feeling in the oral cavity may be a future subject.

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