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Acetaminophen-containing chewable tablets with suppressed bitterness and improved oral feeling

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Abstract

The aim of this study was to develop acetaminophen chewable tablets with suppressed bitterness and improved oral feeling by examination of hard fats as the matrix base and of sweetening agents as corrigents. Witepsol® H-15, W-35, S-55, E-75 and E-85, and Witocan® H and 42/44 were used as hard fats. Witocan® H and 42/44 were selected in view of improved oral feeling. Witocan® H/Witocan® 42/44 mixture tablets showed different melting characteristics and drug release rates dependent on their ratios, and those with the Witocan® H/Witocan® 42/44 ratio of 92.5% (w/w) and more showed good drug release. Sucrose, xylitol, saccharin, saccharin sodium, aspartame and sucralose were used as sweetening agents, and applied alone or with Benecoat BMI-40 or cocoa powder. The Witocan® H tablet with 1% (w/w) saccharin plus 5% (w/w) Benecoat BMI-40 (Sc1-B5), and the Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablet with 1% (w/w) aspartame plus 5% (w/w) Benecoat BMI-40 suppressed bitterness and sweetness excellently, but the former tablet showed better drug release. Thus, the Witocan® H tablet with Sc1-B5 is suggested as the best acetaminophen chewable tablet, exhibiting suppressed bitterness, low sweetness, improved oral feeling and good drug release.

Keywords: Acetaminophen chewable tablet; Hard fat; Bitterness; Sweetness; Oral feeling; Drug release

1. Introduction

Many drugs exhibit bitter taste when orally administered (Nakamura et al., 1990; Shirai et al., 1993, 1994; Katsuragi et al., 1995; Yajima et al., 1999), and the bitter taste often causes non-compliance of patients because of the discomfort (Uchida, 2002). Therefore, suppression of the bitter taste has been an important subject for oral dosage forms. Various methods such as capsules, drug coating, microencapsulation, complexation and chemical modification have been utilized to improve the bitter taste (Nakamura et al., 1990; Shirai et al., 1993, 1994; Yajima et al., 1999). However, these techniques are not always useful or applicable; for example, capsules or coated tablets are often uncomfortable for infants or elderly people, who have trouble in swallowing drugs, due to their bulkiness. Further, the approaches such as drug coating, microencapsulation, complexation and chemical modification are not necessarily simple, and extensive opti-

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mization is required for their practical use. Therefore, the dosage forms which can be produced simply and that the patients can swallow easily may be important and valuable for the masking of the drug taste. The simple way to achieve such dosage forms is to add appropriate masking agents to power, liquid or chewable dosage forms (Popova, 1969; Katsuragi and Kurihara, 1993; Katsuragi et al., 1995, 1996, 1997; Yin et al., 1996; Ishikura et al., 2002; Takano, 2002). As to evaluation of taste intensities including bitterness, the sensation tests by human volunteers have been utilized (Indow, 1966, 1969). An alternative method using a taste sensor have been recently studied because it may permit the examination of dangerous compounds or complete the tests of many substances in a short time (Uchida et al., 2000, 2001; Uchida, 2002). However, since mechanism of taste sensation is complicated, the sensation tests by human volunteers appear to be still a very useful method to determine the taste intensities.

Acetaminophen, an antipyretic, has a bitter taste, but is often applied to infants and children due to its safety, when suppository and syrup dosage forms are often used to take the drug more comfortably (Autret et al., 1994; Van Esch et al., 1995; Coulthard et al., 1998; Hansen et al., 1999). Suppository insertion requires a private space at the administration. In drinking the syrup, a fairly large volume of the liquid and the sweet taste are sometimes a burden for the patients. Actually, in the preliminary studies, we tested tastes about three commercial syrups of acetaminophen, but they exhibited fairly strong sweetness and did not suppress the bitterness very much. To improve these matters, we had developed the acetaminophen-containing chewable tablets using Witepsol® H-15 or cacao butter as a matrix base and some corrigents as bitter masking agents (Suzuki et al., 2003). These chewable tablets could be prepared simply, and were considered to be available to patients having trouble in swallowing because they could be chewed. However, these tablets did not necessarily show comfortable oral feeling, which appeared to be mainly due to the stickiness of the hard fat. Therefore, further examination of the formulations was required to improve oral feeling in addition to bitterness suppression. In the present study, various kinds of hard fats and many sweetening agents were examined to obtain acetaminophen chewable tablets with suppressed bitter taste and improved oral feeling. The dose of acetaminophen per oral administration was 300–500 mg for adults, but it was adjusted to 10 mg/kg for infants. Furthermore, it is not difficult to take some chewable tablets at a time. Considering these features, the drug content of the chewable tablet was set at 100 mg as reported previously.

In the present study, as to hard fats, Witocan® was examined in addition to Witepsol®; Witocan® is utilized as special hard fats in the chocolate and confectionery industry. Currently available sweetening agents, that is, sucrose, xylitol, saccharin, saccharin sodium, aspartame and sucralose, were used as sweetening agents (Japan Food Additives Association, 2001). They show different sweet taste intensities and oral feeling. Xylitol has a sweet taste intensity similar to sucrose but gives a brisk feeling orally. Saccharin and saccharin sodium are 500 times as sweet as sucrose, and aspartame and sucralose showed 200 and 600 times as the sweet taste intensity as sucrose, respectively. In addition to the above sweetening agents, commercial bitter-masking powder mixture made from lecithin (Benecoat BMI-40) (Katsuragi et al., 1997) and cocoa powder (Koyama and Kurihara, 1972; Pickenhagen et al., 1975; Aremu et al., 1995) were utilized as corrigents. As shown in the previous report, the corrigent systems of 1 or 5% (w/w) sucrose plus 5% (w/w) Benecoat BMI-40, or 1% (w/w) sucrose plus 1% (w/w) cocoa powder, or 5% (w/w) sucrose alone gave the best suppression of the bitter taste intensities of acetaminophen-containing Witepsol® H-15 chewable tablets (Suzuki et al., 2003). Therefore, in the present study, acetaminophen chewable tablets were prepared at the similar conditions; that is, they were prepared using hard fats with 1 or 5% (w/w) sweetening agent plus 5% (w/w) Benecoat BMI-40, or 1% (w/w) sweetening agent plus 1% (w/w) cocoa powder, or 5% (w/w) sweetening alone. The obtained tablets were evaluated based on suppression of bitter taste, sweet taste intensity, oral feeling and drug release.

2. Materials and methods

2.1. Materials

Acetaminophen was purchased from Sigma Chemical Co. (USA). Quinine sulfate, sucrose, saccharin, saccharin sodium, xylitol, aspartame and sucralose

were purchased from Wako Pure Chemical Industries, Ltd. (Japan). Hard fats (Witepsol® H-15, W-35, S-55, E-75 and E-85, Witocan® H and 42/44) were purchased from Mitsuba Trading Co. (Japan). Commercial bitter-masking powder mixture made from lecithin (Benecoat BMI-40) was supplied from Kao Corporation (Japan). For cocoa powder, a commercial product was used. All other chemicals were of reagent grade.

2.2. Preparation of chewable tablets

All the chewable tablets (1 g) containing 100 mg of acetaminophen were prepared based on the following casting method: A hard fat or a mixture of hard fats was put in a glass beaker and melted by warming at 45 °C on a water bath. Acetaminophen and/or corrigents were added, the mixture was stirred quickly with a glass bar, then 1 g of the mixture was poured into a mold to yield a disk-shaped tablet (2 cm diameter). The types of chewable tablets described in Table 1 were prepared, and their use and features are in the following.

2.2.1. Formulation A

This type of chewable tablet was prepared to examine the effect of kinds of hard fats on bitter taste and oral feeling of the chewable tablet. The chewable tablets with various hard fats as a matrix base using sucrose and Benecoat BMI-40 each at 5% (w/w) as corrigents were prepared.

2.2.2. Formulation B

This type of chewable tablet was prepared to examine the effect of the Witocan® H/Witocan® 42/44 ratio on melting temperature and drug release rate. A mixture of Witocan® H and Witocan® 42/44 (80:20, 85:15, 90:10, 92.5:7.5, 95:5, 97.5:2.5 or 100:0, w/w) was used as a matrix base. No corrigent was added.

2.2.3. Formulations C-1, C-2, C-3 and C-4

These chewable tablets were prepared to investigate the effect of sweetening agent on bitterness and sweetness of the Witocan® H chewable tablets. Sucrose, xylitol, saccharin, saccharin sodium, aspartame and sucralose were used as sweetening agents. The four kinds of corrigent systems described in Table 1 were examined.

2.2.4. Formulations D-1, D-2, D-3 and D-4

These chewable tablets were prepared using the Witocan® H/Witocan® 42/44 mixture (92.5:7.5, w/w) as a matrix. The four kinds of corrigent systems described in Table 1 were examined.

In all the tablets prepared, the amount of the sweetening agent per tablet was much lower as compared with the acceptable daily intake (Japan Food Additives Association, 2001).

2.3. Measurement of intensities of bitterness and sweetness

Bitter and sweet taste intensities were determined by the sensation tests using healthy men with age of 21–25 based on the methods by Indow (1966, 1969) and Katsuragi et al. (1997). Before measurement, informed consent was completed to each volunteer. Quinine aqueous solutions with a series of concentrations were prepared as standard solutions of bitter taste intensities, and the intensities were defined from 0 to 10

Table 1
Formulations and compositions of the chewable tablets (1 g)

Formulation	Composition [weight ratio]
A	Hard fat/acetaminophen/sucrose/Benecoat BMI-40 [80/10/5/5]
B	Witocan® H–Witcan® 42/44 mixture/acetaminophen [9/1]
C-1	Witocan® H/acetaminophen/sweetening agent [85/10/5]
C-2	Witocan® H/acetaminophen/sweetening agent/Benecoat BMI-40 [80/10/5/5]
C-3	Witocan® H/acetaminophen/sweetening agent/Benecoat BMI-40 [84/10/1/5]
C-4	Witocan® H/acetaminophen/sweetening agent/cocoa powder [88/10/1/1]
D-1	Witocan® H–Witcan® 42/44 mixture (92.5:7, w/w)/acetaminophen/saccharin [85/10/5]
D-2	Witocan® H–Witcan® 42/44 mixture (92.5:7, w/w)/acetaminophen/saccharin/Benecoat BMI-40 [84/10/1/5]
D-3	Witocan® H–Witcan® 42/44 mixture (92.5:7, w/w)/acetaminophen/saccharin/cocoa powder [88/10/1/1]
D-4	Witocan® H–Witcan® 42/44 mixture (92.5:7, w/w)/acetaminophen/aspartame/Benecoat BMI-40 [84/10/1/5]

Table 2
Relationship between defined taste intensity and concentration of quinine sulfate or sucrose aqueous solution

Defined taste intensity	Quinine sulfate concentration for bitterness (%, w/v)	Sucrose concentration for sweetness (%, w/v)
0	0.00000	0.0
1	0.00023	1.0
2	0.00050	1.9
3	0.00094	3.0
4	0.00157	4.3
5	0.00241	6.4
6	0.00388	9.0
7	0.00608	14.0
8	0.00985	22.5
9	0.01572	24.0
10	0.02568	78.0

(Table 2). Also, sucrose aqueous solutions with a series of concentrations were used as standard solutions for measurement of sweet taste intensities, when the intensities were defined from 0 to 10 (Table 2).

The bitter or sweet taste intensities of chewable tablets were evaluated as follows: 1 ml of each standard solution was dropped on the center of the tongue, the solution was retained in the mouth for 10 s, then the mouth was rinsed thoroughly with de-ionized water so that recognition of the taste intensities of the standards was recovered. At 10 min after remembering the taste intensities of each standard solution, the mouth was rinsed fully again, one tablet was put in the mouth, chewed 10 times and retained on the center of the tongue in the mouth for 10 s. At that time, the subject decided the taste intensity of the chewed tablet by comparison with that of each standard solution. For examination of the taste intensities of bitterness and sweetness, the number of the subjects in each group was three.

2.4. Drug release tests

The drug release was generally examined for intact tablets. As to the chewable tablets selected finally, both intact and crushed tablets were examined for drug release. Crushed tablets were prepared by breaking a tablet mechanically into nearly 10 pieces with similar fragment size to simulate the fragmentation of a tablet by chewing. The drug release experiment was performed according to the first method (rotation basket method) of the dissolution test in the Pharmacopoeia of Japan (JP) 14. 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) of the disintegration test in the Pharmacopoeia of JP 14 were used as release media. One tablet or all the fragments obtained by crushing one tablet were put in a basket, immersed completely in 900 ml of the dissolution medium pre-warmed at $37 \pm 0.5\,^{\circ}C$ so that the basket bottom was located at 2.5 cm from the inner bottom of the container, and rotated at 60 rpm at $37 \pm 0.5\,^{\circ}C$. 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 filtrate was diluted 10-fold in volume with fresh medium, and measured spectrophotometrically at 244 nm to determine the amount of released drug. In each drug release test performed, hard fats and corrigents showed no influence on the determination of acetaminophen concentration by this method.

2.5. Measurement of melting characteristics of chewable tablets

The melting features of chewable tablets were examined by differential scanning calorimetry (DSC) using a Rigaku THERMOFLEX TAS200 DAS8230D (Japan). The tablets were roughly crushed, and the obtained particles of 10 mg were used as a sample. The DSC scan speed and scan range were $5\,^{\circ}C$/min and 25–50 °C, respectively. The temperature of the minimum peak of the endothermic DSC curve was defined as a melting temperature of the tablet.

2.6. Statistical analysis

For the comparison, statistical analyses were performed using the unpaired *t*-test. The results at $P < 0.05$ was regarded as significantly different.

3. Results and discussion

3.1. Effect of kinds of hard fats on bitterness and oral feeling

All the tablets were obtained in a disk shape with 2 cm in diameter and 4–5 mm in thickness. Those

Table 3
Melting properties of various hard fats and bitter taste and oral feeling of their acetaminophen-containing tablets with sucrose and Benecoat BMI-40 each at 5% (w/w) as corrigents

Commercial name of hard fat	Grade	Melting point (°C)[a]	Bitter taste intensity[b]	Order of oral feeling[c]
Witepsol®	H-15	33.5–35.5	5.2 ± 0.4	7
	W-35	33.5–35.5	7.0 ± 0.0	6
	S-55	33.5–35.5	8.2 ± 0.3*	4
	E-75	38	5.0 ± 0.0	5
	E-85	42–44	5.0 ± 0.6	2
Witocan®	H	33.5–35.5	5.0 ± 0.0	3
	42/44	42–44	4.5 ± 0.3	1

[a] These melting points were shown by the suppliers.
[b] The bitter taste intensity was determined based on the recognition by human volunteers stated in Section 2.3 in the text and the result is as the mean ± S.E. ($n = 3$).
[c] Smaller number exhibited better oral feeling in the tablets.
* Significant difference, $P < 0.05$ vs. Witepsol® H-15.

tablets were a little harder than solid chocolate, but they could be easily crushed by bite, though their hardness was not measured in detail. Formulation A was used in this experiment. Namely, various hard fats were used as a matrix, and 5% (w/w) Benecoat BMI-40 plus 5% (w/w) sucrose were used as corrigents. The commercial name and melting point of the hard fats applied are described in Table 3. The bitter taste intensities were approximately 5 for Witepsol® H-15, E-75 and E-85, and Witocan® H. Witepsol® W-35 and S-55 exhibited higher bitter taste intensities of 7–8.2. Witocan® 42/44 showed the lowest bitter taste intensity of 4.5. Only the Witepsol® S-55 exhibited a significantly higher bitter taste intensity different from Witepsol® H-15 ($P < 0.05$). The oral feeling of the chewable tablets was related mainly to stickiness to the oral cavity and gingival, and that sensation was ranged in the order of more comfortable feeling as shown in Table 3. Overall, the bitter taste intensities of less than 5–6 were tolerable, and the oral feelings of the order 1–3 were acceptable. Thus, the Witocan® H and 42/44 tablets were adequate as tablets with suppressed bitterness and improved oral feeling. Although the Witocan® 42/44 tablet exhibited bitterness suppression and oral feeling best, the release percentages were less than 6% in both the first and second fluids even at 2 h after start of the release test (data not shown). The poor drug release was considered to be due to higher melting point of Witocan® 42/44, and also the good bitterness suppression might be due to the low drug release. Thus, Witocan® H or the mixture of Witocan® H and Witocan® 42/44, which showed lower melting points, were used in the following experiments.

3.2. Effect of the Witocan® H/Witocan® 42/44 ratio on melting temperature and drug release

Formulation B was used in this experiment. Witocan® H alone and the mixture of Witocan® H and Witocan® 42/44 were applied as a matrix base, and the obtained tablets were examined for melting temperature and drug release extent. Effect of the Witocan® H/Witocan® 42/44 ratio on melting temperature is shown in Table 4. The meting temperature rose with the decrease of the Witocan® H/Witocan® 42/44 ratio. The drug release profiles of the chewable tablets with different Witocan® H/Witocan® 42/44 ratios are described in Fig. 1. The chewable

Table 4
Melting temperature of chewable tablets with different Witocan® H/Witcan® 42/44 ratios

Witocan® H/Witcan® 42/44 ratio (w/w)	Melting temperature (°C) (mean ± S.D.)
100/0	38.5 ± 0.3
97.5/2.5	38.9 ± 0.1
95/5	39.2 ± 0.2
92.5/7.5	39.2 ± 0.1
90/10	39.8 ± 0.5
85/15	40.3 ± 0.1
80/20	41.0 ± 0.1

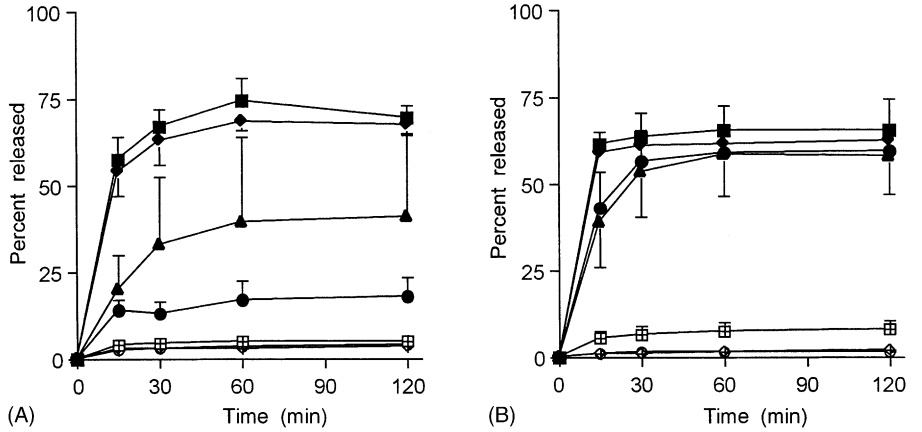

Fig. 1. Release profiles of acetaminophen from tablets prepared using Witocan® H alone or Witocan® H/Witocan® 42/44 mixture as a base. The intact tablets were used in the experiment. (A) First fluid in JP 14; (B) second fluid in JP 14. (■) 100% (w/w) Witocan® H; (◆) 97.5% (w/w) Witocan® H; (●) 95% (w/w) Witocan® H; (▲) 92.5% (w/w) Witocan® H; (⊞) 90% (w/w) Witocan® H; (⊕) 85% (w/w) Witocan® H; (⊕) 80% (w/w) Witocan® H. Each point represents the mean ± S.D. ($n = 3$).

tablets with the Witocan® H/Witocan® 42/44 ratios of 92.5% (w/w) or more showed good drug release. When the drug release extent was evaluated by the percentage of the drug released from the intact tablet at 2 h after the start of the release test, the relationship between melting temperature and drug release extent was obtained as shown in Fig. 2. These results indicated that the chewable tablet made of Witocan® H alone exhibited the lowest melting temperature and best drug release. The chewable tablets with the Witocan® H/Witocan® 42/44 ratios of 10% (w/w) or more exhibited poor drug release. The mixed base of 92.5% (w/w) Witocan® H and 7.5% (w/w) Witocan® 42/44 gave good release extent in only the second fluid. The release extent decreased sharply in a reverse sigmoidal curve around the melting temperature of 39.2 °C. These suggested that the Witocan® H/Witocan® 42/44 mixture must contain Witocan® H at 92.5% (w/w) or more to achieve sufficient release of acetaminophen.

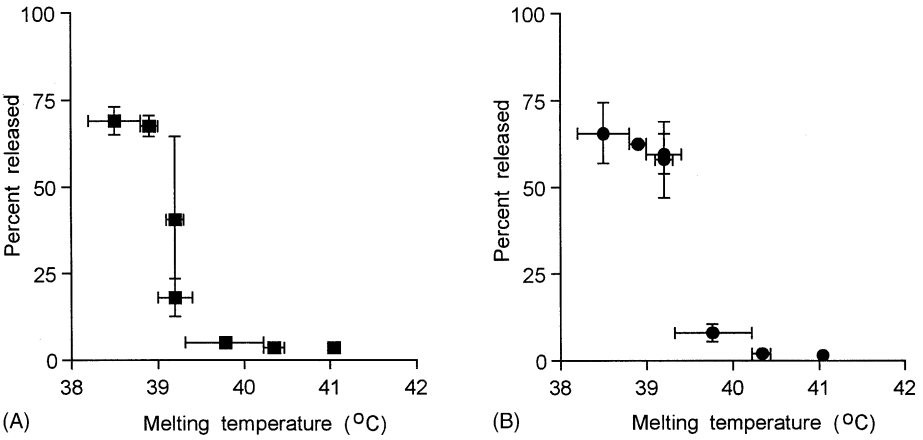

Fig. 2. Relationships between melting temperature and acetaminophen release extent for the Witocan® H/Witocan® 42/44 mixture tablets. (A) Melting temperature vs. percent released in the first fluid in JP 14 at 2 h after the start of the test; (B) melting temperature vs. percent released in the second fluid in JP 14 at 2 h after the start of the test. The melting temperature was defined as the temperature of the minimum peak of the endothermic DSC profile. Each point represents the mean ± S.D. ($n = 3$).

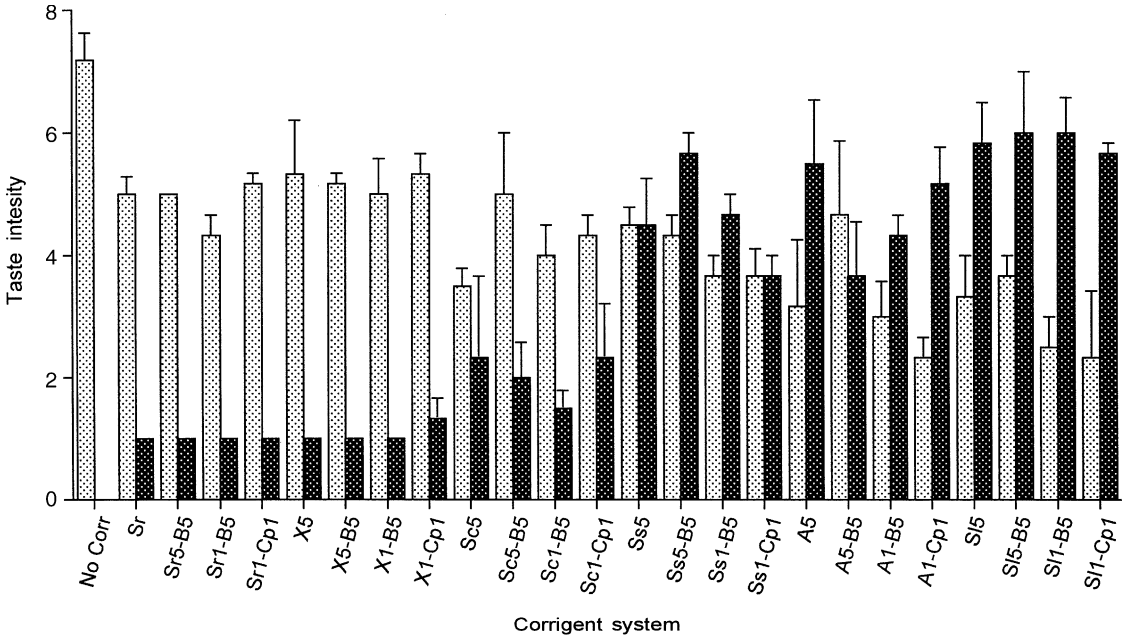

Fig. 3. Bitter and sweet taste intensities of Witocan® H chewable tablets with various corrigent systems. No Corr, with no corrigent; Sr, sucrose; B, Benecoat BMI-40; Cp, cocoa powder; X, xylitol; Sc, saccharin; Ss, saccharin sodium; A, aspartame; Sl, sucralose. The number attached to the corrigent abbreviation showed the percentage of the corrigent in the chewable tablet; for example, Sr5-B5 means the corrigent system of 5% (w/w) sucrose and 5% (w/w) Benecoat BMI-40. (▨) Bitter taste intensity; (▩) sweet taste intensity. Each column represents the mean ± S.E. ($n = 3$). For bitter taste intensities, the corrigent systems except X5, Sc5-B5 and A5-B5 were significantly different from No Corr ($P < 0.05$).

3.3. Effect of sweetening agents on bitter and sweet taste intensities of chewable tablets

Formulations C-1, C-2, C-3 and C-4 were used in this experiment, and the bitter and sweet taste intensities of the chewable tablets were examined. The bitter and sweet taste intensities of the chewable tablets are shown in Fig. 3. The chewable tablet with no corrigent showed the bitter taste intensity of 7.2. In comparison with the chewable tablet with no corrigent, the other chewable tablets showed significantly lower bitterness ($P < 0.05$) for the corrigent systems other than 5% (w/w) xylitol (X5), 5% (w/w) saccharin plus 5% (w/w) Benecoat BMI-40 (Sc5-B5), and 5% (w/w) aspartame plus 5% (w/w) Benecoat BMI-40 (A5-B5).

Saccharin and its sodium salt tended to suppress bitter taste more than sucrose. Sweet taste became much higher in saccharin sodium but increased slightly in saccharin, which was probably because saccharin sodium is easily soluble than saccharin. As a whole, the tablets using saccharin as a sweetening agent showed good balance in bitter and sweet tastes. In particular, the corrigent system of 1% (w/w) saccharine plus 5% (w/w) Benecoat BMI-40 (Sc1-B5) was excellent. Although several tablets with aspartame or sucralose as a sweetening agent inhibited bitterness much more than those with sucrose, they gave much sweeter taste than sucrose. Aspartame and sucralose can suppress bitter taste effectively due to their highly sweetening potential, but high increase in the sweet taste intensity appeared to cause discomfort in taking the tablets; generally, the samples with the sweet taste intensities of four or more were too sweet to take.

In the preliminary study, three kinds of commercial syrups of acetaminophen, being prescription drugs (commercial name not described), were examined on bitterness and sweetness ($n = 3$). Two (the first and second syrups) include saccharin sodium as a sweetening agent, and the other (the third syrup) contains aspartame as a sweetening agent. Their tastes were

examined in the manner as stated previously (Suzuki et al., 2003); namely, the syrups were tasted in the same manner as the standard solution. As a result, the first syrup exhibited the bitter and sweet taste intensities of 4.2 and 5.2, respectively. The second showed the bitter and sweet taste intensities of 5.2 and 5.3, respectively, and the third exhibited the bitter and sweet taste intensities of 4.3 and 5.7, respectively. The first syrup showed the best tastes. The Witocan® H chewable tablet with Sc1-B5 exhibited the bitter taste intensity of 4 and the sweet taste intensity of 1.5, indicating that this tablet suppressed taste intensities better, especially sweetness, as compared with the above commercial syrups.

3.4. Taste intensities and drug release for the Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablets

The Witocan® H chewable tablets improved oral feeling, but the addition of Witocan® 42/44 can improve the oral feeling more. Based on the results in Figs. 1 and 2, the Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablets, exhibiting good drug release, were chosen. The mixture tablets were prepared for the excellent corrigent systems in Fig. 3; that is, D-1, D-2, D-3 and D-4 in Table 1 were prepared. They were examined for taste intensities and drug release.

The results of taste intensities are shown in Fig. 4. The bitter taste intensity of the chewable tablet with no corrigent was 6.2. For each corrigent system, the taste intensities were almost parallel to those in Witocan® H tablets. The corrigent systems except Sc1-B5 showed significant suppression of bitterness ($P < 0.05$). In particular, A1-B5 exhibited the least bitter taste intensity and low sweetness. The drug release profiles of the intact tablets are shown in Fig. 5. All the tablets showed good drug release.

3.5. Drug release from intact and crushed tablets

For the tablets showing excellent taste balance in the Witocan® H tablets (Fig. 3) and Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablets (Fig. 4), the drug release tests were performed at the intact and crushed conditions. That is, the Witocan® H tablet with Sc1-B5 and Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablet with A1-B5 were selected, and their drug release was examined in the intact and crushed forms. The results are shown in Fig. 6. The Witocan® H tablet with Sc1-B5 showed good release in both intact and crushed forms; that is, more than 50% (w/w) of the drug was released in the second fluid at 2 h after the start of the release test. In particular, this tablet showed that the crushed form released approximately 50% of the drug in the second fluid at 1 h after the start of the release test. The Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablet with A1-B5 showed good release in the intact form, but not in the crushed form. These results were possibly related to the melting properties of the tablets. Namely, the Witocan® H tablet with Sc1-B5 melted completely to form liquid droplets during the release test, especially in the second fluid. On the other hand, for the Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablet with A1-B5, soft semisolid remained on the basket after the release test; an aggregated and bulky semisolid was formed markedly in the crushed form, probably leading to poor drug release. These features were consistent with the results in Fig. 2 that the Witocan® H/Witocan®

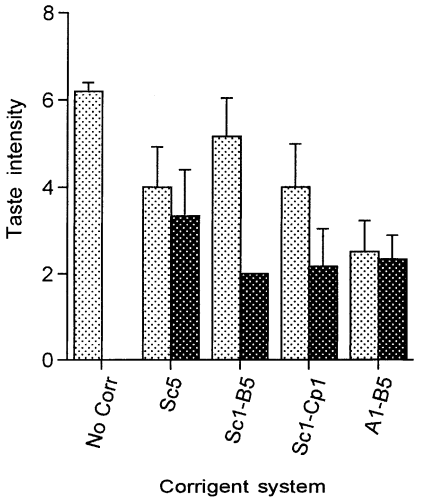

Fig. 4. Bitter and sweet taste intensities of Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture chewable tablets with several corrigents. The abbreviation and expression of corrigent systems were the same as in Fig. 3. (▨) Bitter taste intensity; (■) sweet taste intensity. Each column represents the mean ± S.E. ($n = 3$). For bitter taste intensities, the corrigent systems except Sc1-B5 were significantly different from No Corr ($P < 0.05$).

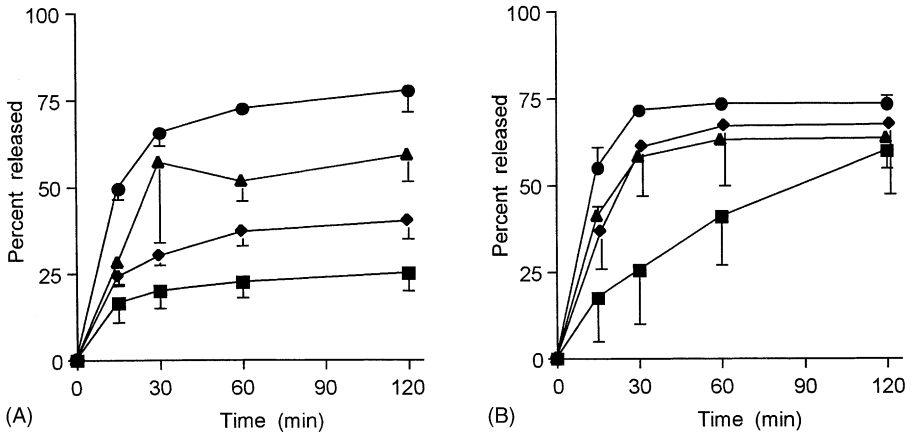

Fig. 5. Acetaminophen release profiles from Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablets with several corrigents. The intact tablets were used in the experiment. (A) First fluid in JP 14; (B) second fluid in JP 14. (■) Sc1-B5; (◆) Sc1-Cp1; (●) Sc5; (▲) A1-B5. Each point represents the mean ± S.D. ($n = 3$).

42/44 ratio of 92.5:7.5 (w/w) was the critical point for drug release. These results indicated that it would be adequate from the viewpoint of drug release to use Witocan® H alone as a matrix base. However, as stated above, the dissolution from the Witocan® H tablet with Sc1-B5 was not complete in the first fluid, and it took 1–2 h for the Witocan® H tablet with Sc1-B5 to release 50% of the drug in the second fluid. Therefore, the quick supply of the drug may not be achieved even by the Witocan® H tablet with Sc1-B5, which will be due to the interaction between the drug and matrix base and to the controlled diffusion of the drug in the matrix. The detailed efficacy will have to be evaluated by the in vivo examination.

Thus, the Witocan® H tablet with Sc1-B5 was suggested as the best chewable tablet. This tablet was more excellent for suppression of tastes than some commercial syrups as described above. Nowadays, many commercial products of acetaminophen other than the above syrups are in the market. The chewable tablets have been already in the market. Therefore, it will be needed for elucidating more clearly the use-

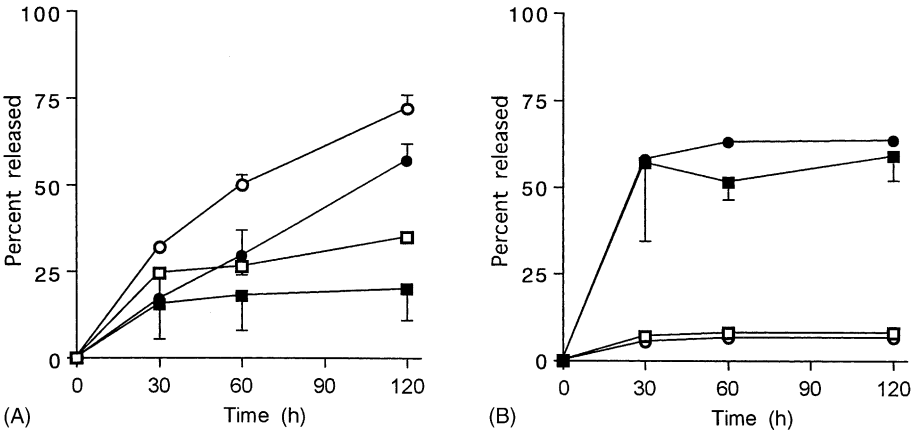

Fig. 6. Acetaminophen release profiles from Witocan® H tablet with Sc1-B5 (A) and Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablet with A1-B5 (B) in the intact and crushed forms. (■) Intact tablet in the first fluid in JP 14; (●) intact tablet in the second fluid in JP 14; (□) crushed tablet in the first fluid in JP 14; (○) crushed tablet in the second fluid in JP 14. Each point represents the mean ± S.D. ($n = 3$).

fulness of the present Witocan® H tablet to compare the characteristics of tastes, dissolution etc. between the tablet and more commercial products other than the tested syrups, which will be a future subject.

4. Conclusion

The present study revealed that Witocan® H and 42/44 would be possibly useful as a chewable tablet base with improved oral feeling. Chewable tablets prepared with Witocan® H or the mixture of Witocan® H and Witocan® 42/44 (92.5:7.5, w/w) as matrix base using sweetening agents as corrigents showed bitterness suppression, though those with the sweet taste intensities of 4 or more were not comfortable in taking. The Witocan® H tablet with Sc1-B5 and the Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablet with A1-B5 were the most excellent chewable tablets for taste balance and oral feeling. The Witocan® H tablet with Sc1-B5 was slightly inferior for oral feeling than the Witocan® H/Witocan® 42/44 (92.5:7.5, w/w) mixture tablet with A1-B5, but the former tablet was more excellent in view of drug release. Thus, the Witocan® H tablet with Sc1-B5 is suggested as the best acetaminophen chewable tablet, exhibiting suppressed bitterness, low sweetness, improved oral feeling and good drug release.

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