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Formulation and evaluation of lactoferrin bioadhesive tablets

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Abstract

For the treatment of chronic inflammation in the oral cavity, we attempted to develop bioadhesive tablets of bovine lactoferrin (B-LF) which has antibacterial properties and immune regulatory functions. B-LF tablets containing pectin, tamarind gum or carboxymethylcellulose (CMC) were prepared by direct compression. Tablets consisting of B-LF, pectin and xylitol passed through 60- or 100-mesh sieves were also prepared. The tablets containing CMC had insufficient bioadhesive force. Although the tablets containing tamarind gum showed the longest residence time in the oral cavity, an unpleasant taste gradually developed. The tablets containing pectin showed the highest value of bioadhesive force and the taste was acceptable. The characteristics of the B-LF tablets were improved by adding an appropriate amount of xylitol and using the ingredients sieved by a 100-mesh sieve. The therapeutic effect was evaluated by using rats with an ulcer on the oral mucosa. In the present study, swelling on the periphery of the ulcer was observed after administration of the B-LF tablets, and then the ulcer has reduced overall.

Keywords: Bioadhesive tablets; Lactoferrin; Pectin; Oral mucosa; Chronic inflammation; Xylitol

1. Introduction

Chronic inflammation of oral mucosa and gingiva is often observed accompanying intractable stomatitis (Sato et al., 1996). The stomatitis reduces the quality of life of patients because it brings intense pain and anorexia. The severity and duration of stomatitis are greatly influenced by immune responses and oral hygienic condition (Duncan and Grant, 2003). Poor oral health predisposes patients to stomatitis, and the elimination of dental problems lowers their susceptibility. Since oral infection is usually induced by various kinds of bacilli, antibiotics with a wide antibacterial spectrum are needed for the treatment. However, these antibiotics cause side effects among the flora of the tract, leading to the appearance of antibiotic-resistant bacteria after long-term administration.

Lactoferrin, an iron-binding glycoprotein that consists of a single polypeptide chain, is an abundant protein in milk secretions (Masson and Heremans, 1971). Lactoferrin is found in most exocrine secretions including tears, nasal secretions, saliva, intestinal mucus and genital secretions (Pentecost and Teng, 1987; Yu and Chen, 1993), and is also identified as one of the major proteins present in neutrophils (Masson et al., 1969). Lactoferrin shows a bactericidal effect by binding with iron ions which are essential for the growth of bacteria (Arnold et al., 1977; Bullen et al., 1978; Arnold et al., 1980). As additional antibacterial properties, direct effects of lactoferrin against some gram negative and gram positive bacteria have been reported (Arnold et al., 1981; Ellison et al., 1988). At physiological concentrations, apolactoferrin directly damages an outer membrane of gram negative bacteria by releasing lipopolysaccharides. Furthermore, lactoferrin acts as a modulator for various immunologic functions (Cumberbatch et al., 2000). It was reported that lactoferrin released from neutrophils at the inflammatory site inhibited production of several cytokines, such as tumor necrosis factor α (TNF-α) and interleukin-1β (IL-1β) (Crouch et al., 1992). In another report, mice that were administered bovine lactoferrin (B-LF) intravenously before injection of lipopolysaccharide showed decreased levels of TNF-α and IL-6 (Machnicki et al., 1993). These cytokines are increased at the stage where stomatitis develops and then inflammatory immune cells flow into the submucosa (Duncan and Grant, 2003). Thus, the immune regulatory

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function of lactoferrin may act to prevent the deterioration of stomatitis.

Mucosal adhesive dosage forms have been investigated as an external preparation that can be administered effectively and safely (Machida et al., 1979), not only for topical diseases but also for systemic ones (Ishida et al., 1981; Satoh et al., 1989; Choi et al., 2000). In this study, we attempted to develop bioadhesive tablets of B-LF for the treatment of chronic inflammation in the oral cavity, aiming to benefit from its antibacterial properties and immune regulatory functions. Tablets administered to the buccal mucosa and gingiva should adhere to the mucosa without quick collapse and should release drugs gradually. Furthermore, it is important that neither the taste nor feeling is unpleasant. We prepared bioadhesive tablets of B-LF using pectin, tamarind gum or carboxymethylcellulose (CMC) as excipients, and estimated the characteristics of the tablets. Furthermore, the ulcer healing effect was evaluated by using rats induced with a buccal mucosal ulcer.

2. Materials and methods

2.1. Materials

B-LF was supplied by NRL Pharma, Inc. (Kanagawa, Japan). Pectin was purchased from Happou Syoukai Co., Ltd. (Tokyo, Japan). The degree of esterification and the mean molecular weight of the pectin were 59.6% and 9500, respectively. We used the purchased pectin without purification. Tamarind gum (Glyloid® 6C) was obtained from Dainippon Pharmaceutical Co., Ltd. (Osaka, Japan). CMC and xylitol were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). All other chemicals were obtained commercially at the purest grade available.

2.2. Animals

Male ddY strain mice weighing 25–30 g and male Sprague–Dawley strain rats weighing 170–220 g were purchased from Tokyo Laboratory Animals Science Co., Ltd. (Tokyo, Japan). The experimental protocol was approved by the Ethics Review Committee for Animal Experimentation of Hoshi University.

2.3. Preparation of B-LF tablets

The compositions of B-LF tablets prepared are shown in Table 1. B-LF tablets containing pectin, tamarind gum or CMC as excipients were prepared by direct compression at a force of 10 kN using a hydraulic hand press (Shimadzu Co., Kyoto, Japan). The tablets were prepared as plate tablets with a diameter of 8 mm. All the ingredients were ground using an agate mortar and pestle, then passed through a 60-mesh sieve. For a discussion on improvement of the taste and preparation characteristics, tablets containing 5–25 mg of xylitol were also prepared. In the case of preparation of the tablets containing xylitol, all the ingredients were used after passing through 60- or 100-mesh sieves.

Table 1
Composition of B-LF tablets

Ingredients (mg tab)	A	B	C	D	E	F	G	H
B-LF	25	25	25	25	25	25	25	25
Pectin	40	–	–	35	30	25	20	15
Tamarind gum	–	40	–	–	–	–	–	–
CMC	–	–	40	–	–	–	–	–
Xylitol	–	–	–	5	10	15	20	25

2.4. Measurement of particle size of excipients

The ingredients passed through 60- or 100-mesh sieves were investigated for size distribution. Green diameter of more than 200 particles of the ingredients was measured at random by microscopic observation.

2.5. Measurement of characteristics of B-LF tablets

2.5.1. Tensile strength

The thickness and the diameter of the tablets were determined using a vernier caliper. The hardness of the tablets was determined by a KIYA Hardness Tester (Fujiwara Scientific Company Co., Ltd., Japan). The tablet tensile strength (T) was calculated using the following equation (Fell and Newton, 1970),

$$T = \frac{2F}{\pi dt}$$

where F, d and t denote the diametral crushing force, the tablet diameter and the tablet thickness, respectively. Measurements were performed for 10 tablets.

2.5.2. Water absorption properties

Water absorption properties of the tablets were assessed according to the method reported by Nakamura et al. (1996). In brief, a measuring pipette was filled with purified water and a scale brought to the starting point. The pipette was then connected to a tray consisting of a glass filter, and a tablet was put on the center of the tray. The distance of movement of the meniscus from the starting point for 30 s (volume of water absorbed, μL) was measured, and the mean of water absorption rates at 5 s intervals from 0 to 20 s (water absorption rate, μL/s) was calculated. The measurement was repeated for six tablets.

2.5.3. Bioadhesive force

The in vitro bioadhesive force of B-LF tablets was determined using a FUDOH Rheometer (Fudoh Kogyo Co., Ltd., Japan). After cerebral dislocation, a mouse peritoneal membrane was excised and mounted on an adapter (no. 3, the diameter: 10 mm) with the mucosal side facing to the outside. The membrane was rinsed with physiological saline before it was used, and the excess moisture was wiped off using a filter paper. A tablet was fastened to the tray of the rheometer using a two-sided tape, and attached to the membrane with a force of 200 g for 30 s. Then, the tray was lowered at a speed of 2 cm/min. The stress on the separation of the tablet from the membrane was measured. The measurement was repeated for five tablets.

2.5.4. Residence time in oral cavity

Three healthy volunteers cooperated in this test after providing informed consent. After they had gargled, moisture of the gingiva was lightly wiped off using a tissue paper. A B-LF tablet was placed between the gingiva and the lower lip and the time until the disappearance of the tablet was measured. The judgment was performed by the volunteers. During the test, they spent their time ordinarily except for prohibition of taking food.

2.5.5. Release test

The release test was performed according to the Japanese Pharmacopoeia XIV paddle method in 250 mL of 1/15 M phosphate buffer (pH 6.8, 37 °C) with constant stirring at 60 rpm. A B-LF tablet was attached on a glass plate with 10 μL of phosphate buffer and the glass plate was put into the dissolution medium in order to keep the tablet at the bottom. The dissolution medium (0.5 mL) was sampled at predetermined times until the tablets disappeared and an equal volume of the buffer was added to compensate after each sampling. The B-LF released was analyzed by HPLC (Rabiller-Baudry and Chaufer, 2001).

HPLC was carried out using an LC-6AD pump and a C-R7A plus chromatopac (Shimadzu, Kyoto, Japan) equipped with a Shodex Asahipak C4P-50 4D column (4.6 mm × 150 mm, Shoko Co., Ltd., Tokyo, Japan) and a SPD-10AV UV detector (Shimadzu) set at 280 nm. The mobile phase was a mixture of 0.5 M sodium chloride in water–acetonitrile–trifluoro acetic acid (63:37:0.03, v/v/v). The flow rate was 0.5 mL/min. Chromatography was carried out at 45 °C, and the injection volume was 20 μL.

2.6. Evaluation of healing effect of B-LF tablets on buccal mucosal ulcer

Rats were anesthetized with diethyl ether, and the buccal surface of the rats was exposed for 20 s to contact with glacial acetic acid using a glass tube of 4 mm in diameter stuffed with absorbent cotton. The procedure causes an immediate mucosal necrosis on the affected area, and chronic ulcer with a well-defined crater develops in 2 days (Slomiany et al., 1999; Slomiany and Slomiany, 2002). On the second day after the procedure (designated as ulceration day 0), the animals developed a relatively uniform ulcer were picked up and one of the animals was killed to measure the crater size of the ulcer. The remainder was divided into a treatment group, a placebo group and a control group. The crater area measured at day 0 was used as the initial ulcer area for the control, the placebo group and the treatment group. In the treatment group, B-LF tablets were adhered on the mucosal ulcer under temporary pentobarbital sodium anesthesia (40 mg/kg) once a day for 7 days, and 100 and 50 μL of water were administered soon and at 30 min after the administration of B-LF tablets. For the placebo group, tablets consisting of 40 mg of pectin and 25 mg of xylitol were prepared by a method similar to that for the B-LF tablets, and administered in the same manner as the treatment group. The control group was not treated with any tablets after ulceration. The animals were killed at days 1, 4, 7 and 10, the buccal mucosa was excised, and the crater size of the ulcer was measured using a vernier caliper. The crater area was calculated using the following equation:

$$\text{Crater area (mm}^2\text{)} = \text{the major axis (mm)} \times \text{the minor axis (mm)}$$

The ulcer healing was assessed using the ratio of the crater area at the observation day to the initial ulcer area.

2.7. Statistical analysis

Variance in a group was evaluated by the *F*-test, and differences in ulcer healing were evaluated by Student's *t*-test. The data were considered to be significantly different when the *p*-value was less than 0.05.

3. Results and discussion

3.1. Effect of polymers on the characteristics of B-LF tablets

The characteristics of B-LF tablets are shown in Table 2. Since CMC has good compressibility for tableting, CMC was used for comparison in this study. The lowest value of tensile strength was observed in the B-LF tablets containing pectin (tablet A). However, the tensile strengths of tablets A, B and C were sufficiently high and all the tablets could be applied to the buccal mucosa without collapse. Since the highest value of thickness was observed in tablet A, it was confirmed that the lowest density tablets were those prepared by using pectin. For the water absorption properties, tablet C containing CMC showed the highest value, followed by tablet A. It was considered that tablet A with the low density showed good water absorption properties compared with tablet B. For bioadhesive

Table 2
Characteristics of B-LF tablets containing different polymer

Tablet	Tensile strength (MPa)[a]	Thickness (mm)[a]	Volume of water absorbed (μL)[b]	Water absorption rate (μL/s)[b]	Bioadhesive force (g)[c]	Residence time (min)[d]
A (pectin)	2.00 ± 0.16	1.31 ± 0.06	9.0 ± 0.9	0.44 ± 0.05	81.8 ± 14.8	96 ± 29
B (tamarind gum)	3.41 ± 0.40	1.14 ± 0.05	7.5 ± 0.6	0.34 ± 0.04	55.6 ± 6.8	136 ± 29
C (CMC)	4.50 ± 0.45	1.19 ± 0.03	12.7 ± 1.2	0.54 ± 0.05	43.4 ± 5.0	36 ± 3

Each value represents the mean ± S.D.
[a] $n = 10$.
[b] $n = 6$.
[c] $n = 5$.
[d] $n = 3$.

Table 3
Effect of xylitol content on characteristics of B-LF tablets consisting of ingredients passed through a 60-mesh sieve

Tablet (xylitol content)	Tensile strength (MPa)[a]	Thickness (mm)[a]	Volume of water absorbed (μL)[b]	Water absorption rate (μL/s)[b]	Bioadhesive force (g)[c]
A_{60} (0%)	2.00 ± 0.16	1.31 ± 0.06	9.0 ± 0.9	0.44 ± 0.05	81.8 ± 14.8
D_{60} (7.7%)	1.64 ± 0.09	1.30 ± 0.00	10.3 ± 0.8	0.48 ± 0.03	74.0 ± 21.5
E_{60} (15.4%)	1.77 ± 0.18	1.30 ± 0.00	10.3 ± 1.0	0.48 ± 0.04	77.4 ± 15.7
F_{60} (23.1%)	2.01 ± 0.21	1.30 ± 0.00	10.0 ± 1.3	0.47 ± 0.03	80.4 ± 15.4
G_{60} (30.8%)	1.44 ± 0.18	1.26 ± 0.05	13.2 ± 1.5	0.58 ± 0.05	76.6 ± 18.0
H_{60} (38.5%)	1.48 ± 0.13	1.23 ± 0.05	10.5 ± 0.6	0.48 ± 0.03	72.4 ± 23.0

Each value represents the mean ± S.D.
[a] $n = 10$.
[b] $n = 6$.
[c] $n = 5$.

force, tablet A showed the highest value and tablet C showed the lowest value. Although tablet B showed the longest residence time, an unpleasant taste gradually developed after application to the oral mucosa. Tablet C adhered weakly to the mucosa and collapsed about 30 min after administration. In contrast, tablet A adhered to the oral mucosa until disappearance and the taste was acceptable. Thus, it was considered that pectin was a good bioadhesive polymer for the preparation of bioadhesive tablets.

3.2. Effect of xylitol contents on the characteristics of B-LF tablets

Since xylitol is low in calories and has little influence on tooth decay, xylitol was added to tablet A containing pectin to improve the taste and the preparation characteristics. Furthermore, as the particle size of ingredients is an important factor in determining the characteristics of B-LF tablets, B-LF tablets consisting of ingredients passed through a 100-mesh sieve were also prepared. The characteristics of B-LF tablets consisting of ingredients passed through 60- and 100-mesh sieves are shown in Tables 3 and 4, respectively. Regarding the tensile strength, tablet D_{60} containing 7.7% xylitol showed a lower value than tablet A_{60}. The tensile strength value increased in tablets E_{60} containing 15.4% xylitol and F_{60} containing 23.1% xylitol, and then decreased in tablets G_{60} containing 30.8% xylitol and H_{60} containing 38.5% xylitol. Although a similar tendency was shown in tablets A_{100}, D_{100}–H_{100}, the values were higher than the tablets prepared by using a 60-mesh sieve. These results showed that the addition of a small amount of xylitol decreased the tensile strength, but addition of the proper amounts of xylitol did not decrease the value. Furthermore, it was confirmed that tablets E_{100} containing 15.4% xylitol and F_{100} containing 23.1% xylitol showed the highest values of tensile strength. The thicknesses of tablets G_{60} containing 30.8% xylitol and H_{60} containing 38.5% xylitol were lower than those of tablets A_{60}, D_{60}–F_{60}. This was considered to be a result of the decreased addition of pectin in tablets G_{60} and H_{60}, which allowed preparation of a tablet with low density by means of its high plasticity. Similarly, the thicknesses of tablets G_{100} and H_{100} were lower than those of tablets A_{100}, D_{100}–F_{100}. In terms of the water absorption properties, tablets D_{100}–F_{100} tended to show higher values than tablets D_{60}–F_{60}. The size distributions of the ingredients passed through 60- or 100-mesh sieves are shown in Fig. 1. The particles sieved by a 100-mesh sieve were smaller and showed a narrower range than the particles sieved by a 60-mesh sieve, for all the ingredients. It was considered that the dissolution rate of the particles sieved by a 100-mesh sieve might increase than that of the particles sieved by a 60-mesh sieve. Although the diameter of capillaries on the tablets prepared by using a 100-mesh sieve might decrease, the number of the capillaries should increase. Thus, water could penetrate widely on the surface of tablets D_{100}–F_{100} in a short time. Although the water absorption properties tended to rise with increasing xylitol content, the values of tablets H_{60}, G_{100} and H_{100} decreased. This was considered to be a reason why the viscosity of the penetrating water was increased by dissolution of xylitol and penetration to the upper side of the

Table 4
Effect of xylitol content on characteristics of B-LF tablets consisting of ingredients passed through a 100-mesh sieve

Tablet (Xylitol content)	Tensile strength (MPa)[a]	Thickness (mm)[a]	Volume of water absorbed (μL)[b]	Water absorption rate (μL/s)[b]	Bioadhesive force (g)[c]
A_{100} (0%)	2.23 ± 0.24	1.23 ± 0.05	9.0 ± 0.6	0.43 ± 0.03	88.2 ± 35.3
D_{100} (7.7%)	1.98 ± 0.16	1.23 ± 0.05	11.7 ± 1.2	0.53 ± 0.06	94.8 ± 37.8
E_{100} (15.4%)	2.46 ± 0.27	1.25 ± 0.05	11.7 ± 1.8	0.53 ± 0.09	91.4 ± 27.3
F_{100} (23.1%)	2.44 ± 0.30	1.23 ± 0.05	13.5 ± 1.1	0.63 ± 0.04	96.6 ± 28.8
G_{100} (30.8%)	1.69 ± 0.22	1.20 ± 0.00	11.7 ± 0.8	0.53 ± 0.03	85.0 ± 29.8
H_{100} (38.5%)	1.71 ± 0.43	1.20 ± 0.00	9.5 ± 0.8	0.45 ± 0.04	78.0 ± 23.0

Each value represents the mean ± S.D.
[a] $n = 10$.
[b] $n = 6$.
[c] $n = 5$.

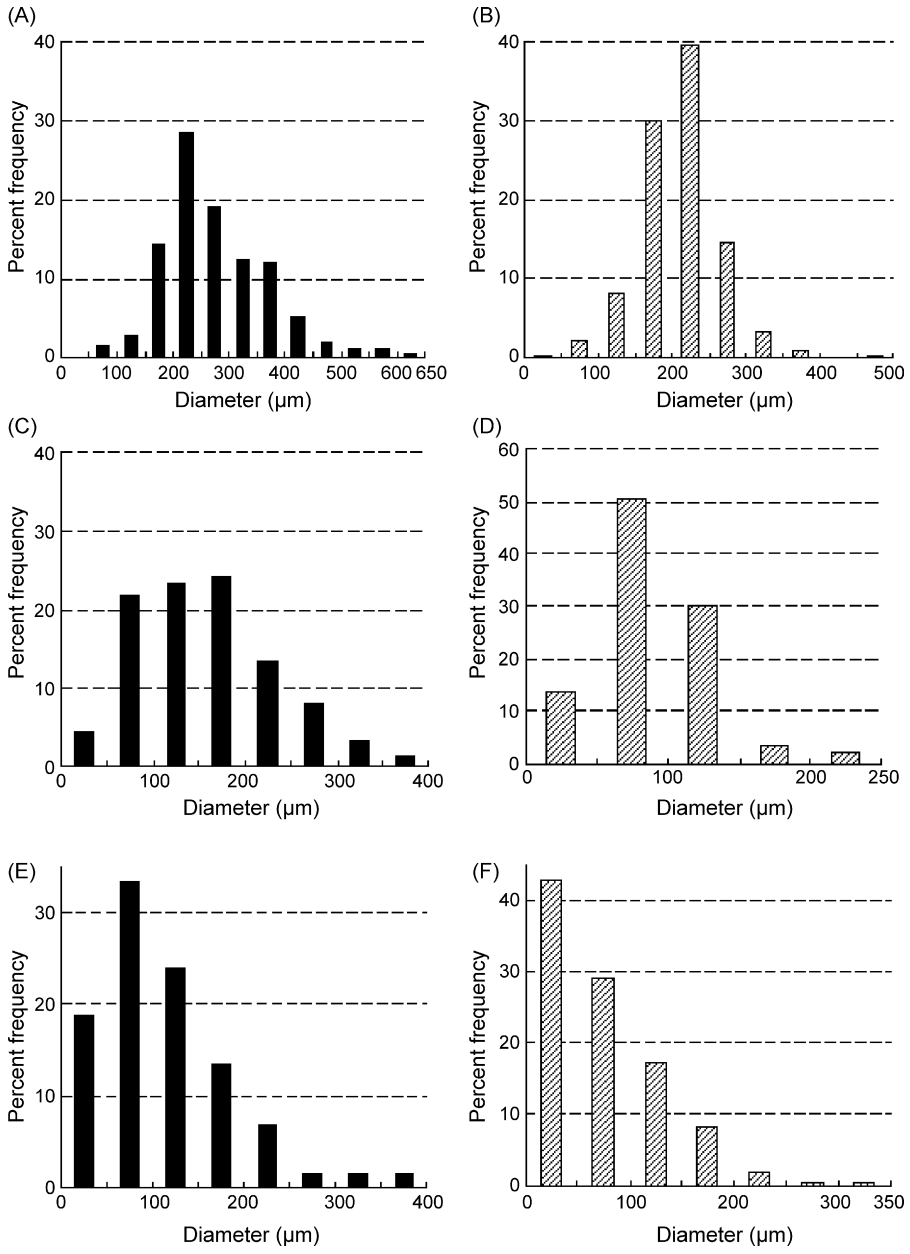

Fig. 1. Particle size distribution of the ingredients. (A) Pectin sieved by a 60-mesh sieve, (B) pectin sieved by a 100-mesh sieve, (C) xylitol sieved by a 60-mesh sieve, (D) xylitol sieved by a 100-mesh sieve, (E) B-LF sieved by a 60-mesh sieve, (F) B-LF sieved by a 100-mesh sieve.

capillaries was inhibited in those tablets. Regarding the bioadhesive force, tablets D_{100}–F_{100} showed higher values than the others. It was considered that the B-LF tablets could adhere to the mucosa by gelation of pectin. The gelation should occur after wetting by water. Hence, tablets D_{100}–F_{100}, which showed high water absorption, might show higher values of bioadhesive force. In contrast, tablets G_{100} and H_{100} might show the lower values of bioadhesive force because of a decrease of the pectin content and the water absorption properties. There was little difference in the bioadhesive force among tablets A_{60}, D_{60}–H_{60}. Since the particle size of pectin was large in these tablets, it was considered that the dissolution property of pectin would be barely improved even if wetting in the tablets increased. From these results, it was confirmed that the tablets containing xylitol showed not only increased sweetness and feeling of coolness, but also improved tensile strength and bioadhesive force by the addition of optimal amounts of xylitol and using ingredients passed through a 100-mesh sieve.

3.3. Release of B-LF from bioadhesive tablets

The release profiles of B-LF from bioadhesive tablets are shown in Fig. 2. Tablet A_{100}, tablet D_{100} containing 7.7% xylitol and tablet F_{100} containing 23.1% xylitol, which showed relatively high values for bioadhesive force, were chosen for the release test. The release data until 80% of B-LF released were fitted to the zero-order equation. The slope (k_0) of the regression line and the time required to release 50% of B-LF

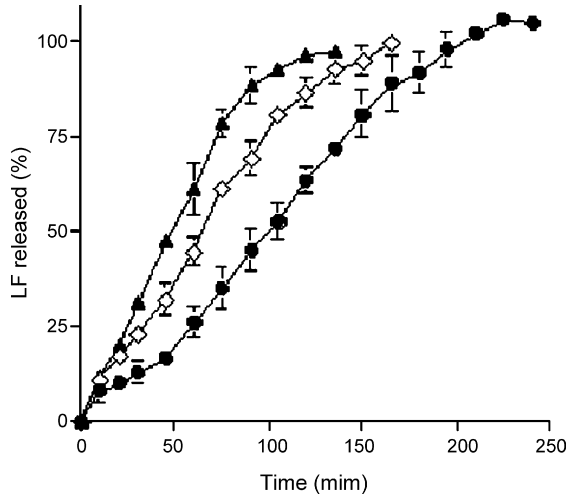

Fig. 2. Release profiles of B-LF from B-LF tablets containing pectin as a bioadhesive polymer in 1/15 M phosphate buffer (pH 6.8). *Key*: Tablet A_{100} of xylitol-free (●), tablet D_{100} containing 7.7% xylitol (◊), tablet F_{100} containing 23.1% xylitol (▲). Each point represents the mean ± S.D. ($n = 3$).

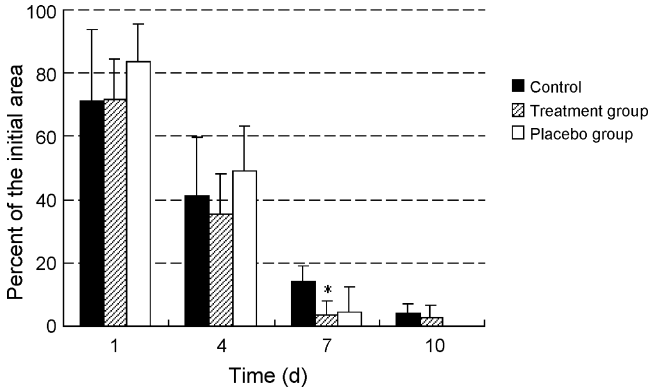

Fig. 3. Effect of B-LF tablets containing pectin as a bioadhesive polymer on healing of rat buccal mucosal ulcer model. For a treatment group, tablet F_{100} was use as B-LF bioadhesive tablets. For a placebo group, placebo tablets consisting of pectin and xylitol were used. Each value represents the mean ± S.D. ($n = 4$). $^{*}p < 0.05$ vs. control.

($T_{50\%}$) calculated are shown in Table 5. From the value of R^2, near zero-order release of B-LF from B-LF bioadhesive tablets was indicated. Since the release of B-LF reached 100% at the same time as disappearance of the B-LF tablet, it was considered that the release of B-LF accompanied the dissolution of pectin and xylitol. From the result, the rapid release of B-LF from tablet D_{100} was observed as compared with tablet A_{100}. Besides, tablet F_{100} containing 23.1% xylitol showed the more rapid release of B-LF. In this study, the tensile strength, the water absorption properties and the bioadhesive force were improved by adding appropriate amounts of xylitol and using ingredients passed through a 100-mesh sieve. However, the addition of xylitol to the B-LF tablets did not support sustained release. Since the residence time in oral cavity of tablet F_{100} was 59 ± 7 min, it was considered that the relatively slow release was observed in the tablet F_{100}. However, a sustained release tablet seems advantageous for the treatment of the chronic inflammation in the oral cavity, investigations of B-LF tablets containing various types of pectin for further control of release characteristics are underway.

3.4. Effect of B-LF tablets on healing of buccal mucosal ulcer

Since chronic inflammation in the oral cavity is often accompanied by intractable stomatitis, the therapeutic effect of B-LF tablets was evaluated by using rats with an ulcer on the buccal mucosa. In this study, tablet F_{100} containing 23.1% xylitol was used as a B-LF bioadhesive tablet. A dissolution test was performed using placebo tablets, and it was confirmed that the disappearance time of the placebo tablets was almost the same as that of tablet F_{100}. When the tablets were administered to the rats under pentobarbital anesthesia, dryness in the oral cavity was observed. Water was applied periodically to the oral cavity after the administration of the tablets. In Fig. 3, the ratios of the ulcer area at each observation day to the initial ulcer area are shown. In the groups treated with the tablets, adhesion of the tablets to the ulcer for over 40 min was observed. In the placebo group, decrease of the ulcer area until the 4th day was inhibited compared with control, probably because of the stimulation by the adhesive tablets and dryness in the oral cavity. However, since the ulcer tended to heal at an early time as compared with the control, it seemed that the placebo tablets covered and protected the ulcer after gelation on the mucosa. In the treatment group, the ulcer at day 1 and 4 tended to decrease as compared with the placebo group. Hence, B-LF tablets did not inhibit ulcer healing at the initial stage. At day 7, the ulcer tended to decrease as compared with the placebo group and had decreased significantly compared with the control. At day 10, the crater of all animals in the placebo group and two animals in the treatment group disappeared. As the result of statistical analysis, there was not significant difference between the placebo group and the treatment group at day 10. In Fig. 4, photographs of the mucosal ulcer at 1, 4, 7 and 10 days after ulceration are shown. Arrows show the mucosal ulcer or the scar. At day 1, swelling on the periphery of the ulcer was observed in the treatment group. At day 4, the ulcer got a long shape in the control group and the placebo group. In contrast, the ulcer has reduced overall and could be hardly distinguished at day 7 in the treatment group. The mechanism of the mucosal swelling was not revealed yet. For explanation of swelling histological studies will be acceptable. Production of the pro-inflammatory cytokines may be responsible for infiltration of inflammatory cells, such as neutrophils and macrophages (Szpaderska et al., 2003). Diminished production of the pro-inflammatory cytokines IL-6 and IL-8, and stimulated production of the anti-inflammatory cytokine IL-10

Table 5
Release parameters of B-LF from B-LF tablets

Tablet	K_0 (%/min)	R^2	$T_{50\%}$ (min)
A_{100}	0.518	0.992	99
D_{100}	0.765	0.995	64
F_{100}	1.001	0.998	49

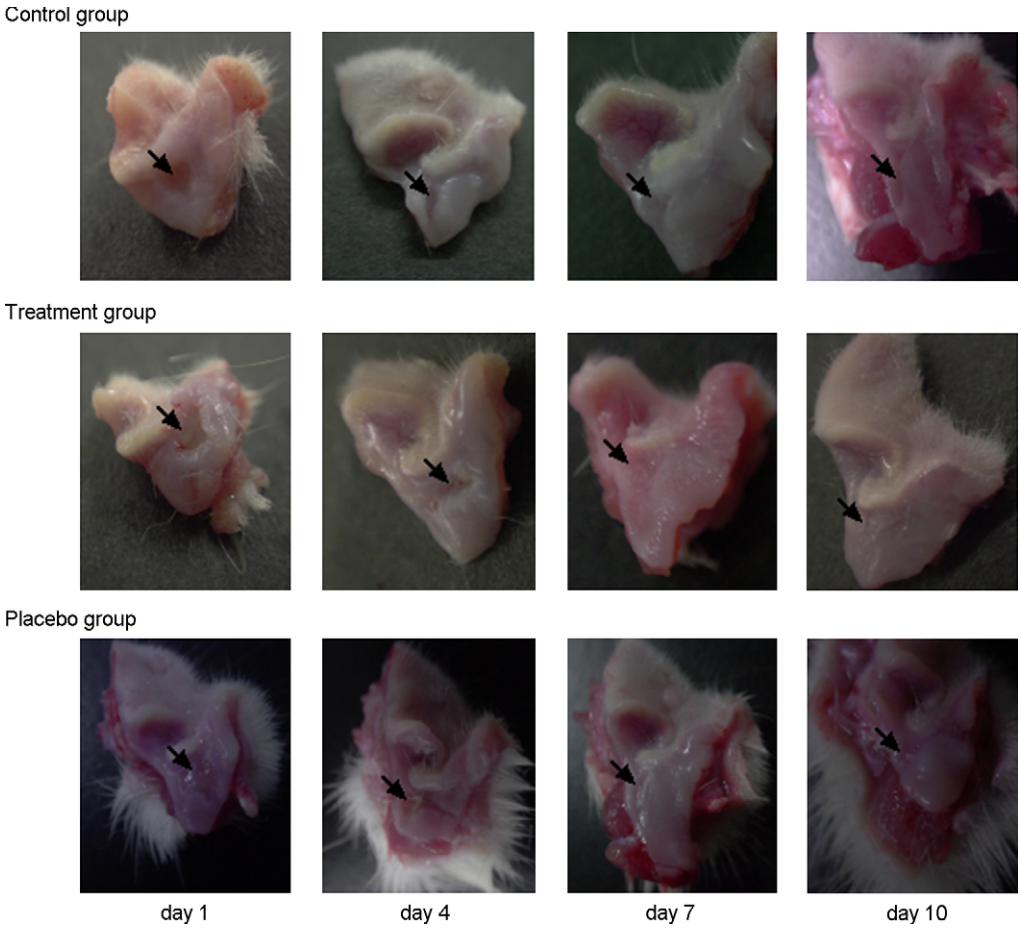

Fig. 4. Photographs of mucosal ulcer at 1, 4, 7 and 10 days after ulceration.

may inhibit the inflammatory cell recruitment. Lactoferrin has the immune regulatory function and decreases the production of the pro-inflammatory cytokines. Hence, it is considered that the immune regulatory function of B-LF may induce the swelling on the oral mucosa, and then achieve the earlier reduction of the ulcer area.

4. Conclusion

B-LF tablets containing pectin showed the highest value of bioadhesive force and could adhere to the buccal mucosa until they disappeared in the oral cavity. The addition of xylitol to the B-LF tablets improved the water absorption properties. Furthermore, the tensile strength and the bioadhesive force were improved by adding appropriate amounts of xylitol and using ingredients passed through a 100-mesh sieve. The release of B-LF from the B-LF tablets quickened as the xylitol content increased. In the evaluation of the healing effect, swelling on the periphery of the ulcer was observed after administration of the B-LF tablets, and then the ulcer has reduced overall. In the treatment group, the ulcer tended to decrease as compared with the placebo group at days 1, 4 and 7. In general, chronic inflammation in the oral cavity may result from several causes, such as bacteria and repeated physical stimulus. Bioadhesive B-LF tablets having antibacterial properties might be useful for the treatment of the chronic inflammation caused by bacteria in the oral cavity.

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