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Research Article

Pectin-Based Bioadhesive Delivery of Carbenoxolone Sodium for Aphthous Ulcers in Oral Cavity

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Abstract. The objective of this study was to prepare and evaluate the pectin-based dosage form for buccal adhesion. Carbenoxolone sodium, which is used for the treatment of aphthous ulcers in oral cavity, was used as a model drug. The pectin buccal discs were prepared by direct compression. The water uptake and erosion of pectin disc increased progressively with the swelling time. The bioadhesion of dried pectin discs decreased when either the discs were hydrated or the buccal tissue was wet with a small volume of medium. The influencing factors such as pectin type, pectin to lactose ratio, and sweetener type on the formulations were investigated. The results demonstrated that buccal discs prepared from pectin with a high degree of esterification (DE) showed a weaker and more friable characteristic than that with low DE. Decreasing pectin to lactose ratio resulted in the high dissolution rate with low bioadhesive properties. Addition of sweetener in the formulations also affected the hardness, friability, and bioadhesive properties of the discs. The pectin discs containing sweetening agent showed a higher drug release than those without sweetener. The results suggested that pectin-based bioadhesive discs could be used to deliver carbenoxolone sodium in oral cavity.

KEY WORDS: aphthous ulcers; bioadhesive drug delivery; buccal; carbenoxolone sodium; pectin.

INTRODUCTION

An aphthous ulcer is a type of mouth ulcer which presents as a painful open sore inside the mouth caused by a break in the mucus membrane. The condition is also called aphthous stomatitis, especially if there are multiple or recurring mouth ulcers. Recurrent aphthous stomatitis is one of the most common oral conditions. At least 10% of the population suffers from it (1,2). Aphthous ulcers can be classified into three different types: minor, major, and herpetiform (3). Minor aphthae are generally located on the labial or buccal mucosa, the soft palate, and the floor of the mouth. They can be singular or multiple, and tend to be small and shallow. Major aphthae are larger and involve deeper ulceration. Herpetiform aphthae frequently are more numerous and vesicular in morphology. The lack of clarity regarding the etiology of aphthous ulcers has resulted in treatments that are largely empiric. These treatments include antibiotics, anti-inflammatories, immune modulators, anesthetics, and alternative remedies (1,3). These drugs are normally formulated in ointments, pastes, lozenges, or mouthwashes, and applied topically in order to avoid systemic side effects (3).

Although corticosteroids are frequently used for treatment of aphthous ulcers, carbenoxolone sodium (CBX), which is a synthetic derivative of glycyrrhizinic acid derived from liquorices (a salt of 18β-glycyrrhizic acid succinic acid esters), has been effectively used by some family physicians in Thailand (4). It has been used to soothe ulcers by increasing the production of mucus from the lining of the stomach and esophagus (5). CBX has been reported for its anti-inflammatory and anti-allergic effects when applied externally and successfully used in viral-induced oral mucosal ulcers and aphthous ulcers (5,6). However, CBX is only available in the liquid dosage forms, e.g., topical solutions, topical spray, and mouthwashes, which have been found to be incapable of maintaining the local concentration of drugs for a prolong period of time. The dilution and rapid elimination of topically applied drugs due to flushing action of saliva are a major difficulty for the treatment in oral cavity. A bioadhesive buccal dosage form which could be stuck on the inner surface of the cheek (buccal mucosa) for a prolonged period of time was developed (e.g., 7,8). The bioadhesive dosage form can directly apply to the affected areas and may also reduce the frequency of the application and the amount of drug administered, which might improve patient compliance and acceptance.

Pectin, a naturally occurring polysaccharide, is regarded as safe for human consumption and has been used success-

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fully for many years in food and beverage industries as thickening agents, gelling agents, and colloidal stabilizers. It is finding increasing applications in the pharmaceutical industry (e.g., 9–12). Structurally, pectin is a partial methyl ester of (1–4)-α-D-galacturonic acid interrupted with (1,2)-α-L-rhamnose units and other neutral sugars. The degree of esterification (DE) less than 50% is low-DE pectin while DE more than 50% is high-DE pectin (13). Pectin has also been proposed as a bioadhesive polymer for GI mucoadhesive delivery (7,14–18). Schmidgall and Hensel (14) and Liu *et al.* (15) reported that pectin with high net electric charges showed a high mucoadhesion. Recently, the mucoadhesive performance of different types of pectin on to the gastrointestinal tract was investigated by texture analysis and viscometric, rheological, and wetting studies (16–19). For buccal delivery, Miyazaki *et al.* (7) prepared buccal adhesive tablets containing pectin and hydroxypropylmethylcellulose for sustained release of diltiazem. The maximum adhesive force to rat peritoneal membrane increased with increasing pectin concentration in the tablets. Takeda *et al.* (20) developed bioadhesive tablets of bovine lactoferrin (B-LF) using pectin as a bioadhesive polymer. Sustained release of B-LF from the tablets was observed as the esterification of pectin was increased or the Ca^{2+} was added in the tablets.

In this study, the evaluation of pectin as a buccal bioadhesive polymer was performed. The instrumental variables and test conditions when testing with texture analyzer under simulated buccal conditions using porcine buccal tissue were also validated. The pectin discs containing carbenoxolone sodium (CBX) were subsequently prepared and the buccal adhesive properties and the release of CBX were tested.

MATERIALS AND METHODS

Materials

Two different pectins (type CU201 and CU701) were kindly provided by Herbstreith & Fox KG (Germany). Pectin CU201 has a 70% DE and molecular weight of 200 kDa while pectin CU701 has a 38% DE and molecular weight of 80 kDa, and these are referred to as CU201 and CU701 respectively. CBX, spray-dried lactose, xylitol, sucrose, glucose, and magnesium stearate were of pharmaceutical grade and used as received without further purification. Simulated saliva fluid (SSF, pH 6.75) was freshly prepared and used in this study.

Porcine buccal tissue was used in this study because of its non-keratinized morphology that is similar to human buccal epithelium (21). Porcine buccal tissues were obtained from animals immediately after slaughter at a local slaughterhouse (Nakhon Pathom, Thailand). The tissues were washed with deionized water to remove undigested food from lumen and then placed in normal saline solution at 4°C and used within 6 h. The underlying connective tissues were subsequently removed to isolate the mucosal membrane, as previously described (17).

Preparation of Pure Pectin Discs

Discs of 200-mg sample powder were prepared by direct compression using a single punch hydraulic press (Model 15011, Specac, USA) with a 9.53-mm-diameter flat-faced tooling. The discs were compressed at a pressure of 2 tons for 30 s and kept in a desiccator until used.

Swelling and Erosion Studies

The rate of SSF uptake by the pure pectin disc was determined by equilibrium weight gain method similar to that reported previously (12). The pectin discs were accurately weighed (W_0) and placed in closed plastic containers with the mesh underneath the tablets, rotating at 150 rpm using an environment shaker–incubator (model ES-20, Biosan, Latvia), with the SSF at 37±0.5°C. After 2, 5, 10, 20, 60, and 120 min, each container was removed from the incubator; the disc with the pre-weighed mesh was withdrawn from the medium and lightly blotted with tissue paper to remove excess test liquid and then re-weighed (W_1) on an analytical balance (model AG204, Mettler-Toledo, Greifensee, Switzerland). After the swelling studies, the wet samples were then dried in an oven at 80°C for a 24-h time period, allowed to cool in a desiccator, and finally weighed until constant weight was achieved (final dry weight, W_2). The experiment was performed in triplicate for each time point, and fresh samples were used for each individual time point. The percentage change in weight due to absorbed liquid or water uptake was estimated at each time point from Eq. 1:

$$\%\ \text{weight change} = \frac{W_1 - W_2}{W_2} \times 100 \tag{1}$$

The tablet erosion (ES) at different times was estimated from the following equation:

$$\text{ES} = \frac{W_0 - W_2}{W_0} \times 100 \tag{2}$$

The percentage of the remaining tablets after erosion was calculated from Eq. 3:

$$\%\ \text{remaining} = 100 - \text{ES} \tag{3}$$

Study on Test Conditions for Bioadhesive Test for Buccal Tissue

Bioadhesive testing of the sample discs was carried out using a texture analyzer (TA.XT plus, Stable Micro Systems, UK), with 50-N load cell equipped with a bioadhesive holder. The disc was attached to a cylindrical probe (10 mm in diameter) by double-sided adhesive tape. The buccal tissues (about 20×20 mm^2) were equilibrated in pH 6.75 SSF (37± 0.5°C) for 15 min before placing on the stage of bioadhesive holder. Small volume of SSF (i.e., 100 or 500 μL, with or without 2.7 g/L of mucin) was dropped on the tissue prior to the test. The probe with sample disc was then moved downward to attach the tissue with the specified contact force (i.e., 0.05, 0.1, 0.2, and 0.5 N) and contact time (i.e., 30, 60, 180, and 300 s) before withdrawal with the speed of 0.5 mm/s. By using the texture analyzer, the maximum force to separate the probe from the tissue (i.e., maximum detachment force, F_{max}) could be detected directly from Texture Exponent 32 software, and the total amount of forces

involved in the probe withdrawal from the tissue (work of adhesion, W_{ad}) was then calculated from the area under the force *versus* distance curve. The unhydrated (dried) pectin discs were tested and compared to the 5-min pre-hydrated discs. The probe without disc was also tested to check the uniformity of the buccal tissues. In order to confirm reproducibility and validity of the obtained data, six to ten measurements were performed for each condition. These parameters were used to compare the different test conditions or formulations.

Formulation of Bioadhesive Discs

Each type of pectin was blended with spray-dried lactose at a ratio of 3:1, 2:2, or 1:3 using a porcelain mortar. Magnesium stearate was also added in the mixture (1% w/w) as the lubricant. Table I shows the formulation of pectin-based bioadhesive disc with and without CBX. Discs of 60 mg of mixture were direct-compressed using the same instrument of the pure pectin discs. The discs were compressed at a pressure of 2 tons for 30 s and kept in a desiccator until used. Pectin discs without spray-dried lactose were also prepared and used for comparison purposes. The suitable ratio of pectin and spray-dried lactose was selected in order to load the drug and sweetening agent. The model drug used in this study was CBX and the percentage of the loading dose was 1 mg per disc. The sweetening agents investigated were xylitol, sucrose, and glucose (3 mg per disc).

Physical Properties of Bioadhesive Discs

The friability, hardness, and thickness of the sample disc were determined using an Erweka abrasion tester (Heusenstamm, Germany), texture analyzer (TA.XT plus, Stable Micro Systems) with a 2-mm stainless steel probe (P/2), and Mitutoyo thickness caliper (Mitutoyo, Japan), respectively. Ten discs were individually measured in thickness and hardness tests, while a total of 20 discs were used for friability test.

Bioadhesive Test

Bioadhesive test for the sample disc was performed as described above. According to the results in the mentioned section, the unhydrated samples of formulated bioadhesive discs and buccal tissues wet with 100-μL SSF containing mucin were then used in the further study. The contact force and contact time were set at 0.05 N and 60 s respectively. At least six measurements were performed for each formulation.

In Vitro Drug Release Study

The release of CBX from discs was studied using modified Franz diffusion cells performed at 37±0.5°C. The SSF (pH 6.75, 16 mL) was used as a test medium. Samples (3 mL) were taken from the receptor phase at certain time intervals and replaced with the same amount of fresh SSF. The taken samples were filtered and assayed for CBX at 278 nm using a UV spectrophotometer (model Lambda 2, Perkin Elmer, Germany) in a 1-cm quartz cell. Each *in vitro* study was performed in triplicate.

RESULTS AND DISCUSSION

Swelling and Erosion of Pectin Discs

The gel formation on pectin discs were observed during the swelling test. Visual observation indicated that the pectin discs appeared to swell almost from the beginning, and a viscous gel mass was created when they came into contact with the medium. The results from the swelling and erosion studies were provided as the percentage weight change and percentage remaining of sample mass (Fig. 1). The swelling behavior indicated the rate in which the pectin disc absorbed water from the test medium and swelled. The percentage of the remaining discs reflected the amount of polymer dissolved and eroded in the medium. Our previous study (12) showed that the swelling of pectin disc, in various media including gastrointestinal media, started from the beginning and continued until 120 min of the experiment, and the weight loss from the discs increased progressively with the swelling time. In this study, the swelling and erosion behavior of pectin disc in SSF was similar to those in gastrointestinal media (12). Compared to the previous study, the water uptake of pectin discs in SSF was higher than that in simulated intestinal fluid (12). This may be due to the effect of both sodium chloride and potassium dihydrogen phosphate in the SSF. The discs of high-DE pectin (CU201) showed a slightly higher ability to absorb water and swell in SSF than those of low-DE pectin (CU701), whereas the erosion of these pectin discs was insignificantly different, ranging between 30% and 38% at

Table I. Formulation of Pectin-Based Bioadhesive Disc Containing Carbenoxolone Sodium (60 mg/disc)

Formulation	Pectin (mg)	Spray-dried lactose (mg)	Magnesium stearate (mg)	Sweetening agent (mg)			Carbenoxolone sodium (mg)
				Xylitol	Sucrose	Glucose	
1 (4:0)	59.4	–	0.6	–	–	–	–
2 (3:1)	44.6	14.9	0.6	–	–	–	–
3 (1:1)	29.7	29.7	0.6	–	–	–	–
4 (1:3)	14.9	44.6	0.6	–	–	–	–
Control 1	58.4	–	0.6	–	–	–	1
Control 2	29.2	29.2	0.6	–	–	–	1
A	27.7	27.7	0.6	3	–	–	1
B	27.7	27.7	0.6	–	3	–	1
C	27.7	27.7	0.6	–	–	3	1

120 min. Although low-DE pectin is more hydrophilic than high-DE pectin, its molecular weight is lower (ca. 70,000 Da) compared to that of high-DE pectin (200,000 Da). It seems that molecular weight plays a more important role in water absorption than hydrophilicity. This agreed with other reports (e.g., 22,23).

Effect of Test Condition on Buccal Bioadhesion Test

Two types of pectin (CU201 and CU701) were selected for studying the effect of test conditions, i.e., pre-hydration time, volume of medium, contact time, contact force and medium composition in order to validate the test condition. Figure 2 shows the F_{max} and W_{ad} of unhydrated and 5-min pre-hydrated pectin discs after attachment to buccal tissue which was wet with small volume of SSG (100 μL). The results demonstrated the mucoadhesive performance of unhydrated pectin discs against buccal tissue. The water transfer from epithelial layer of the tissue into dried pectin disc may increase the adhesive and cohesive properties of the mucoadhesive bond (24). The F_{max} and W_{ad} of unhydrated pectin discs were higher than those of 5-min pre-hydrated pectin discs. It is possible that the excessive quantity of aqueous medium induced the hydrated polymers to form gels and eventually a slippery mucilage, resulting in the loss of bioadhesive properties as the polymers dissolve in the available water (17).

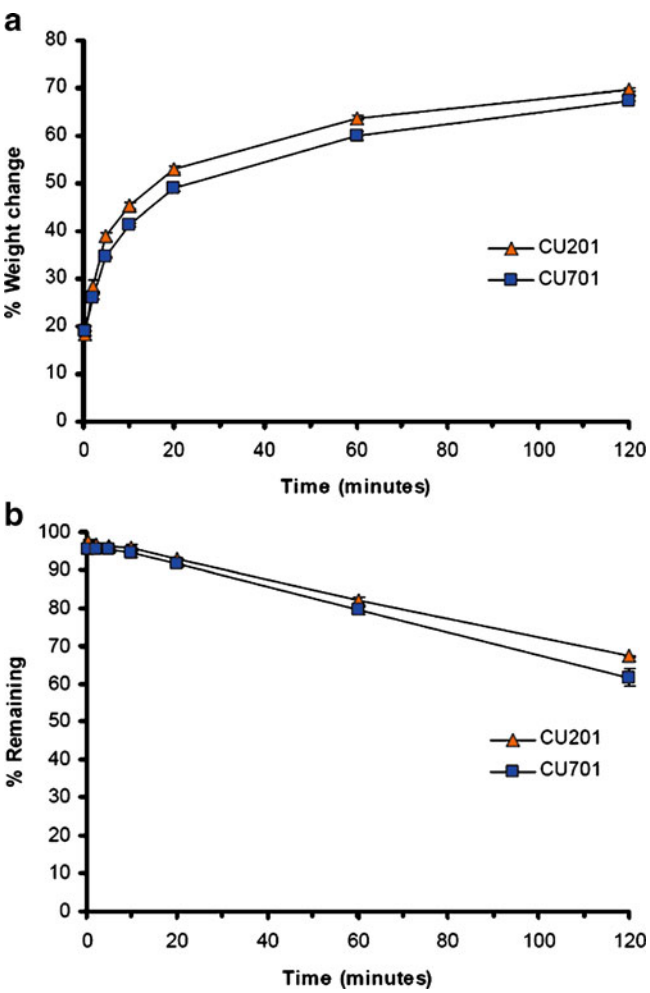

Fig. 1. **a** Percentage weight change and **b** percentage remaining of different pectin discs (n=3) in simulated saliva fluid pH 6.75

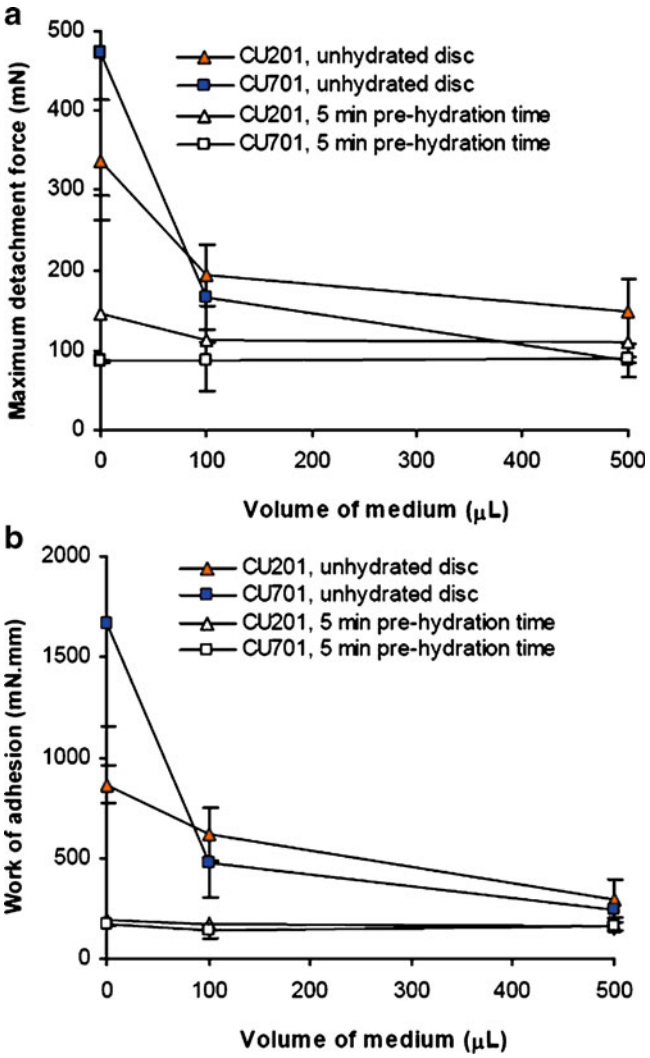

Fig. 2. Effect of pre-hydration time and volume of medium on **a** maximum detachment force and **b** work of adhesion against porcine buccal tissue which was wet with 100-μL simulated saliva fluid (n=6–10)

As the buccal tissue was wet with a small amount of SSF, both F_{max} and W_{ad} of unhydrated pectin discs significantly decreased and seemed to be a plateau as the volume of SSF was increased from 100 μL to 500 μL. This indicated that the excess amount of water in buccal tissue led to a decrease in bioadhesion. A large amount of water transfer from tissue to pectin discs facilitated the overwet phenomenon in the oral cavity. Moreover, a hydrophilic pectin polymer can absorb water rapidly. Hence, the adhesive joint between the disc and mucus was no longer strengthening. The overwet phenomenon also occurred in the pre-hydrated pectin discs, as their mucoadhesive strength was not influenced by the increase in medium volume. Gurny *et al.* (25) suggested that the excess polymer hydration led to a reduction of the strength of polymer–mucosa bond since the density of the functional groups promoting the adhesion decreased.

Furthermore, the dry discs of CU701 showed a higher F_{max} and W_{ad} than those of CU201. This may be due to the

large amount of carboxyl groups of CU701, resulting in higher wettability of the dry disc by the water in the tissue than those of CU201. This agreed with the previous report (19) in which the thermodynamic work of adhesion of CU701 was higher than CU201. This implied that CU201 showed a weaker bioadhesion while CU701 had a stronger bioadhesion. It is possibly due to the difference in the MW and the number of methoxy groups in pectin structure. A higher MW and the presence of hydrophobic moieties in pectin structure may result in the lower thermodynamic work of adhesion. Sanzgiri *et al.* (26) also found that the force of adhesion depended on the hydrophilicity of the polymers; the polymers with more hydrophilicity demonstrated more adhesion. In order to investigate the effect of the test condition for buccal adhesive test, the buccal tissues wet by 100-μL SSF prior to the test were further used.

Figures 3 and 4 demonstrate the effect of contact time and applied contact force between the pectin discs (CU201 and CU701) and buccal tissue, respectively, on the F_{max} and W_{ad} of pectin discs. The bioadhesion of dried pectin discs increased with the increase in contact time (Fig. 3). It was limited for CU201 when tested with a contact time of 300 s; the hydrated pectin particles from the disc still attached at the buccal tissue and the separation of pectin disc from the measuring probe were observed. Thus, the F_{max} could not be measured. This indicated that the adhesive properties of pectin disc of CU201 on buccal tissue were higher than the cohesive forces between particles in the compacted discs. Shojaei *et al.* (27) reported that increasing the contact time between copolymer (acrylic acid and 2-ethylhexyl acrylate) film and buccal tissue yielded a linear increase in mucoadhesive forces for up to 60 s; a further increase in contact time (120–300 s) led to a plateau. They explained that cohesive energy of the copolymers may decrease substantially after the first minute of contact leading to physical deformation of the polymer due to water sorption.

In Fig. 4, the F_{max} of dried pectin disc on buccal tissue was not significantly different when the contact force between 0.05 N and 0.5 N was applied, while the W_{ad} seemed to increase with the increase in contact force. The values of W_{ad} of dried pectin disc against buccal tissue were substantially

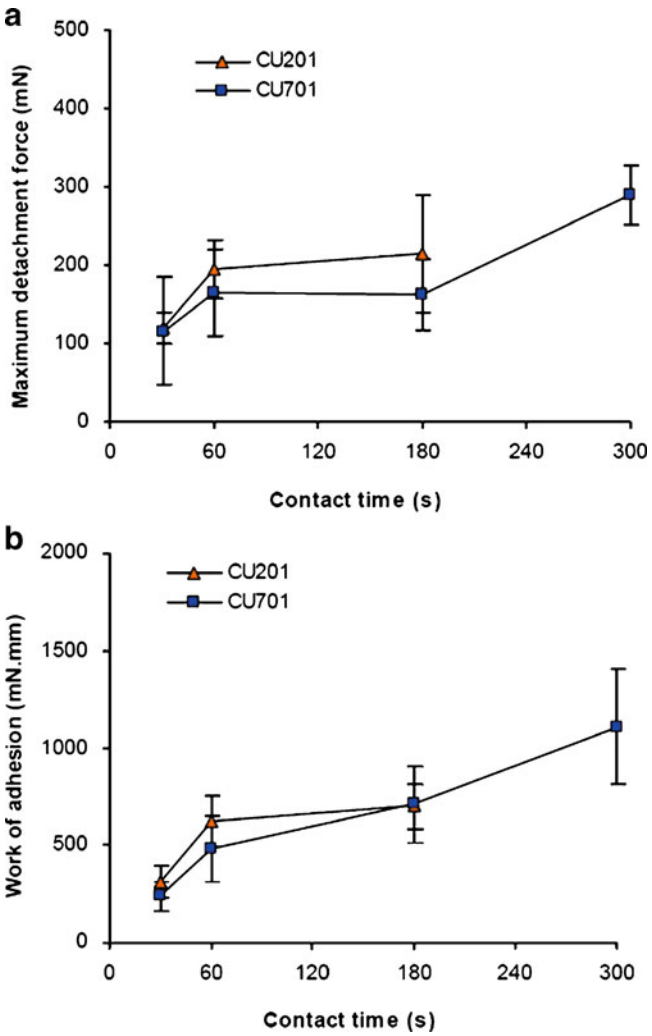

Fig. 3. Effect of contact time between the dried pectin discs (CU201 and CU701) and buccal tissue which was wet with 100-μL simulated saliva fluid on **a** maximum detachment force and **b** work of adhesion against porcine buccal tissue (n=6–10)

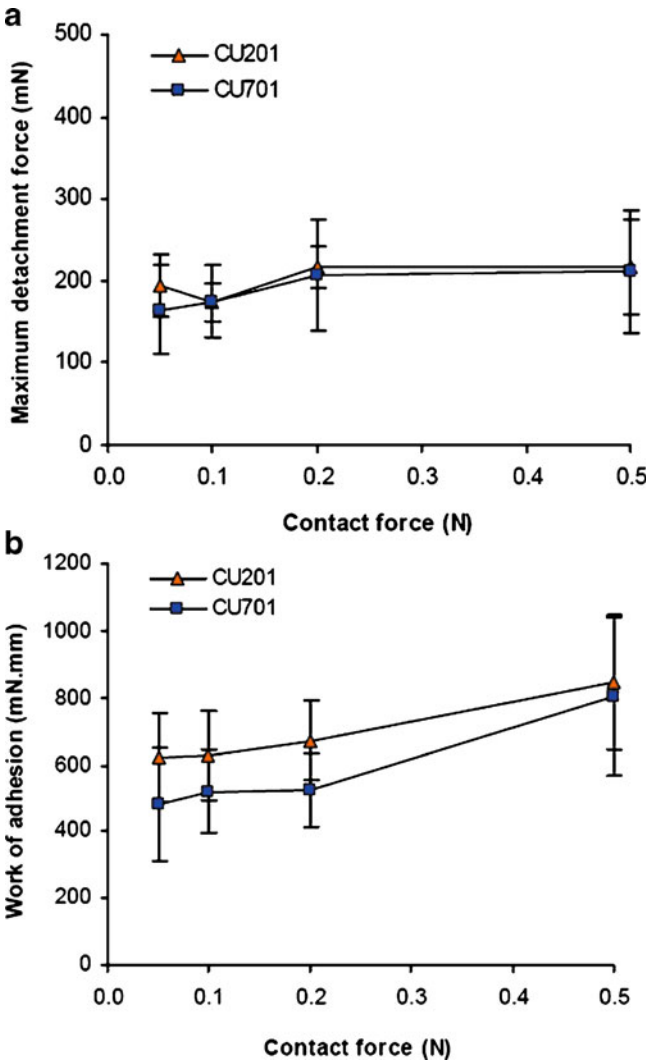

Fig. 4. Effect of contact force applied between the dried pectin discs (CU201 and CU701) and buccal tissue which was wet with 100-μL simulated saliva fluid on **a** maximum detachment force and **b** work of adhesion against porcine buccal tissue (n=6–10)

higher than those against small intestinal tissue, as reported earlier (17), for all contact force applied. This is probably due to the difference in the hydration state of pectin discs. The results suggested that the bond strength of dried pectin discs to tissue was stronger than those of hydrated one due to the dehydration effect on tissue.

Figure 5 shows the effect of mucin in SSF on F_{max} and W_{ad} of high and low-DE pectin discs against buccal tissue, which was wet with medium to simulate the buccal environment. The test condition was different from that of buccal tissue immersing in 200-mL SSF which has been used to compare with other GI mucosas (17). The results also showed that addition of mucin in medium could not increase the mucoadhesive performance of dried pectin discs.

Formulation of Buccal Adhesive Discs

The various ratios between pectin and spray-dried lactose were studied for the friability, hardness, and thickness of the discs. Table II shows the results of the physical properties of sample discs. The results demonstrated that pectin discs made of high-DE pectin (CU201) were soft and fragile, while those made from low-DE pectin (CU701) were significantly stronger and lower in friability. However, Takeda *et al.* (20) found different results in which the high-DE pectin showed the higher value of tensile strength. This is probably due to the high-DE pectin used in their study composed of some soluble solid, i.e., sucrose. The thickness of pectin discs made of these two types of pectin was insignificantly different ($p>0.05$); the disc made of CU201 was slightly thicker than that of CU701. This also indicated that the particles of pectin CU201 were packed or attached together with a weak bonding or force.

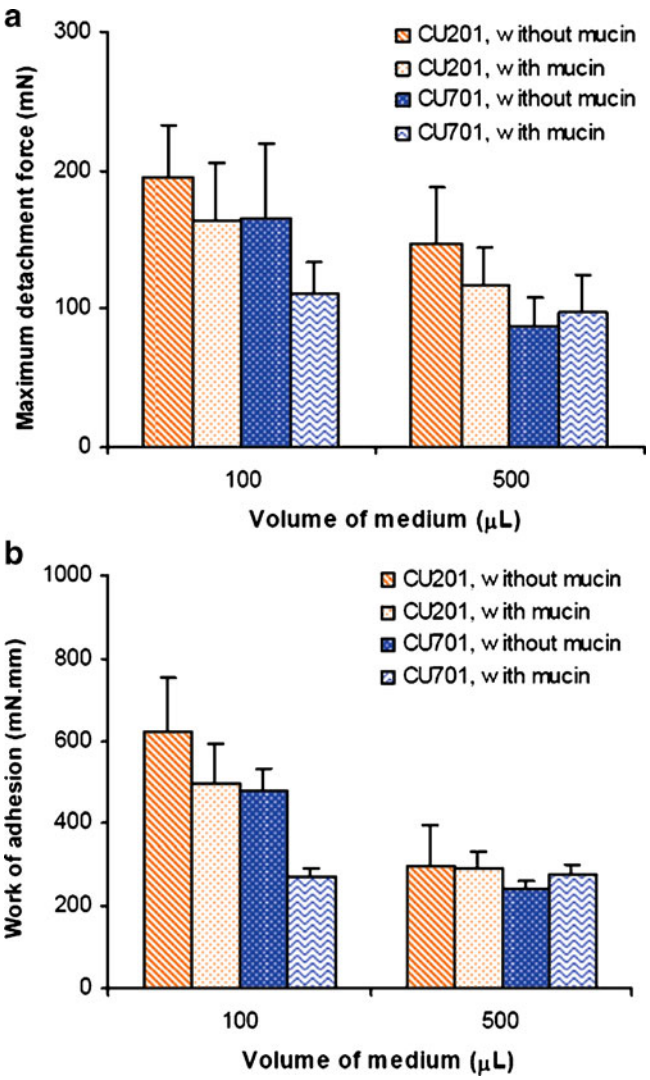

Fig. 5. Effect of mucin in the test medium on **a** maximum detachment force and **b** work of adhesion of dried pectin discs (CU201 and CU701) against porcine buccal tissue which was wet with 100-μL or 500-μL medium ($n=6$–10)

The pectin discs made from a mixture of low-DE pectin (CU701) and lactose were also stronger than those made from a mixture of high-DE pectin (CU201) and lactose. Pectin was found to consolidate mainly by fragmentation with little plastic deformation and high elastic recovery (28). The high elasticity of pectin, especially high-DE pectin with higher molecular weight (about 200,000 Da), may result in the discs with low compact strength. On the contrary, low-DE pectin with lower molecular weight (about 70,000 Da) may provide a more rigid and brittle structure with limited elastic deformation, and thus resulted in a higher compact strength. The improved hardness of the discs by the addition of lactose may result from the brittle characteristics of lactose. Furthermore, the cohesive force between pectin particles in dry state was very weak and the particles of spray-dried lactose could increase those forces. Increasing the amount of lactose in the formulation (from pectin to lactose ratio of 4:0 to 1:3) obviously increased the mechanical properties of the discs made from high-DE pectin. The pectin to lactose ratio of 1:1 gave the lowest friability and relatively high hardness.

Based on the results obtained from the friability, thickness, and hardness test, the formulation of pectin to spray-dried lactose ratio of 1:1 was selected for further studies. The formulations of CBX bioadhesive disc (60 mg per disc) are shown in Table I. The discs without spray-dried lactose and sweetening agent (control 1) and without sweetening agent (control 2) were also prepared for comparison purposes. The chosen formulations were prepared by addition of 1 mg CBX and 2 mg sweetening agent (formulations A, B, and C). The friability, hardness, and thickness of the discs of formulations with CBX are also shown in Table II. For the CBX-loaded formulations, the addition of lactose also enabled the improvement of the physical properties of the buccal discs, i.e., the hardness increased and the friability decreased. It is probably due to the advantage of spray-dried lactose as it could be used as direct compression vehicle even if it is combined with other excipients. The sweetening agent, i.e., xylitol, sucrose, or glucose, was added to the formulations containing pectin to improve the taste. The amount of sweetening agent was kept constant at 5% w/w. The results showed that, for the discs made from high-DE pectin, the addition of a small amount of xylitol decreased the hardness of the discs, but addition of sucrose or glucose increased the hardness. However, the discs made of high-DE pectin showed a high number of friability of about 4%. In case of the discs made from low-DE pectin, the addition of sweetening agent improved the mechanical properties of the buccal discs.

Table II. Physical Properties of Pectin-Based Bioadhesive Discs with or without Carbenoxolone Sodium

Pectin type	Formulation	Pectin/lactose ratio	Hardness (g, n=10)	Thickness (mm, n=10)	Friability (%, n=20)
High-DE pectin (CU201)	1	4: 0	12.2±2.4	0.79±0.02	100.00
	2	3: 1	73.0±9.2	0.76±0.03	51.79
	3	1: 1	177.0±12.7	0.74±0.02	2.74
	4	1: 4	202.6±29.0	0.70±0.03	4.92
	Control 1	4: 0	31.7±2.4	0.74±0.04	74.47
	Control 2	1: 1	148.6±19.2	0.73±0.02	1.14
	A/xylitol	1: 1	114.8±9.2	0.73±0.04	3.91
	B/sucrose	1: 1	214.9±12.7	0.72±0.03	4.39
	C/glucose	1: 1	200.7±28.9	0.74±0.01	3.81
Low-DE pectin (CU701)	1	4: 0	189.5±17.9	0.73±0.02	0.91
	2	3: 1	171.7±21.0	0.73±0.03	1.28
	3	1: 1	164.2±10.6	0.71±0.03	1.62
	4	1: 4	213.5±20.7	0.71±0.03	2.16
	Control 1	4: 0	135.0±8.7	0.72±0.03	1.72
	Control 2	1: 1	167.7±28.8	0.71±0.04	0.99
	A/xylitol	1: 1	185.7±25.7	0.71±0.02	0.98
	B/sucrose	1: 1	197.3±28.9	0.72±0.01	0.52
	C/glucose	1: 1	178.8±28.8	0.71±0.02	1.47

Bioadhesive Properties and *In Vitro* Drug Release

Table III shows the W_{ad} of pectin-based bioadhesive discs containing CBX. As the swelling of pectin polymer can be disturbed by the quick dissolution of lactose added in the formulations, the bioadhesive properties of the discs decreased, compared to the discs without lactose, for the formulations with high-DE pectin but did not significantly change for the formulations with low-DE pectin. High-DE pectin showed a higher W_{ad} than low-DE pectin when tested on the porcine buccal tissue, resulting from its high MW which facilitated coil entanglement. This agreed with the findings of a previous report performed in porcine gastrointestinal mucosa (17).

The release profiles, in SSF, of CBX from pectin-based bioadhesive discs are shown in Fig. 6. Drug release from bioadhesive discs is controlled by the formation of a gel layer around the tablet in contact with aqueous media. The formation of the gel is dependent on disc hydration, which relies on many factors that influence the surface gel: viscous, swelling, porous, and homogeneous properties. Different pectin discs (without lactose) showed a difference in drug release, i.e., CU201 discs demonstrated a faster drug release resulting from a high water uptake or swelling. In addition, the low tablet hardness and high friability (Table II) may also

Table III. Work of Adhesion (mN/mm) of Pectin-Based Bioadhesive Discs Containing Carbenoxolone Sodium (n=6–10)

Formulation	High-DE pectin (CU201)	Low-DE pectin (CU701)
Control 1	606.0±259.8	305.1±59.8
Control 2	344.5±54.5	269.7±51.2
A/xylitol	467.7±71.7	262.7±73.6
B/sucrose	410.5±94.2	331.8±67.0
C/glucose	398.2±88.0	302.0±61.7

The unhydrated discs and buccal tissues wet with 100-μL simulated saliva fluid containing mucin were used. The contact force and contact time were set at 0.05 N and 60 s respectively

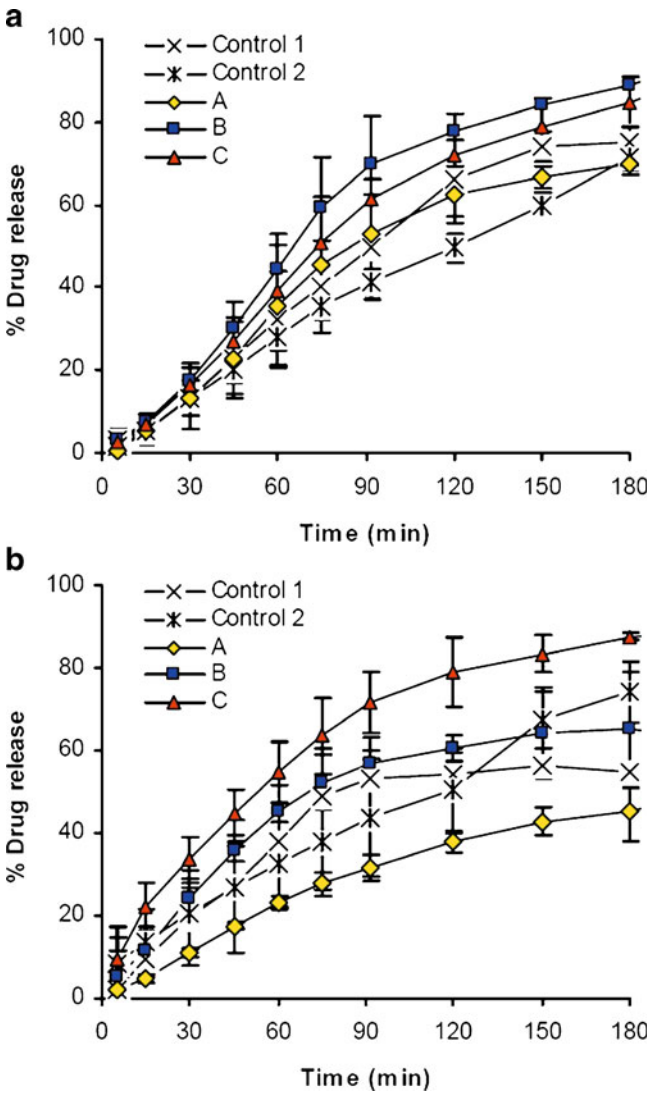

Fig. 6. Drug release profiles of carbenoxolone sodium from pectin-based bioadhesive discs in simulated saliva fluid; **a** CU201 and **b** CU701 (n=3)

have an effect on a faster drug release of CU201 discs. The addition of lactose resulted in a slower drug release. The formulations containing sweetening agent showed varying release patterns of CBX. In general, the higher drug release from the pectin discs containing the sweetening agent, as compared to drug release from 'control 2', may be attributed to dissolution of xylitol (or sucrose or glucose) molecules, which are the component of the discs, creating pores and thus facilitating the solvent front penetration. A high soluble solid concentration creates increased porosity on dissolution, resulting in an increase in release rate. Indeed, high soluble solid concentrations lead to an initially faster linear drug release. However, at this level, the disc is completely wet, and the swelling of polymer occurs. This indicates that release is controlled by diffusion of the drug through the swollen polymer and consequently by erosion of the swollen polymer. Hence, diffusion in the matrix disc appears to be an important factor in controlling the drug release rate of pectin-based buccal discs (29). The exception is for low-DE pectin discs containing xylitol of which the drug release was slower than other formulations. The drug could not be completely released after 3 h of experiment even when the discs were completely dissolved or eroded. It is possible that the interaction between CBX and excipients resulted in the incomplete drug release.

CONCLUSION

The water uptake and erosion of pectin disc increased progressively with the swelling time. The bioadhesion of pectin discs decreased when either of the discs was hydrated or the buccal tissue was wet with a small volume of SSF, indicating that the hydration of pectin disc affected the mucoadhesive properties. Water movement and buccal tissue dehydration play an important role in the bioadhesion of dried pectin disc against buccal tissue. The CBX-loaded pectin discs for aphthous ulcers in oral cavity were prepared by direct compression method. The results demonstrated that pectin buccal disc prepared from high-DE pectin showed a weaker and more friable characteristic than those of low-DE pectin. Increasing the amount of lactose in the formulations affected the hardness and friability of the discs, especially for those using high-DE pectin. Decreasing the amount of pectin produced discs with high dissolution rate and low bioadhesive performance. Addition of sweetener in formulation influenced the hardness, friability, bioadhesive properties, and drug release from the discs. In conclusion, pectin is a potential bioadhesive polymer for buccal bioadhesive drug delivery system.

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