

HPMC Based Mucoadhesive for Delivery of Triamcinolone Acetonide: Mucoadhesion and Drug Release Properties, An *In Vitro* Study

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Abstract

Topical corticosteroid is the first-line drug for treating immune-mediated oral lesions, 0.1 % being the most effective concentration. However, conventional topical Triamcinolone acetonide (TA) applications are poorly retained on the oral mucosa. Hydroxypropyl methylcellulose (HPMC) polymer patches are used as buccal mucosa drug delivery systems, as they enhance a drug's ability to adhere to the oral mucosa and reduce the frequency and amount of drug application.

The objective of this study was to prepare a new HPMC-based buccal muco-adhesive polymer patch for the delivery of 0.1 % TA. The solubility, water absorption, muco-adhesion and *in vitro* drug release study using high-performance liquid chromatography (HPLC) were compared with a commercial product.

The results revealed that the 3 % and 2 % HPMC patches had significantly lower dissolution rates, a favorable property, compared with that of the commercial product ($p < 0.05$). The 3 % HPMC group demonstrated the highest dissolution time. Every concentration of the newly developed muco-adhesive polymer patches had higher water absorption than that of the commercial patches at 1 and 5 min. In addition, the 3 % and 2 % HPMC patches demonstrated significantly higher water absorption compared with the commercial patches at 10 and 30 min. There was no significant difference in muco-adhesion between the developed patches with commercial product. All HPMC groups did not show significantly higher drug release compared with the commercial product group at every time point. 3 % HPMC group had the highest drug release. The 3 % HPMC group had significantly higher drug release than 1 % HPMC at 2, 4 and 6 h.

We demonstrated the potential of a buccal muco-adhesive polymer patch as an alternative treatment for oral ulcerations. The buccal mucosa patches had a higher dissolution time compared with the commercial product. The 3 % HPMC had lower dissolving and higher drug release at 2 to 10 h. The newly developed muco-adhesive polymer patches had improved properties pertaining to drug application. Further study is needed to improve some of the properties of the oral patches and to implement a clinical study.

Keywords: Muco-adhesive, Hydroxypropyl methylcellulose (HPMC), Triamcinolone acetonide, Muco-adhesion, Buccal patch.

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Introduction

During the past, several years, investigations have resulted in advances in pharmaceutical technology concerning drug formulations and innovative routes of administration. Recurrent Aphthous Ulcers (RAUs) and Oral Lichen Planus (OLP) are common painful mucosal conditions affecting the oral cavity.¹ There is no specific diagnostic test for RAUs, thus, diagnosis is mainly based on patient history and clinical manifestations. The underlying etiology of RAU remains unclear, and no curative treatment is available.² OLP results from a chronic inflammatory cell-mediated immunological dysregulation, and likely has a multifactorial origin or non-specific etiology.³ OLP lesions in reticular form are often asymptomatic, however, the atrophic, erosive, and ulcerative forms of OLP can cause a burning sensation or severe pain.³ The diagnosis of OLP is based on the histopathological results of biopsies.

Clinicians frequently use corticosteroids for the treatment of RAU and OLP. Triamcinolone acetonide (TA) is the first-line drug for treating RAU, and can be administered in the form of orabase or mouthwash with concentrations ranging from 0.05–0.5 %, applied 3-5 times per day.² It is particularly indicated for patients with small lesions, and one study reported that 0.1 % TA was the most effective concentration.² Although these forms provide high drug levels in the oral cavity, they can be easily displaced from the applied region due to the washing effect of saliva, swallowing, and tongue movements. These effects decrease therapeutic drug levels.⁴⁻⁷ Topical applications also have limitations, including low retention on the oral mucosa.

Muco-adhesive polymers have been extensively used in buccal mucosa drug delivery systems, as they enhance a drug's ability to adhere onto the oral mucosa.⁸ The drug will contact the mucosal membrane, be easily dispersed throughout the mucosa, and will have high patient compliance because the polymers are non-irritating.⁹ The polymers that have been investigated are polyacrylates, ethylene vinyl alcohol, polyethylene oxide, poly alcohol, poly (N-acryloylpyrrolidine), polyoxyethylenes, self-cross-linked gelatin, sodium alginate, natural gums, and cellulose ethers such as methylcellulose, hydroxypropylcellulose, hydroxypropyl methylcellulose (HPMC), and sodium carboxymethylcellulose.^{10,11}

Muco-adhesive HPMC or hypromellose is non-toxic and used in a wide variety of pharmaceutical and food preparations. HPMC is a cellulose ether and is one of the most common hydrophilic carriers used in controlled oral drug delivery systems, due to its ability to swell when contacted by water or fluid.¹²⁻¹⁷ HPMC offers a wide range of properties that would enhance adhesion to the mucosa, which in turn increases the contact time of the drug with the oral mucosa.¹⁸ This polymer is produced by the synthetic modification of naturally occurring polymer cellulose and is safe for human use. The uses of HPMC as a thickening agent and a bio-adhesive are well documented.^{18,19} To improve HPMC's properties, glycerin has been added to the formula because of its moisturizing and emollient properties.²⁰ A preparation of 2.5 % HPMC grade K100M has been reported as the most appropriate formulation for buccal

mucosa application, because it has suitable mechanical properties, and exhibits high cohesion and bio-adhesion.¹³ Buccal muco-adhesive polymer patches prepared using 1 % HPMC have also been reported as the best formulation. This product showed a 539.44 N/m² muco-adhesive stress and water absorption of 333.33 % of its weight after 10 minutes. The average dissolution time for these patches was 3 hours 24 min. A study evaluating a buccal healing film containing TA found that the optimum composition was 2 % methycellulose, 0.1 % glycerin and 3 % HPMC. In 2015, an oral paste formulation of triamcinolone acetonide containing 60 % plastibase, 3.3 % pectin, 6.6 % gelatin and 30 % carboxymethylcellulose showed similar characteristics compared to a reference formulation (Adcortyl[®]; Bristol-Myers Squibb Co. Ltd., New York, USA) for the treatment of recurrent aphthous stomatitis.²¹

The objective of the present study was to prepare an HPMC-based muco-adhesive patch for delivering TA that possessed appropriate dissolution time, water absorption, muco-adhesion and drug release comparable with commercial patches.

Materials and Methods

Materials

Test materials were different concentrations of hydroxypropyl methylcellulose (HPMC; Methocel F4M, Namsiang Group Co.Ltd., Thailand) with 0.025 mg Triamcinolone acetonide (S.Tong Chemicals Co., Ltd., Thailand) and glycerin (0.1 %) (99.5 % USP/BP, Siam Absolute Chemicals Co.Ltd., Thailand). HPMC commercial patches (Traful Direct, Daiichi Sankyo Healthcare Co.Ltd., Japan) were used as positive controls.

Buccal patch preparation and drug loading

HPMC was dissolved in 60 ml of distilled water at a concentration of 1, 2, or 3 % (mass/volume). Glycerin (0.1 %) was added to the preparations in a beaker. All of the solutions were poured into clean, dry glass petri

dishes and the resulting clear viscous solutions left at room temperature until all air bubbles disappeared. The resultant films were dried in an oven at 55°C for 48 h, loaded with 0.1 % TA dissolved in a distilled water and ethanol (65:35) solution, soaked in the TA solution and dried for 1 d each at -20°C, 4°C, and 25°C. Finally, the films were left at room temperature for 24-48 h²² to allow the residual solvent to evaporate and cut into 9-mm diameter patches.

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Buccal tissue preparation

Buccal tissue from 3-4-year-old pigs was obtained from a local slaughterhouse. Each piece of tissue was washed with deionized water to remove undigested food from the surface. Sixty specimens, thickness 3–5-mm, were prepared and placed in a 0.9 % NaCl solution at 8°C and used within 6 hours.

Artificial saliva preparation

Simulated Saliva Fluid (SSF, pH 7) was used as a substitute for human saliva.²³

Dissolution assay

Each buccal patch (n=5 for each HPMC concentration) was soaked in a beaker containing 20 ml SSF at the room temperature. Each beaker, containing a magnetic stirrer, was placed on a stirring machine and the stirrer rotated at 90 rpm using an environment shaker-incubator. The solutions were collected after

the patches had completely dissolved, and the time required for dissolution was recorded.

Water absorption assay

The porcine buccal tissues were soaked in SSF at pH 7 at 37°C for 60 min, then dried with filter paper. Five buccal patches for each concentration of HPMC were used and their weights recorded. The buccal patches were placed on the porcine buccal tissues and the patch weights recorded at 1, 5, 10, and 30 min using a 3 decimal place digital balance (Sartorius, SPC Calibration Center, Thailand). The weight differences were calculated using equation 1.

$$\frac{W_2 - W_1}{W_1} \times 100$$

Where W_1 was the dried patch weight and W_2 was the patch weight after immersion in SSF. This experiment was conducted five times and the results expressed as mean \pm SE.

Muco-adhesive study

The buccal mucosa patches were tested using a texture analyzer machine (TA.XT Plus, Stable Micro Systems, Godalming, Surrey, UK), equipped with a 50-N load cell and a bio-adhesive holder. Each patch was attached to a 10-mm diameter cylindrical probe with double-sided adhesive tape. The patches were equilibrated in SSF at pH 7 and (37 \pm 0.5)°C for 15 min and placed on the platform of the bio-adhesive holder. The probe with the buccal patch attached was moved downward to attach the patch to the tissue with a contact force of 0.2 N. The buccal patch was left in contact with the tissue for 30 s and withdrawn at a speed of 10 mm/s as in a previous study.^{18,24} The maximum force (N) needed to separate the probe from the tissue was directly derived and the data were compared among the different HPMC concentrations and commercial product groups

In vitro drug release validation²⁵

The HPLC assay allowed for detection of TA at a retention time of 5.8 minutes. Linearity of the standard

calibration curves were obtained with triamcinolone acetonide reference standard solutions. Each solution was injected three times in the chromatographic system. The linearity was estimated by linear regression analysis by the least square regression method. The correlation coefficient was calculated (Equation 2).

$$11y = (8 \times 10^{-9})x - 0.0042 \quad R^2 = 0.9989$$

Where y = concentration of drug releasing

x = analyzed amount of drug releasing from HPLC

In vitro drug release study using HPLC

One patch was soak into a centrifuge tube of SSF. All centrifuge tube were shook by shaker in room temperature. Then the drug release solution 500 μ l each tube were got off from tube at 2, 4, 6, 8 and up to 10 hours. 500 μ l of the 2 ml sample volume were drawn and replaced with 500 μ l of SSF every time an analysis was conducted, 0.5/2 of sample were removed each time an analysis was conducted. To compensate for the diluting effect, the drug release value for each sample was adjusted according to the modified relationship (equation 3).²⁶

$$A_{adj}(h) = A(h) + 0.5/2x \sum_{n=0}^{n=h-2} A$$

Where $A_{adj}(h)$ = adjusted amount of drug releasing at hour

$A(h)$ = analyzed amount of drug releasing at hour

All samples were analyzed by chromatographic system from Shimadzu products (Shimadzu Corporation, Japan) consisted of pump (model LC-10ADvp), autosampler (model SIL-10Avp) and UV absorbance detector (model SPD-10Avp). The separation was performed by a Inertsil ODS-3, 5 μ m, 250 x 4.6 mm ID (GL Sciences, Japan) analytical column. The mobile phase was methanol-water-phosphoric acid (75/25/0.5, v/v). Mobile phase degassed by aspiration for 5 min prior to use. The flow-rate

was 1.0 ml/min and the temperature was ambient. The eluate was monitored by UV absorbance at 252 nm.²² Each in vitro study were performed in five times.

Statistical analysis

The values were analyzed with Kruskal-Wallis H test for all sample group. Then, pairwise comparisons were performed using Mann-Whitney test. The level of significance was 0.05 for all statistical analyses.

Results and Discussion

Dissolution time

The mean dissolution times of the patches

prepared using different HPMC concentrations and a commercial product are illustrated in Figure 1. There was a statistically significant difference between dissolution time of HPMC sample ($H(2)=16.71, p=001$), with a mean rank of 18 for 3 %, 13 for 2 %, 7 for commercial product and 4 for 1 % HPMC.

It was found that the 3 % HPMC group demonstrated the highest dissolution time of (7.11 ± 0.68) h. The 2 % HPMC (5.06 ± 0.39) h, commercial product (3.81 ± 0.45) h, and 1 % HPMC (2.92 ± 0.69) h groups displayed decreasing dissolution times compared with the 3 % HPMC group.

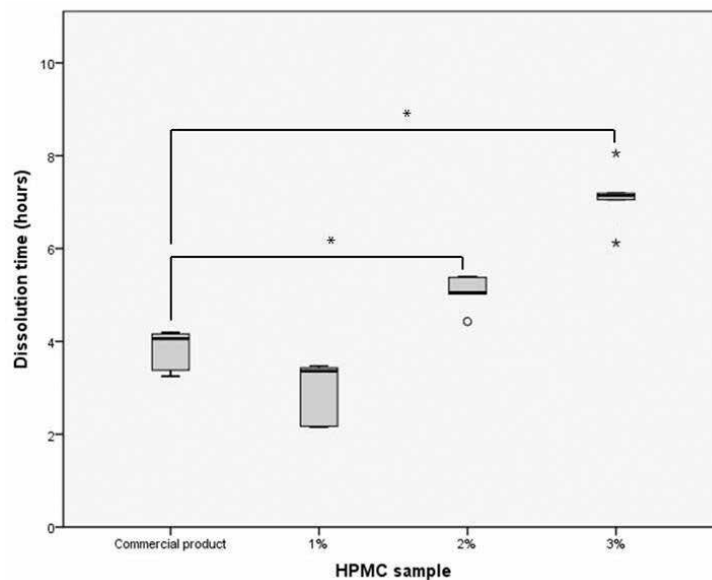


Figure 1 Dissolution times of the different HPMC sample and commercial product groups.

* Indicates a significant difference from commercial product ($p<0.05$).

The results revealed that the 3 % and 2 % HPMC patches had significantly lower dissolution rates, a favorable property, compared with that of the commercial product ($p<0.05$). These HPMC patches could thus remain in the oral cavity for a longer time. Our results support a previous finding that increasing HPMC concentration significantly increased dissolution time ($p<0.05$). However, human saliva contains digestive enzymes that SSF does not, indicating that future in situ

studies are needed to determine the actual dissolution rate of the newly developed muco-adhesive polymer patches in the oral cavity.

Water absorption

The water absorption results are shown in Figure 2. Every concentration of the newly developed muco-adhesive polymer patches had higher water absorption than that of the commercial patches at 1

minute. In addition, the 2 % and 3 % HPMC patches demonstrated significantly higher water absorption compared with the commercial patches at 10 and 30 min. The commercial product had the lowest water absorption at each time point, which would result in minimal changes in the concentration of a loaded drug.

Although we found no clear relationship between HPMC concentration and water absorption, a prior study reported that HPMC percentage had an inverse relationship with water absorption. Because increasing concentration polymer decreases polymer chain space, so it decreases water penetration.

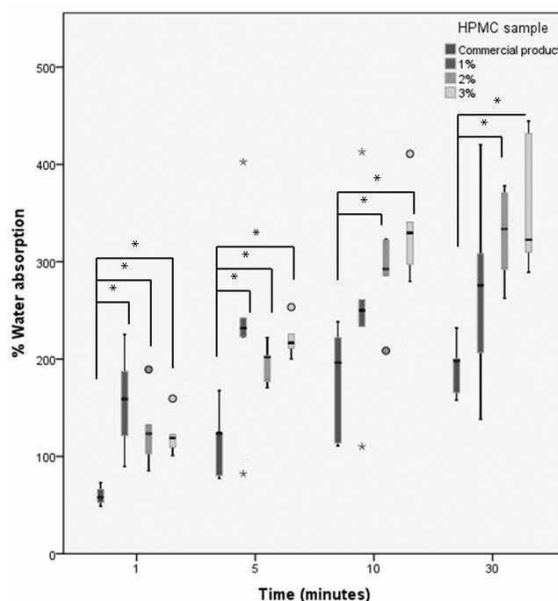


Figure 2 Water absorption of patches with different HPMC concentrations at different time point.
* indicates a significant difference compared with control ($p < 0.05$).

Although the 3 % HPMC patches had the longest dissolution time, they also demonstrated high water absorption. The patch dissolution rate indicates the length of time that the patch will remain in the oral cavity, while water absorption plays an important role in muco-adhesion. When either excess hydration of the patches occurs or the buccal tissue is wet, the muco-adhesiveness will be less.²⁴ We observed almost immediate swelling of the patches during the absorption test. The absorption assay as a percentage of patch weight change at 1, 5, 10, and 30 min after immersion in SSF showed that after 30 min the patches began to detach from the porcine buccal tissue. A previous study indicated that molecular weight plays a more important role in water absorption than does the hydrophilicity of a polymer.²⁴ Low-molecular-weight polymers can penetrate the

mucosa layer well and the optimum molecular weight is between 10 and 4,000 kDa²⁷ whereas our patches have an average molecular weight of 86 kDa. To obtain suitable water absorption, the molecular weight of the polymer should be adjusted to the optimum range.

Muco-adhesive force

The muco-adhesive force assay was performed using an instrument that measured the maximum detachment force (F_{max}). No significant differences in muco-adhesive force and work of adhesion were found between the different HPMC concentration and the commercial product groups ($p > 0.05$). The muco-adhesiveness of the patches was determined. No significant difference in muco-adhesiveness was found between the groups ($p > 0.05$). However, the 1 % HPMC group had the highest detachment force 0.37 ± 0.30 N. (Fig. 3). This

finding could stem from the flexibility of the polymer chains and their low water absorption. The 2 % HPMC, commercial product, and 3 % HPMC groups demonstrated decreasing muco-adhesive force compared with the 1 % HPMC group. The same trend was found in a prior study, where

the 4 % HPMC group demonstrated the lowest detachment stress per area and the 1 % HPMC group had the highest detachment stress per area. Our observations indicated that there was sufficient adhesion between the patches and the dried porcine buccal mucosa.

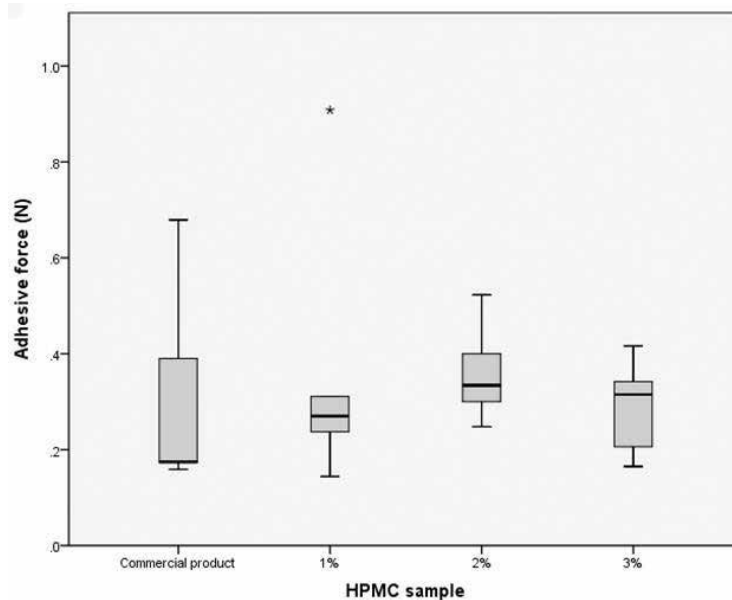


Figure 3 Adhesive force of the patches with different HPMC samples and commercial product.

Adhesion decreased after artificial saliva was included in order to mimic the oral cavity. Although not significantly different, the 1 % and 2 % HPMC groups had a higher detachment stress compared with the commercial product, and all HPMC concentration groups had a lower detachment stress than that of the commercial product. Higher water absorption could alter the drug concentration and a critical degree of hydration of the muco-adhesive polymer affects optimum swelling and thus bio-adhesion.²⁸⁻³⁰ An acceptable polymer should have sufficient water absorption to increase the penetration of the polymer chains into the mucosal network. Penetration enhancers are substrates added to the patch formulation to improve adhesiveness, and can be used alone or in combination to improve the bioavailability of a loaded drug without increasing its toxicity.²⁷ Some enhancers are enzyme inhibitors, such as aprotinin, bestatin, and Puromycin. These inhibitors effectively

reduce proteolytic enzyme activity in the saliva.²⁷

HPLC analysis of *in vitro* drug release

All HPMC concentration groups did not show significantly higher drug release at every time point compared with the commercial product group (Table 5 Appendix, Figure 9). 3 % HPMC group had the highest drug release profiles. 3 % HPMC had significantly higher than the commercial product at 2 hours. The commercial product group had lower drug release than the 3 %, followed by 2 % and 1 % of HPMC, respectively. The 3 % HPMC group had significantly higher drug release than 1 % HPMC at 2, 4 and 6 hours. After 4 hours, we found that the 1 % HPMC patches were completely dissolved, and total drug was released from the patches, and after 8 hours, the 2 % HPMC patches were completely dissolved, resulting in total drug release. The 3 % HPMC and commercial patches required 10 hours or more to completely dissolve. From this results, we did not find

the same as study of dissolving property because analysis of *in vitro* drug release study did not use the stirring machine.

We found that dissolution did not significantly affect drug release by the commercial product. An acceptable patches had higher and prolong drug releasing,

moreover they could still attach on buccal tissue without dissolving. Our results indicated that TA was still released from the 3 % HPMC patches after 8 to 10 h. From the results, the conventional topical of TA were applied 2-3 times per 24 h, so the 3 % HPMC were an acceptable patches.

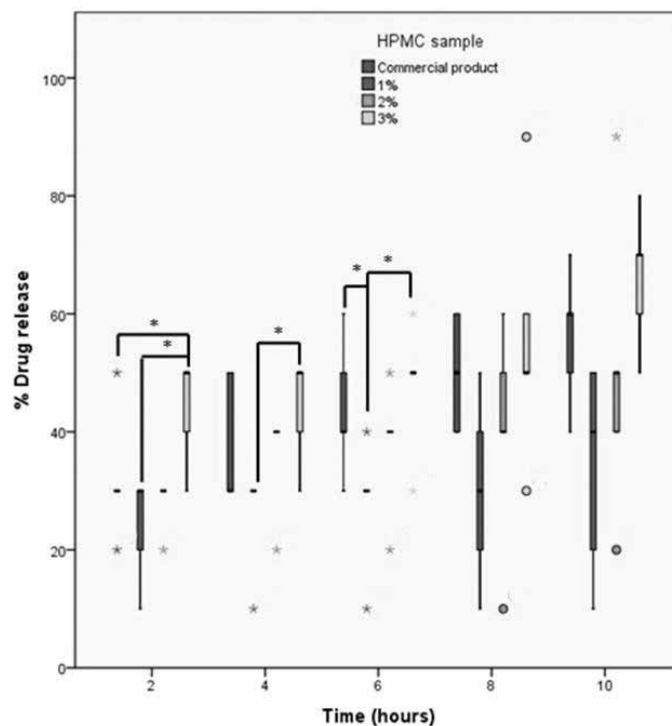


Figure 4 *In vitro* triamcinolone acetonide release profiles of the HPMC patches and commercial product. * indicates a significant difference compared with control ($p < 0.05$) with 10 μ l injection volume.

Thus, to achieve the optimal treatment level, higher drug concentrations should be loaded into the buccal patches. Furthermore, HPMC concentration and the particle size of polymer can greatly influence the patches properties. Increasing the polymer concentration or smaller particle size decrease in drug-release rate. HPMC polymers with smaller particle size have more surface area relative to equivalent weights with larger particle size. Because the greater surface area provides for better polymer-water contact, thus increasing complete polymer hydration and gelation occurs. This leads to the more effective formation of the protective gel barrier of the patches so critical to muco-adhesive drug delivery system. For this reason, increasing the polymer

concentration does not result in decreases in drug-release rate because drug release does not only result from polymer erosion, but also from drug diffusion through the hydrated polymer layers and polymer particle size. If polymer concentration is too low, complete patch formation will be formed that decreased the patch properties. The smaller polymer particle size was found in premium form of identify special product. This effect of slower release for higher polymer levels causes from the longer period of time required to reach the disentanglement in muco-adhesive drug delivery system. An increase in polymer level tends to decrease the sensitivity of the formulation to minor variations.

This study revealed that the newly developed

polymer patches (3 % HPMC) could be an alternative treatment for oral ulcerations because this formulation had a higher amount of drug released from 2–10 hours compared with the commercial product. Furthermore, the 3 % HPMC had higher drug release than 1 % and 2 % HPMC. We could not explain to cut-point definitely for the best concentration because no one was the best all. 3 % HPMC were chosen because they had higher and prolong drug release. The TA were dissolved complete in H₂O and ethanol. but in this study, the patches were tested in SSF. So, drug releasing that were investigated by HPLC, were less than in completely dissolved solution. An increase in polymer level tends to decrease the sensitivity of the formulation to minor variations.³¹ The patches could hold at mucosa more than 8 hours that adequate for oral ulcer treatment compared with conventional topical drug.

However, definitive diagnosis should be obtained before patch used. This a new developed muco-adhesive polymer patches should not be used by the following persons considered to have infectious lesion. Persons considered to have infection who have white plaque, which are easily wipe off by rubbing with gauze that candida infection is suspected. Having yellow pus at the affected area or having systemic symptoms such as fever, malaise or swelling of lymph nodes that viral infection is suspected can be exacerbated by the steroids. A future study should investigate the interaction between HPMC and TA by Fourier Transform Infrared Spectroscopy (FT-IR spectra) or X-ray diffraction. Higher solubility of the drug generally leads to faster release. In addition, selection of HPMC polymer type, molecular weight, and viscosity will improve the newly developed oral patches.³² There are polymer combinations other than HPMC with good texture and muco-adhesiveness such as chitosan, polyacrylic acid, and pectin that can be used as a vehicle for oral patches. A previous study found that the adhesive force of carbopol/poloxamer/HPMC films increased with increased HPMC content in the film, and the release of TA from TA-loaded carbopol/poloxamer/

HPMC polymer films *in vitro* increased with increased drug loading.⁴ A study of gel formulations of polaxamer 407, carbopol 934, chitosan, and HPMC with TA compared with a commercial product containing 0.1 % TA (Kenacort-A Orabase[®]) observed that the bio-adhesiveness of the formulations depended on the bio-adhesive polymer concentration and molecular weight of chitosan. The bio-adhesive performance of the chitosan-based formulations was improved with the inclusion of HPMC. Texture profile analysis (TPA) results indicated that the mechanical properties of the developed gels were improved compared with the commercial product.³³

Conclusions

The buccal muco-adhesive polymer patches fabricated from HPMC for the delivery of 0.1 % TA demonstrated significantly an acceptable *in vitro* dissolution time. The 3 % HPMC group had higher drug release than the commercial product. However, the HPMC patches had higher water absorption than that of the commercial product. There was no significant difference in muco-adhesion between the patches with different HPMC concentrations and the commercial product. Therefore, HPMC could be used to produce a buccal muco-adhesive polymer patch as an alternative treatment for oral ulcers. In laboratory testing these patches are comparable to a commercial patch and could lead to a better response to drug treatment. Further study is needed to improve the water absorption and muco-adhesive properties of the oral patches.

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