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Research Article

Formulation and *In Vitro* Release Kinetics of Mucoadhesive Blend Gels Containing Matrine for Buccal Administration

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Abstract. Enterovirus 71 (EV71) is a pathogenic factor of severe hand, foot, and mouth disease (HFMD). No vaccine or specific treatment is currently available for EV71 infection. Hence, we developed a buccal mucoadhesive gel containing matrine to protect against HFMD. Mucoadhesive gels were prepared by Carbopol 974P and were combined with Carbopol 971P, sodium carboxymethyl cellulose (CMC-Na), or hydroxypropylmethy cellulose (HPMC K100M). The formulations were characterized in terms of tensile testing and continuous flow techniques for mucoadhesion. The rheological studies and in vitro drug release characteristics were also investigated. The results showed that combinations of two polymers significantly improved mucoadhesion, especially Carbopol 974P blended with HPMC. Carbopol 974P to HPMC blend ratios of 1:1 and 2:1 induced better mucoadhesion in the tensile test and continuous flow method, respectively. The most sustained release was obtained at a Carbopol 974P to HPMC ratio of 2.5:1. A predominantly non-Fickian diffusion release mechanism was obtained. The gel containing 2.5% Carbopol 974P combined with 1% HPMC showed good mucoadhesion properties and sustained drug release.

KEYWORDS: Matrine; Buccoadhesive; Polymer blend; Gel; HFMD

INTRODUCTION

Hand, foot, and mouth disease (HFMD) caused by intestinal viruses is a common infectious disease in children younger than 5 years of age. Among these viruses, enterovirus 71 (EV71) is primarily found in severe, progressive forms of HFMD. Serious HFMD outbreaks caused by EV 71 have been frequently reported in the Asia-Pacific region. There is no vaccine to protect against the EV71, nor any specific treatment. Painful erosions commonly occur with 1–2 days in the oral mucosa, which cause difficulty eating and drinking. The symptom of loss of appetite does not require a specific treatment. However, multiple oral ulcers and fasting can result in bacterial infection and dehydration, thus affecting the health of infected children. Current treatments for HFMD oral ulcers in China include sprays or powders made of traditional Chinese herbs, such as Kaihoujian Spray, Kangfuxin Solution, and Qingdai San. The major drawback of these medicines is the lack of retention of the dosage at the site of application due to their easy removal by salivation, ingestion, swallowing, and tongue movement. These factors increase the frequency medicine use. However, this limitation has been resolved by mucoadhesive polymers. Mucoadhesive polymers can be sufficiently wetted by mucus, and they allow for extended retention periods by mutual adsorption and interpenetration. Mucoadhesive drug delivery has been used in a range of forms, such as tablets, films, nanoparticles, and gels (1–3). Advantages of the administration of mucoadhesive hydrogels to the oral cavity include easy dispersion throughout the entire oral cavity, formation of close contact with the mucosal surface, retention on the buccal mucosa for prolonged retention times, and the ability to provide prolonged drug release.

Mucoadhesive capacity is generally insufficient using mono-polymers, and the release of hydrophilic drugs from single polymer gels is often too fast. Blending two polymers is an easy way to optimize mechanical characteristics and to adjust mucoadhesion and release properties. Blending is much less expensive and faster than the development of new polymers and/or new polymerization routes. A blend of two polymers is commonly used in tablets, films, nanoparticles, patches, gels, *etc.* (4–8). Mixing two polymers often results in the formation of interpolymer complexes, which can promote mucoadhesion. Many studies have demonstrated that interpolymer complexes in 1:1 stoichiometry have the highest mucoadhesive force (9,10). Carbopol 974P exhibited superior mucoadhesiveness to Carbopol 971P, CMC-Na, and HPMC in our previous study. Therefore, in this study, Carbopol 974P was separately blended with Carbopol 971P, CMC-Na, and HPMC in 1:1 ratios (*w*/*w*).

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Antiviral chemicals, such as ribavirin aerosol for the treatment of HFMD oral herpes or ulcers, are unsatisfactory for use in infants and children due to their considerable side effects. HFMD is caused mainly by the accumulation of damp-heat and toxicity in the body, which can be treated with heat-clearing and detoxifying herbs (11). Matrine (structure shown in Fig. 1) is the main active component of *Sophora flave* (*Ku Shen*) and is easily soluble both in water and chloroform, methanol, and acetone. Matrine is clinically used for its heat-clearing and detoxifying properties. Matrine exhibits a variety of pharmacological activities, such as anticancer, anti-inflammation, antidiabetic, and antiviral properties. Matrine exerts significant effects against EV71 *in vitro* and *in vivo*, suppressing viral RNA copy numbers in RD cells, thus reducing the mortality of mice from a lethal dose of EV71 and relieving clinical symptoms (12).

The aim of this study was to prepare a new suitable mucoadhesive gel of matrine for the treatment of oral ulcers in children with HFMD. Matrine mucoadhesive gel was intended to be retained on the oral mucosa for a required time period and to provide sustained drug release. The gels were prepared by separately combining Carbopol 974P with Carbopol 971P, CMC-Na and HPMC, and were then compared with Carbopol 974P alone. The influence of the combination of two polymers on the mechanical behavior, mucoadhesive properties and *in vitro* drug release was investigated.

MATERIALS AND METHODS

Materials

Carbopol 974P and Carbopol 971P were obtained from Lubrizol Advanced Materials Ltd. (New Milford, USA). HPMC K100M was acquired from Dow Chemical Ltd. (Michigan, USA). CMC-Na was from Ashland-Aqualon Ltd. (Kentucky, USA). Matrine was obtained from Run Shanxi Days of Biological Technology Ltd. (Si Chuan, China). High-performance liquid chromatography (HPLC)-grade methanol was purchased from Tedia Company. (Ohio, USA). All other chemicals were of analytical grade.

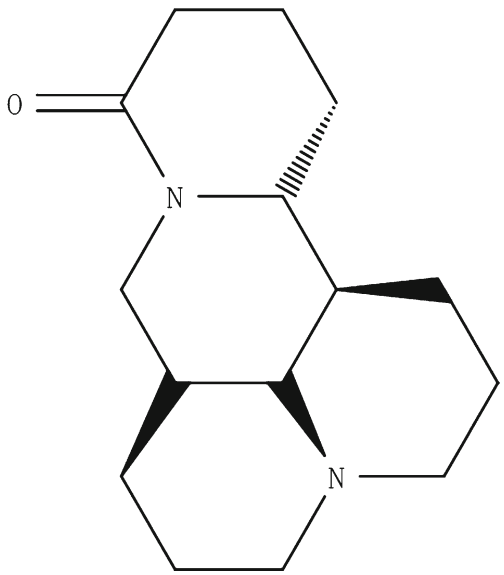

Fig. 1. Structure of matrine

Preparation of Mucoadhesive Gels

Carbopol gels were prepared by adding polymers to water and were left overnight. Carbopol/HPMC blended gels were prepared by first adding HPMC to cooled water (4°C) to obtain a homogeneous solution, and then Carbopol was added to the former solution. Carbopol/CMC-Na blended gels were prepared by adding Carbopol to CMC-Na solution. The Carbopol formulations were neutralized to a pH of 7 using triethanolamine. The formulations of the matrine gels are provided in Table I. Photos of the formulated gels are presented in Fig. 2.

Rheological Study

Rheological studies were performed using an AR-G2 Rheometer (TA Instruments, USA) at 37°C. All measurements were performed at various shear rates ranging from 1 to 60^{-s}. A rheological gram was obtained by plotting the viscosity as a function of shear rate. The relationship between shear stress and shear rate was analyzed with the Ostwald-de Waele model (Power Law) (13,14) (Eq. 1):

$$\tau = K \cdot \gamma^n \quad (1)$$

where τ is the shear stress (Pa·s), γ is the shear rate (s^{-1}), K is the consistency coefficient (Pa·s^n) related to the hydrogel viscosity, and n is the flow index (dimensionless) indicating the type of fluid category. The value of n is equal to 1 for Newtonian fluids and not equal to 1 for non-Newtonian fluids ($n < 1$ for a pseudoplastic system, and $n > 1$ for a dilatant system). Greater deviations of n from 1 indicate stronger non-Newtonian of the sample is. R^2 is the coefficient of the regression in terms of the log-log plots of shear stress *versus* shear rate.

Mucoadhesion Study

Various *in vitro* methods are used to determine mucoadhesion, such as tensile testing and continuous flow techniques, which are well-established methods. Tensile

Table I. Formulations of Buccoadhesive Matrine gels (% *w*/*w*)

Codes	Carbopol 974P	Carbopol 971P	CMC-Na	HPMC K100 M	Matrine	Ethyl paraben
F1	1				2	0.01
F2	1	1			2	0.01
F3	1		1		2	0.01
F4	1			1	2	0.01
F5	1.5				2	0.01
F6	1.5			1	2	0.01
F7	2				2	0.01
F8	2			1	2	0.01
F9	2.5				2	0.01
F10	2.5			1	2	0.01

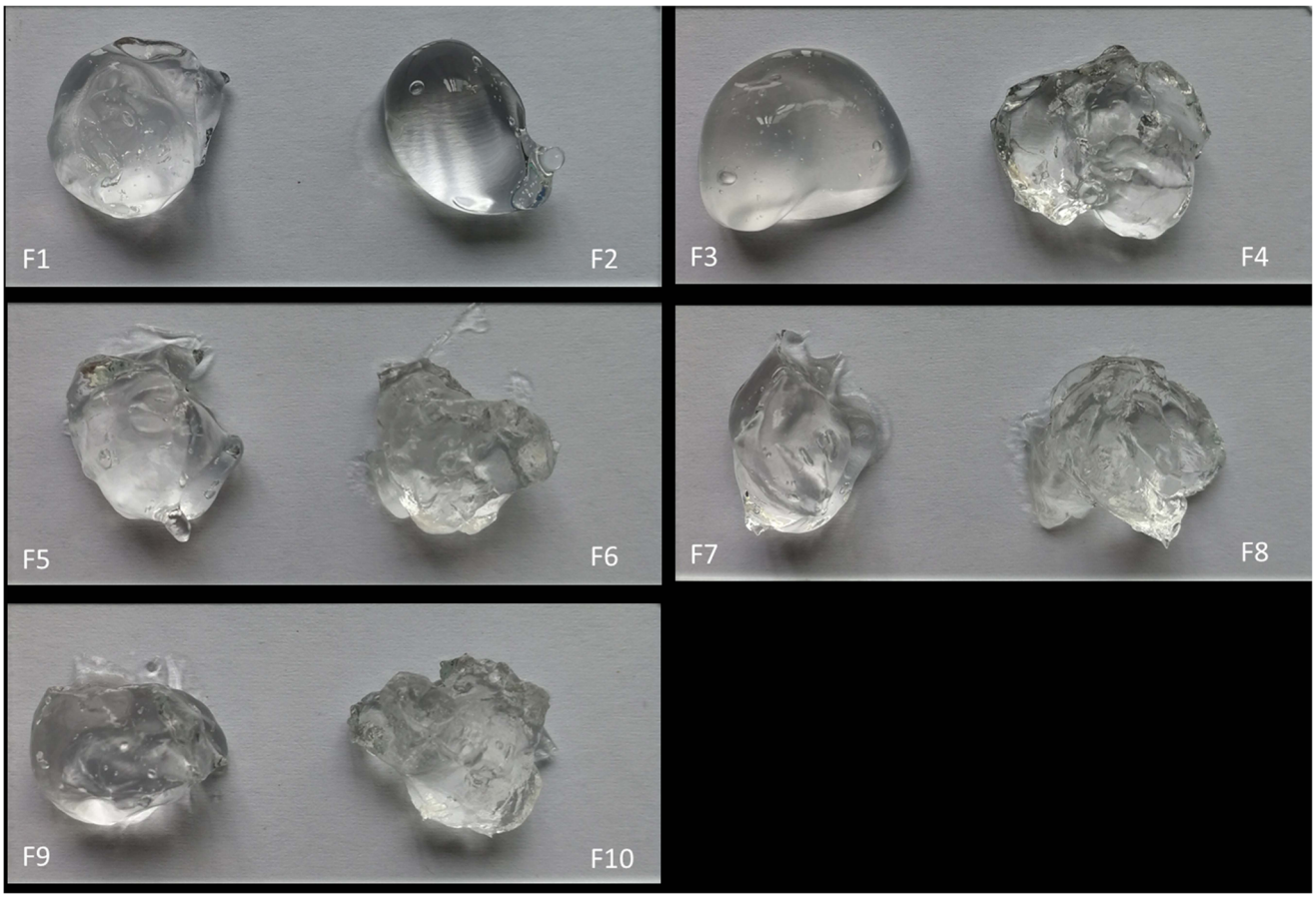

Fig. 2. Photos for the formulations

studies are based on measuring the maximum adhesive strength required to detach the polymer from the mucus or adhesive surface (15–18). The continuous flow technique consists of washing with an appropriate artificial fluid at a constant flow rate and determining residence time of the mucoadhesive polymer (19–21). Different studies with different *in vitro* methods have reported widely conflicting results regarding the ranking of polymer adhesiveness (22,23). In this study, we employed two *in vitro* methods to evaluate the mucoadhesive properties of gels and compared the results of the two methods.

(I) Tensile testing. The maximum detachment force was determined by tensile testing. We employed the modified procedure of Agarwal and Qi (24–26), using a poly(isoprene) plate (surface 6 cm^2) as the adhesion material (Fig. 3). The upper plate was glued to plywood using cyanoacrylate adhesive, and the plywood was hung from an iron stand *via* an iron ring. The lower plate as the formulation holder was attached to the hook with a steel wire. Gel (2 g) was spread on the lower plate and put in contact with the upper plate. Water was added to the infusion bottle with an infusion set until the two plates detached from each other. The water collected in the bottle was weighed (g).

(II) Continuous flow technique. The continuous flow technique of mucoadhesion was performed using an apparatus modified according to Rao K and Buri (Fig. 4) (21,27). The mucosa of the intestine was freshly excised from porcine intestine, washed with saline solution, cut into segments (5 cm in length), and stored at − 80°C. Intestine segments were maintained in phosphate (pH 6.6) prior to use at

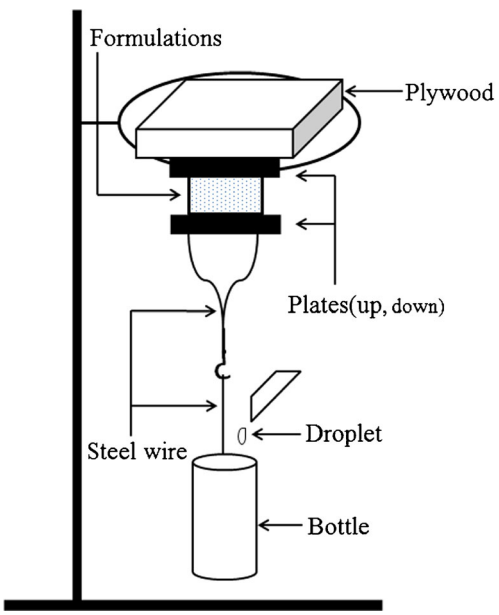

Fig. 3. Modified apparatus for *in vitro* measurement of adhesive force

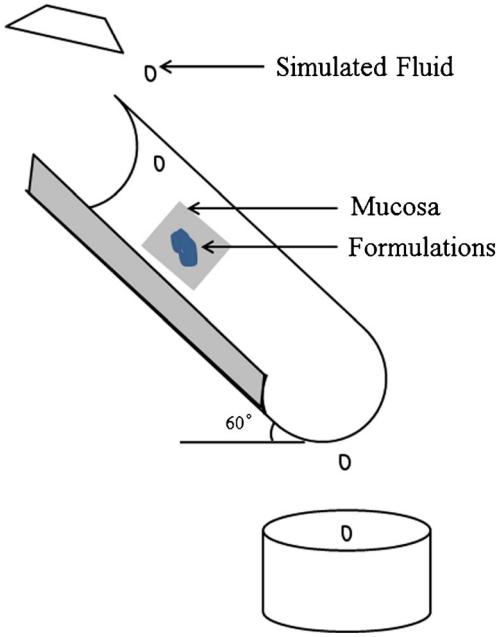

Fig. 4. Modified apparatus for mucoadhesion testing

37°C. The iron sheet was covered by polyethylene film adjusted to 60°, and the segment was fixed on the film. The formulation was spread on the middle of the segment (2 cm^2), and a steady state flow at a rate of 10 ml/min of simulated saliva fluid (2.38 g Na_2HPO_4, 0.19 g KH_2PO_4, and 8.00 g NaCl per liter of distilled water adjusted with phosphoric acid to pH 6.75) was added to the segment until the formulation dropped or was cleared out. The time required was calculated.

High-Performance Liquid Chromatography

Matrine was analyzed by validated high-performance liquid chromatography (HPLC) methods. The HPLC system consisted of a 1260 model pump (Agilent), a DAD detector (Agilent), and a reverse-phase C_{18} column (250 × 4.6 mm, 5 μm; Agilent) at 30°C. The mobile phase was composed of methanol: 0.05 M triethanolamine (60:40, *v/v* %) adjusted to a pH of 7.5 with H_3PO_4 at a flow rate of 1.0 ml/min. The samples were detected at 205 nm. Under these conditions, the peak of matrine appeared at a retention time of 7.4 min. The calibration curve was obtained by linear regression of the peak area *versus* concentration in the range of 10 to 240 ng/ml (r^2 = 0.9999).

Drug Content Evaluation

Gels for *in vitro* diffusion studies were analyzed for matrine content within the range of 100 ± 10. Precisely, 0.25 g gel was dissolved in 1 ml of 10% $CaCl_2$ solution and was transferred to a 50 mL volumetric flask. The volume was adjusted to 50 mL with simulated saliva fluid. The drug-free gels were also treated in the same manner as the blank solutions. All resulting solutions were filtered using 0.22-μm syringe filters before subjecting the solutions to HPLC analysis.

In vitro Matrine Release Studies

Matrine release rates from 0.5 g gels were determined using Franz diffusion cells with an area of 3.14 cm^2 through a cellophane membrane, as reported by Dong L and Qi H (25,28). The cellophane membrane is semipermeable. The gels were easily spread over the cellophane membrane. Simulated saliva fluid was used as the diffusion medium and was maintained in a "sink condition" at 37 ± 0.5°C, with constant stirring at 600 rpm to ensure homogeneity. Samples were directly withdrawn from the receptor compartment at appropriate time intervals and were immediately replaced with the same volume of fresh simulated saliva solution. The amount of matrine in each sample was analyzed by HPLC.

Drug Release Kinetic Studies of gel Formulations

Common models have been proposed to study the drug release kinetics of the oral mucoadhesive gel (29–31). The zero-order model (Eq. 2) describes drug release that is independent of its concentration. The first-order model (Eq. 3) describes drug release that depends on its concentration. The Higuchi model (Eq. 4) describes drug release from an insoluble matrix that is proportional to the square root of time and is based on Fickian diffusion. The Korsmeyer-Peppas model (Eq. 5) describes Fickian and non-Fickian diffusion behavior in terms of the value of the coefficient, applied for the first 60% of drug release. The coefficient of regression (R^2) was calculated from regression analysis using Microsoft Excel statistical functions.

$$\frac{M_t}{M_\infty} = K_0 t \tag{2}$$

$$\ln\left(1-\frac{M_t}{M_\infty}\right) = -K_1 t \tag{3}$$

$$\frac{M_t}{M_\infty} = K_h t^{1/2} \tag{4}$$

$$\ln\frac{M_t}{M_\infty} = \ln K_{kp} + n\ln t \tag{5}$$

The n value (diffusional exponent) in equation Eq. 5 is used to characterize different release mechanisms: n = 0.45 for Fickian diffusion (indicating a diffusion-controlled delivery system); n = 0.89 for super case II or zero-order release kinetics (indicating a swelling-controlled delivery system); and an n value between 0.45 and 0.89 for superposition of both phenomena (anomalous transport or non-Fickian diffusion) (32,33).

Stability Studies

The optimized gel formulations underwent stability studies at 30 ± 2°C and 65 ± 5% relative humidity (RH) for

6 months, and samples were obtained monthly. Drug content, pH, adhesive force, and mucosal retention time were examined.

Statistical Analysis

The means and standard errors for all values were calculated. For group comparisons, a one-way analysis of variance (ANOVA) was employed in the SPSS software, version 13.0.

RESULTS AND DISCUSSION

Rheological Study

The use of rheological tests for the characterization of the hydrogels is important for understanding rheological behavior including the ease of administration and the recovery of formation after application, as well as the interaction between polymers. The rheological flow curves of the formulations are presented in Fig. 5 and the parameters of the Power Law equation are shown in Table II.

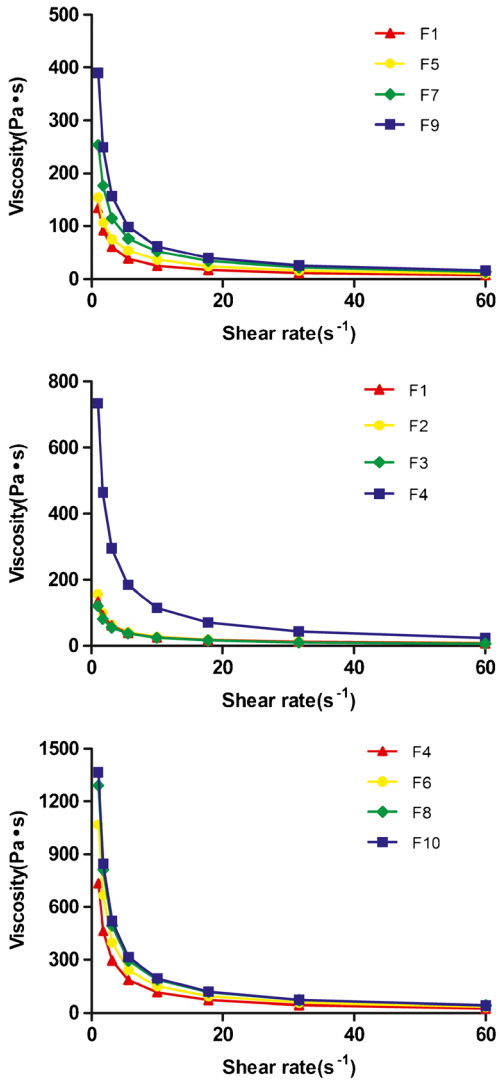

Fig. 5. Rheological studies of formulated gels

Table II. Power Law Model Parameters Obtained for Hydrogels Tested at 37°C

Codes	*n*	*K*	R^2
F1	0.363	2.103	0.9841
F2	0.286	2.166	0.9911
F3	0.285	2.092	0.9980
F4	0.165	2.882	0.9879
F5	0.333	2.206	0.9941
F6	0.157	3.025	0.9947
F7	0.282	2.420	0.9968
F8	0.155	3.115	0.9966
F9	0.217	2.586	0.9974
F10	0.139	3.143	0.9963

Rheological studies of the gel formulations indicated that the gels exhibited pseudo-plastic rheology, as evinced by decreased viscosity with increasing shear rates and the values of flow index n obtained from the Ostwald-de Waele model ($n < 1$). Shear thinning is an important property of gels intended for buccal application, because the gels can easily be spread on the mucosa at high rates of shear.

The viscosity of gels increased with increasing concentrations of Carbopol 974P. Viscosity is defined as the resistance of a material to flow and higher viscosities of a material indicate greater resistance to flow (34). Practically, viscosity is a measurement of the internal friction of a fluid. Carbopol 974P is a highly cross-linked polymer, and the network of cross-linked polymers is much denser than that of linear polymers. Higher concentrations induced stronger polymeric networks and much more internal friction required to be overcome to reach the flow state, which was indicated by the higher values of *K* and lower values of *n*.

The addition of Carbopol 971P and CMC-Na to Carbopol 974P did not change the viscosity of the gels, whereas the blends of Carbopol 974P and HPMC had greater viscosity than Carbopol 974P. In our previous study, the viscosities of 1% CMC and 1% HPMC were much lower than the viscosities of 1% Carbopol 971P or 1% Carbopol 974P. The various changes in the rheological properties of the blended gels resulted from different chain entanglements, conformational changes, and non-covalent and covalent interactions (35). Carbopol 971P and CMC-Na are anionic, and electronic repulsion occurred when these gels were blended with Carbopol 974P, which could cause a reduction in cohesion and entanglement. HPMC is non-ionic and is found to format interpolymer complexes with poly(carboxylic acids), such as poly(acrylic acid) and Carbopol (10). Hydrogen bonding is the main force for interpolymer interactions between non-ionic polymers and poly(carboxylic acids). Increasing hydrogen bonding leads to more internal friction of the gels and, thus, higher viscosities. The values of n were more deviating from 1 when blending other polymers with Carbopol 974P, especially the blends of HPMC and Carbopol974P, indicating that the pseudo-plastic properties strengthened after blending.

It is useful to understand the relationship between the viscosity and mucoadhesive properties of the hydrogels. Concentrations, chain flexibility and entanglement between

molecules are important factors that affect gel viscosity and mucoadhesion. In our previous study, polymers with greater viscosity usually had better mucoadhesive abilities, which was consistent with other reports (2,20,36,37). Carbopol 974P blended with HPMC had a complex structure and intensive entanglement among chains, inducing higher viscosity and greater mucoadhesion.

Adhesion from Tensile Testing

As shown in Fig. 6, the adhesive strength of Carbopol 974P gels significantly increased with increasing concentrations from 1 to 2.5% ($P < 0.01$). Factors affecting the bioadhesion of polymers have been reported, including molecule weight, flexibility, swelling, hydrogen bonding capacity, charge, cross-linking density, and the concentration of polymers (38–40). Blending 1% Carbopol 971P, 1% CMC-Na, or 1% HPMC with 1% Carbopol 974P to prepare gels corresponded to adhesive strengths that could be compared as follows: blends of 1% HPMC >> blends of 1% CMC-Na > blends of 1% Carbopol 971P ≈ 1% Carbopol 974P. The adhesive force of the interpolymer complex consisting of HPMC and Carbopol 974P was the strongest among the three types of blends due to the simultaneous formation of a large number of hydrogen bonds. HPMC is rich in –OR groups, and therefore, hydrogen bonds contribute significantly to the mucoadhesion strength. There was no difference between the adhesive forces of 1% Carbopol 974P and the blends of Carbopol 971P/Carbopol 974P, perhaps because of the similarity of their molecular structures, which resulted in weak interactions between the molecules of the polymers. The results of adhesive strength and rheological studies showed that the adhesive strength was correlated with the viscosity of the gels. The viscosities of blends of Carbopol 971P and blends of CMC-Na were almost the same as that of 1% Carbopol 974P, and their adhesive forces did not markedly change. Higher viscosities of the blends of HPMC formulations had stronger adhesive forces, perhaps because the factors related to viscosity also influenced the adhesive forces, such as flexibility, hydrogen bonding, molecular weight, and cross-linking. Viscosity represents internal forces, whereas adhesive strength is defined as the force required to detach the polymer from the surface. In tensile testing, fractures occurred not only in the platform-surface but also within the platform and within the surface. Intermolecular interactions within the gels, such as viscosity, might contribute to the adhesive strength. However, the relationship between viscosity and mucoadhesive properties remains a topic of debate. For example, according to Philip (4), buccoadhesive gels containing 2% Carbopol 934 showed greater viscosity than combinations of Carbopol 934 and HPMC, whereas blends of HPMC and Carbopol934 were found to have maximum buccoadhesive strength.

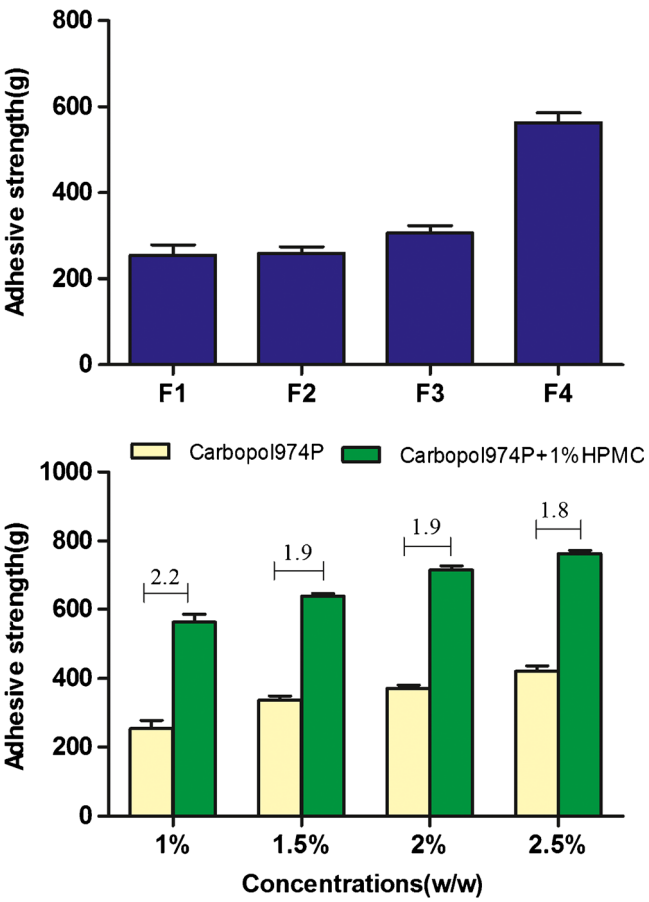

Fig. 6. Effect of formulation content on adhesive force ($n = 4$)

It was found that the adhesive strength of 2.5% Carbopol 974P with 1% HPMC was the strongest of all formulations. Comparing the blends of Carbopol 974P/HPMC with Carbopol 974P, the greatest increase in adhesive force was observed in Carbopol 974P/HPMC 1:1 (*w*/*w*), in which the adhesive forces of the blends were 2.2 times higher than those of pure Carbopol 974P gels. This finding corresponded to the findings of previous studies. Agarmal *et al.* demonstrated that the maximum bioadhesive strength was observed in compacts of Carbopol 974P and HPMC K4M in a ratio of 1:1, followed by ratios of 1:4, 1:2, and 0:1 (24). Beads coated with a chitosan/PVP blend at a 5:5 ratio showed the highest mucoadhesion and bioadhesion compared with single polymers or other ratios (41). *In vivo* examination of films prepared by poly(acrylic acid) (PAA) and methylcellulose (MC) demonstrated that PAA/MC 50/50 (wt %) had the longest retention time on rabbits' corneas (42). These findings were due to hydrogen bonding between the blends through their various hydrogen donor and acceptor groups. Carbopol 974P/HPMC at ratios of 1.5:1, 2:1, and 2.5:1 had similarly increased adhesion strengths compared to pure Carbopol 974P gels, which may be because the hydrogen bonds intensity was not significantly affected by the Carbopol 974P/HPMC ratio in the experimental range. AQ *et al.* also found that the bioadhesion of pellets consisting of different ratios of HPMC/HPC did not significantly differ between any two formulations. This finding was due to the similarity of the chemical structures of HPMC and HPC, resulting in very similar hydrogen bonding intensities for all HPMC/HPC ratios (43).

Adhesion *via* Continuous Flow Technique

The results of continuous flow techniques are shown in Fig. 7. In accordance with tensile studies, increasing the concentrations of polymers could increase the retention time

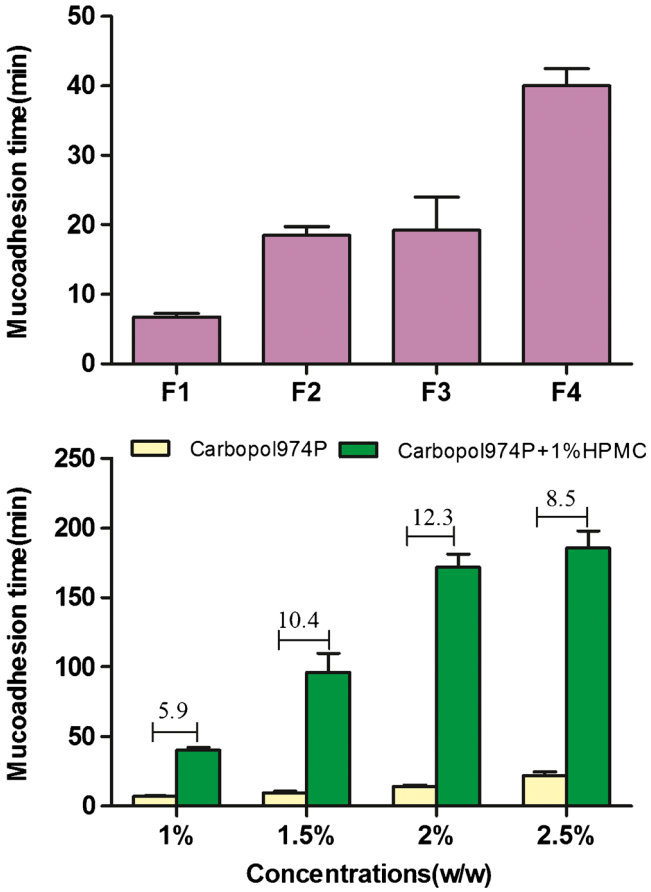

Fig. 7. Effect of formulation content on mucosal retention time (n = 4)

of gels on the mucosal surface. Blending Carbopol 971P, HPMC or CMC-Na with Carbopol 974P significantly prolonged the retention time ($P < 0.01$), and blends of HPMC with Carbopol 974P also exhibited better mucoadhesion. The adhesive strengths were ranked as follows: blend of 1% HPMC >> blend of 1% CMC-Na ≈ blend of 1% Carbopol 971P > 1% Carbopol 974P, which differed from tensile tests and rheological studies.

There are significant amounts of water under continuous flow conditions. Water competes against the hydroxyl groups of sugars present in mucosa surfaces for the formation of hydrogen bonds with the carboxylic groups of the polymers (44). This finding indicates that the mucoadhesive effect of hydrogen bonding decreases for poly(acrylic acid) and cellulose derivatives, affecting their adsorption onto mucus membranes (22). Under these conditions, water enters the polymer network, which results in swelling and, consequently, an entanglement of polymer chains into the mucus (45). Thus, swelling becomes important for functional groups, such as –OH the mucin surface and interpenetrate with the chains of the mucin. On the other hand, the surface of the hydrogels was initially viscous and dense, allowing the strong adherence. Later, when the swelling was too great, the polymer on the surface tended to dissolve or be washed away by the fluid. As a result, the retention time was based on the balance between the dissolution of the polymers on the surface of the gel and the swelling of the polymer molecules in the inner core (43). CMC-Na has a high water uptake, and water penetrates the polymer net and promotes the relaxation of Carbopol 974P chains, then becoming available to create close contact with the mucous layer. Carbopol 974P is highly cross-linked, whereas Carbopol 971P is less cross-linked. The cross-link density is inversely proportional to the degree of swelling. As a result, the mucoadhesive retention times of blends of Carbopol 974P with CMC-Na or Carbopol 971P were much longer than those of 1 and 2% Carbopol974P only. However, in our previous study, without blending, the mucoadhesive times of 1% CMC-Na and 1% Carbopol971P were much shorter than that of 1% Carbopol 974P. This finding may be attributed to slippery mucilage in CMC-Na or Carbopol 971P only caused by too much water present and too greater the degree of swelling, causing CMC-Na or Carbopol 971P to be rapidly removed by the fluid. Once combined with Carbopol 974P, the high density of cross-linking decreased the dissolution rate of polymer chains in the aqueous environment (46) and maintained the swelling gel structure, thus providing high flexibility, close entanglement and higher mucoadhesion. Thus, cross-linking is another important factor of mucoadhesion in continuous flow techniques because of its resistant to dissolution. The increased mucoadhesion extent of Carbopol 974P/HPMC in the continuous flow technique was greater than that obtained in the tensile test, and the average increased mucoadhesion of Carbopol 974P/HPMC in the continuous flow test was 4.75 times higher than that found in the tensile test. This finding might be due to the aqueous condition of the continuous flow experiment. HPMC hydrophilic characteristics favor swelling and allow water to penetrate easily into the gel matrix, which is responsible for gradual chain entanglement and strong contact with the mucin chains (47), thus improving the mucoadhesion capacity of Carbopol alone. In addition, the formation of insoluble interpolymer complexes of Carbopol 974P and HPMC improved the retention time under aqueous conditions.

In correlation with the tensile testing, the most effective mucoadhesion was observed with blends of 2.5% Carbopol 974P and 1% HPMC. However, the largest increase was found for HPMC/Carbopol 974P 1:2 (w/w), which was different from that found for the tensile testing. Some studies have also indicated that the maximum mucoadhesion of polymer blends does not always correspond to a 1:1 ratio. Films based on blends of poly(acrylic acid) (PAA, molecule weight 450,000) and (hydroxypropyl) cellulose (HPC, molecule weight 100,000) showed that HPC content in the blend of 30–35 mol% lowered the mucoadhesive property, whereas the addition of HPC up to 70 mol% improved the mucoadhesive properties (48); 70 mol% of HPC was almost the same as PAA/HPC 2:1 (weight ratio), which was consistent with the results obtained in the present study. Different results were even found between blends of Carbopol and HPMC. A mucoadhesive layer of bi-layered buccal tablets was prepared by a simple blend of Carbopol940 and HPMC (29,000–43,000 mPa in water solution 2% (w/v)), and *in vitro* mucoadhesion forces of Carbopol940:HPMC blends were ranked in the order of 3:1 > 1:3 > 1:1, which were higher than Carbopol or HPMC alone (47). The maximum tensile force of buccoadhesive tablets prepared by mixing Carbopol 934 with HPMC (viscosity grade 500 mPa) was examined,

which increased for Carbopol 934/HPMC ratios of 1:1, 3.6:1, and 6:1 and corresponded to greater adhesion strength (49). Therefore, the different testing methods can indicate different superiorities of polymer blends ratios, and the types of Carbopol and viscosities of HPMC can also influence the proper mucoadhesive ratios of Carbopol and HPMC blends. In the present study, the viscosity of HPMC K100 M was 112,936 mPa in 2% solution; thus, the ratio might smaller than that reported in above literatures.

Drug Content Uniformity

The drug content of the gel formulations ranged from 98.20 to 106.39% and was within the desired range of 90 to 110%.

In vitro Drug Release Studies

During the first and second hours of the release profiles (Fig. 8 and Table II), matrine released from Carbopol 974P-only gels (F1, F5, F7, F9) decreased with increasing polymer concentrations, and the amount of drug released from F9 was less than F1 ($P < 0.05$). It was possible that, at the higher concentrations, the drug was trapped in smaller polymers, and the density of the polymer chain structure was increased, which increased the diffusion resistance and the substance's moving area, thus decreasing the release rate (2). Blending 1% CMC-Na (F3) or 1% HPMC (F4) with 1% Carbopol 974P did not significantly affect matrine release, while the cumulative release from blends of Carbopol 971P/974P (F2) was less than that of F1 after 1 or 2 h ($P < 0.01$). At the eighth hour, matrine released from the formulations showed no differences. Among all the characteristics of the drug and polymer in drug release, such as drug solubility and changes in glassy core, gel layer thickness may play the most important role (50). CMC-Na and HPMC are long-chain linear polymers, forming softer gels that are more susceptible to erosion. Carbopol gels are cross-linked polymers with limited solubility in water; thus, the erosion of the gel layer is much slower. As a result, drug released from CMC-Na/Carbopol and HPLC/Carbopol gels depends on the characteristics of Carbopol. Carbopol at a pH > 4.5 swells and fully hydrates, but it does not dissolve. A gelatinous layer formed by Carbopol consisted of discrete microgels made up of many polymer particles, in which the drug was dispersed (51). Carbopol 974P showed non-homogeneous viscosity with water channels present in the gel structure, and Carbopol 971P with flexible microparticles formed a more homogeneous hydrophilic matrix. Matrine solubility in water was approximately 2 g/ml (52). For highly water-soluble drugs, the diffusion through water-filled interstitial channels between microgels of Carbopol 974P yielded a faster release rate, while a slower release rate was obtained from the homogeneous structure of Carbopol 971P.

As shown in Fig. 8 and Table III, increasing the content of Carbopol 974P in the polymer blends decreased the release rate of matrine, in accordance with Carbopol 974P alone. When the blend ratios of Carbopol 974P to HPMC increased to 2:1 and 2.5:1, the cumulative release after 1 h was significantly decreased compared to Carbopol 974P

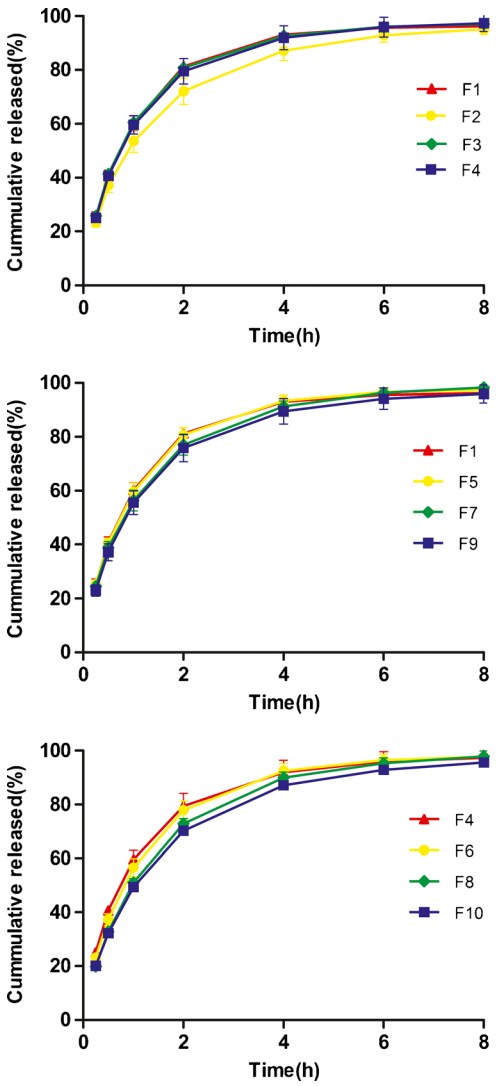

Fig. 8. Drug release profiles for matrine formulations ($n = 4$)

Table III. Cumulative Release of Drug at Certain Times

Codes	Cumulative release after 1 h (%)	Cumulative release after 2 h (%)	Cumulative release after 8 h (%)
F1	60.25 ± 2.73	81.29 ± 1.15	96.21 ± 1.50
F2	53.59 ± 4.14[a]	72.09 ± 4.91[a]	95.13 ± 1.93
F3	60.53 ± 0.92	80.74 ± 0.97	97.07 ± 1.28
F4	59.64 ± 3.39	79.47 ± 4.78	97.34 ± 3.07
F5	59.60 ± 3.24	80.78 ± 2.80	97.33 ± 1.42
F6	56.59 ± 3.27	77.86 ± 3.47	97.78 ± 2.13
F7	56.36 ± 3.89	77.02 ± 3.77	98.30 ± 1.32
F8	51.02 ± 1.49[a,c]	72.78 ± 2.02[a]	97.91 ± 2.10
F9	55.54 ± 4.37[b]	75.87 ± 5.10[b]	95.98 ± 3.86
F10	49.37 ± 1.26[a,d]	70.18 ± 1.58[a,d]	95.63 ± 1.28

[a] The comparison with F1 at $P < 0.01$
[b] The comparison with F1 at $P < 0.05$
[c] The comparison between F7 and F8 at $P < 0.05$
[d] The comparison between F9 and F10 at $P < 0.05$

Table IV. Drug Release Kinetics of Buccal Mucoadhesive Gels

	Zero Order		First Order		Higuchi		Korsmeyer-Peppas		
Code	R^2	K_0	R^2	K_1	R^2	K_h	R^2	K_{kp}	n
F1	0.7114	0.0809	0.9114	0.4005	0.8563	2.8756	0.9967	0.6112	0.6237
F2	0.7944	0.0849	0.9713	0.3587	0.9176	2.9998	0.9949	0.5452	0.6036
F3	0.7252	0.0813	0.9464	0.4263	0.8668	2.9081	0.9962	0.6146	0.6148
F4	0.7388	0.0828	0.9637	0.4356	0.8771	2.9005	0.9956	0.6064	0.6261
F5	0.7277	0.083	0.9434	0.4472	0.8691	2.8591	0.9968	0.6044	0.6149
F6	0.7548	0.0878	0.9702	0.4711	0.8895	2.7831	0.9985	0.5716	0.6458
F7	0.7741	0.0868	0.9907	0.4883	0.9033	2.8747	0.9966	0.5715	0.6005
F8	0.7962	0.0940	0.9918	0.4676	0.9189	2.7149	0.9987	0.5152	0.6816
F9	0.7632	0.0853	0.9608	0.3861	0.8955	2.8891	0.9971	0.5630	0.6376
F10	0.8077	0.0914	0.9795	0.3787	0.9266	2.8225	0.9991	0.4976	0.6494

alone, especially at a ratio of 2.5:1. However, over the first hour of release, there was no difference between blends of Carbopol 974P/HPMC at ratios of 1:1 or 1.5:1 with Carbopol 974P alone. This result indicated that the ratio of Carbopol 974P/HPMC was inversely proportional to drug diffusion. This behavior could not be attributed to the increased concentration of polymer but was mainly due to the increasing amount of interpolymer complexes and the complicated hydrogel network, making the gel layers thicker and denser. Some studies have demonstrated that different blend ratios have different effects on drug release properties. Polymer complex of PVP (K25 or K90) and Carbopol were mixed at weight ratios of 1:3, 1:2, 1:1, 2:1, and 3:1, and the slowest release rate was obtained at a PVP K25 to Carbopol ratio of 1:1, while the ratio was 3:1 with PVP K90 and Carbopol (53). The authors attributed this finding to the fact that PVP K90 has a higher MW than PVP K25, thus producing higher viscosity. Hydrogels were also prepared by blending gelatin with agar or κ-carrageenan at ratios of 9:1, 7:3, and 5:5, and the slowest drug release was obtained for the ratio of 5:5, which was believed to be due to the interpenetrating polymer network (54). The blend ratio of Carbopol 974P and HPMC of 2.5:1 had the slowest drug release, which might have been due to the high viscosity of HPMC K100 and the more complicated network formed by interpolymer complexes of Carbopol 974P/HPMC. However, over the time, the matrix channels in the hydrogel were filled by the swelled polymers, and the drug dissolved and diffused throughout the matrix; hence, there was no difference among all the formulations.

Kinetics of the Drug Release Mechanism

The release mechanism of the gels was analyzed by the commonly used mathematical equations (Table IV). The highest coefficient regression values (R^2) were obtained for the Korsmeyer-Peppas model. The n values for the Korsmeyer-Peppas model indicated that matrine released from the gels underwent non-Fickian (anomalous) diffusion, and the rate of drug release was due to the combination of drug diffusion and gel swelling. There was no relationship between the concentration of Carbopol 974P and the n value. According to the K_{kp} values, the release rates of blends of Carbopol 971P and Carbopol 974P were slower than those of CMC-Na and HPMC. The water uptake of CMC-Na is higher than HPMC, which could enhance the amount of water entering the gel and could provide greater osmotic pressure, thus increasing the drug release (55). Therefore, F3 exhibited slightly faster release than F4. Incorporating HPMC into Carbopol could increase the n value, thus indicating that swelling and erosion of the polymer are important in drug release. A blend of Carbopol 974P with HPMC at a ratio of 2:1 had the maximum effect of increasing the n value, indicating more insoluble interpolymer complexes to relaxation and swelling. The K_{kp} values of the Korsmeyer-Peppas model decreased with

Table V. Stability Study of Matrine Gels

Month	Drug content (%)	pH	Adhesion force (g)	Adhesion time (min)
0	100.48 ± 2.40	7.03 ± 0.05	752.3 ± 15.3	220.3 ± 16.7
1	103.13 ± 0.87	6.99 ± 0.03	760.7 ± 17.6	224.7 ± 16.6
2	101.16 ± 1.31	6.98 ± 0.05	767.3 ± 12.5	219.7 ± 18.7
3	100.36 ± 0.82	7.00 ± 0.03	775.3 ± 12.1	217.3 ± 12.7
6	101.23 ± 2.60	7.02 ± 0.06	771.0 ± 10.8	235.7 ± 11.6

increasing concentrations of Carbopol 974P, both in formulations of pure Carbopol974P gels and in blends with HPMC. This finding reflected a slight decrease in the drug release rate with increasing Carbopol 974P concentrations, showing a strong correlation with the viscosity of the gels, in accordance with the literature (56). Compared to Carbopol 974P only, the greatest decreased K_{kp} values among the different ratios of blends of Carbopol 974P/HPMC was found for the 2.5:1 blend. Additionally, the 2.5:1 blend showed the most sustained release. Matrine is water-soluble, and therefore, the first-order and Higuchi models better described matrine release than the zero-order model according to R^2.

Stability Studies

The optimized gel was stored at 30°C/65%RH for 6 months. The gels remained clear and transparent, and there were no significant differences in the drug content, pH, adhesive force, or mucosal retention time (Table V). The results suggested that the gel formulation could remain stable for long-term storage.

CONCLUSIONS

A new oral mucoadhesive gel formulation containing matrine for the treatment of HFMD oral herpes or ulcers was successfully prepared. Matrine gels could be easy to spread evenly in the mouth, remain on the oral mucosa for long durations, and provide sustained drug release. Blending Carbopol 974P with HPMC significantly increased the mucoadhesive force and promoted the retention time, due to the formation of interpolymer complexes. Blending Carbopol 974P with Carbopol 971P had the opposite results in the two *in vitro* mucoadhesion tests, and the proper ratio of Carbopol 974P/HPMC was also different between the two tests. In the tensile test, the best ratio was 1:1, while in the continuous flow test, the best ratio was 2:1. This finding might be due to the different conditions of the two tests. In tensile testing, hydrogen bonding and viscosity are important to mucoadhesion, whereas under water-abundant circumstances, swelling and cross-linking played important roles for mucoadhesion. The proper ratio of polymer blends for good mucoadhesion is not only influenced by the testing conditions but also specific characteristics of the polymers, such as viscosity. Matrine released from all the formulations followed non-Fickian (anomalous) diffusion mechanisms; 2.5% Carbopol 974P blended with 1% HPMC was the most appropriate formulation and showed better mucoadhesion, sustained drug release, and good stability. Therefore, matrine buccal mucoadhesive gel could be a promising delivery system for the treatment of oral ulcers from HFMD.

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