ORIGINAL ARTICLE

Development and evaluation of novel-trans-buccoadhesive films of Famotidine

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J. Adv. Pharm. Tech. Res.

ABSTRACT

The present investigation highlights the novel trans-buccoadhesive films of Famotidine, an H2 receptor antagonist used as an anti-ulcerative agent. The buccal films were fabricated by solvent casting technique with different polymer combinations of hydroxypropyl methylcellulose, carbopol-934P and polyvinyl pyrrolidone. Drug–polymer interaction studies by Fourier transform infrared spectroscopy show that there is no significant interaction between drug and polymers. The fabricated films were evaluated for their physicochemical characters like weight, thickness, surface pH, percentage moisture absorption, percentage moisture loss, swelling percentage, folding endurance, water vapor transmission and drug content. Stability study of buccal films was performed in natural human saliva. *Ex vivo* permeation studies were conducted using fresh sheep buccal mucosa and buccoadhesive strength was calculated by modified balance method and showed sufficient strength in all the formulations. Good correlation was observed between the *in vitro* drug release and *in vivo* drug release, with a correlation coefficient of 0.995. Drug diffusion from buccal films showed apparently zero order kinetics and release mechanism was diffusion controlled after considerable swelling.

Key words: Buccal film, buccal mucosa, buccoadhesive strength, Famotidine, zero order

INTRODUCTION

Drugs administered through the buccal route have a rapid onset of action and leads to improved bioavailability of drugs. The buccal route can bypass the first-pass metabolism, contact of the drugs with the gastrointestinal fluids and paves way for easy access to the membrane sites so that the delivery system can be applied, localized and removed easily. Furthermore, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity.[1] The sublingual route is generally employed for the delivery of drugs having high permeability across the mucosa and is used in the treatment of acute disorders, whereas the buccal route is used in the treatment of chronic disorders when a prolonged release of the active substance is required.[2]

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Access this article online

Quick Response Code:

Website: www.japtr.org

DOI: 10.4103/2231-4040.79800

Famotidine is a histamine H2-receptor antagonist. It is widely prescribed in gastric ulcers, duodenal ulcers, Zollinger–Ellison syndrome and gastroesophageal reflux disease. The low bioavailability (40–45%) and short biological half-life (2.5–4.0 hours) of Famotidine following oral administration favors development of a sustained release formulation.[3,4] It was reported that Famotidine undergoes first-pass metabolism resulting in a bioavailability of 50%.[5] The present investigation highlights the development and evaluation of novel trans-buccoadhesive films of Famotidine with the objectives to avoid the first-pass effect, improve the bioavailability, minimize the dose, improve the duration of action and hence produce controlled drug delivery of Famotidine. The method was employed for the development of buccoadhesive film by solvent casting technique using the polymers of hydroxy propyl methylcellulose-K4M (HPMC), carbopol-934P (CP) and polyvinylpyrrolidone-K30 (PVP).

MATERIALS AND METHODS

Famotidine was obtained as a gift from Aurobindo Labs Ltd. (Hyderabad, India); HPMC, CP and PVP were procured from Drugs India (Hyderabad, India); fresh sheep buccal mucosa, for determining buccoadhesive strength and *ex vivo* permeation studies, was procured from a local slaughter house in Rajampet, India. All other chemicals and reagents employed were of analytical grade. The buccoadhesive films were developed by solvent casting technique with the use of "O" shaped ring placed over a glass plate as a substrate.

Drug–Polymer Compatibility Studies by FTIR

Drug–polymer compatibility studies were performed by Fourier transform infrared spectroscopy (FTIR).[6] In order to confirm that the entrapment of drug within the polymeric systems involves only the physical process and no interaction between the drug and polymer, FTIR absorption spectra of pure drug and all the polymers used like HPMC, CP, PVP and the combination of drug and polymers were analyzed to show no significant interaction between drug and polymers. The FTIR spectra are shown in Figures 1 and 2.

Preparation of Buccoadhesive Films of Famotidine

The buccal mucoadhesive films were prepared by solvent casting technique employing "O" shaped ring placed on a glass surface as a substrate by using different polymers of HPMC, CP and PVP.[7,8] The calculated quantities of polymers were dispersed in either water or ethanol. The CP polymeric solution was neutralized using triethanolamine. An accurately weighed 20 mg famotidine was incorporated in polymeric solutions after levigation with 30% w/w propylene glycol which served the purpose of plasticizer as well as penetration enhancer. The solution was mixed occasionally to get a semisolid consistency. Then, the solution was subjected to sonication in a bath sonicator to remove the air bubbles. Then, this was casted on a glass surface employing "O" shaped ring, having a diameter of 4.0 cm, and covered with funnel for controlling the evaporation of solvent and allowed to dry at room temperature overnight. The dried films were separated and the backing membrane

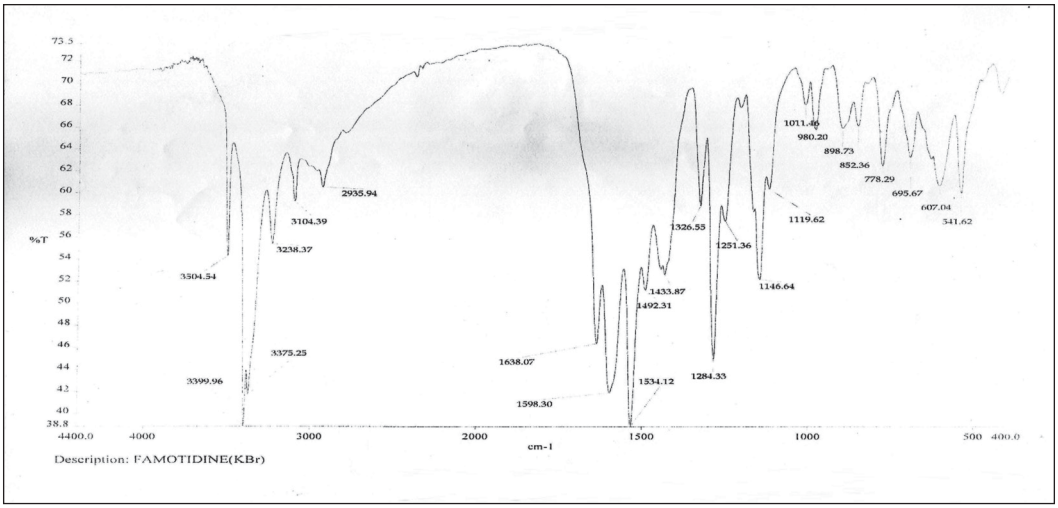

Figure 1: FTIR spectra of famotidine

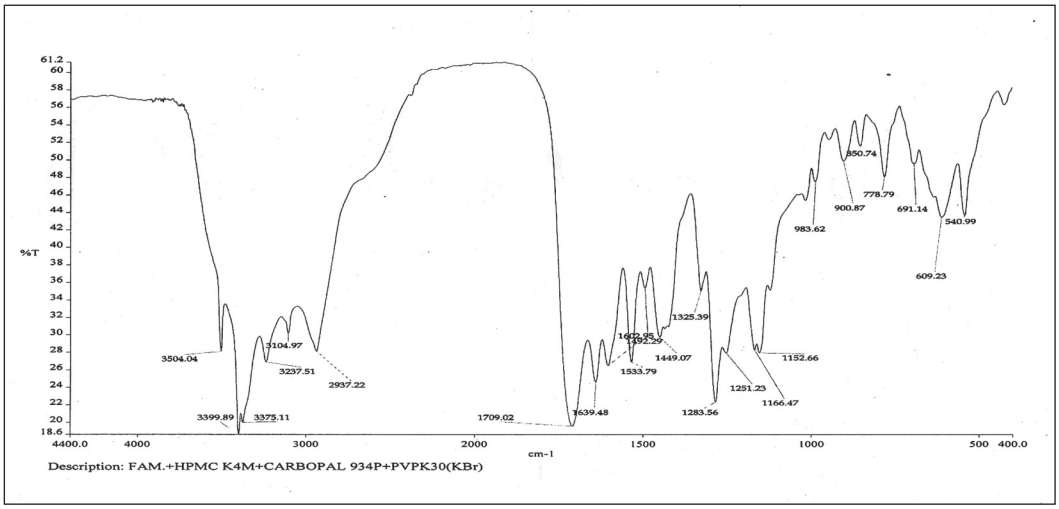

Figure 2: FTIR spectra of famotidine and polymer mixtures

used was aluminum foil. Then, the formulations were stored in desiccators kept at room temperature and 58% relative humidity (RH) to maintain the integrity and elasticity of the films until further use. The polymeric buccoadhesive films were also prepared without the drug. The compositions of formulation of both drug free and famotidine buccal films are given in Table 1.

Weight and thickness of films

Three films of each formulation were taken and weighed individually on a digital balance (ESSAE, Goa, India, DS-852J). The average weight of three films was found out. Similarly, three films of each formulation were taken and the thickness of films was measured using Digital Vernier Caliper (Absolute Digimate) at six different places and the mean value was calculated.

Surface pH

Buccal films were left to swell for 2 hours on the surface of an agar plate prepared by dissolving 2% (w/v) agar in warmed isotonic phosphate buffer (IPB) of pH 6.8 under stirring and then pouring the solution into a Petri dish till it gels at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen film. The mean of two readings was recorded.[9]

Percentage moisture absorption

The percent moisture absorption (PMA) test was carried out to check the physical stability of the buccal films at high humid conditions.[10] In the present study, the moisture absorption capacity of the films was determined as follows. Three 1-cm diameter films were cut out and weighed accurately then the films were placed in a desiccator containing saturated solution of aluminum chloride, keeping the humidity inside the desiccator at 79.5%. After 3 days, the films were removed, weighed and percentage moisture absorption was calculated. Average percentage moisture absorption of three films was found as follows.

$$\text{Percentage moisture absorption} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

Table 1: Composition of buccoadhesive films of Famotidine

Formulation code	Polymers (%)			Solvents (ml)		
	HPMC	CP	PVP	Ethanol (70% v/v)	Distilled water	PG
F1	2	0	-	6.0	3.5	0.5
F2	1.9	0.1	-	6.0	3.5	0.5
F3	1.8	0.2	-	6.0	3.5	0.5
F4	1.7	0.3	-	6.0	3.5	0.5
F5	1.6	0.4	-	6.0	3.5	0.5
F6	1.5	0.5	-	6.0	3.5	0.5
F7	1.9	-	0.1	6.0	3.5	0.5
F8	1.8	-	0.2	6.0	3.5	0.5
F9	1.7	-	0.3	6.0	3.5	0.5
F10	1.6	-	0.4	6.0	3.5	0.5
F11	1.5	-	0.5	6.0	3.5	0.5

Percentage moisture loss

This test was also carried to check the integrity of films at dry condition. Three 1-cm diameter films were cut out and weighed accurately and kept in desiccators containing fused anhydrous calcium chloride. After 72 hours, the films were removed and weighed. Average percentage moisture loss of three films was found.[10]

$$\text{Percentage moisture loss} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Swelling percentage (%S)

Drug loaded films were placed in a thoroughly cleaned Petri dish having 50 ml of pH 6.8 phosphate buffer. An increase in the weight of the film was noted in 15 minute intervals for 60 minutes and the weight was calculated. The swelling percentage was calculated by using the following formula:[11]

$$\%S = \frac{X_t - X_0}{X_0} \times 100$$

where %S is the swelling percentage, X_t the weight of swollen film after time t, and X_0 is the weight of film at zero time.

Folding endurance

Folding endurance of the film was determined by repeatedly folding one film at the same place till it broke, or folded up to 300 times manually, which was considered satisfactory to reveal good film properties.[12] The number of times a film could be folded at the same place without breaking gave the value of the folding endurance. This test was done for three films.

Water vapor transmission rate

For this study, vials of equal diameter were used as transmission cells. These cells were washed thoroughly and dried in an oven. About 1 g of calcium chloride was taken in the cell and the polymeric films measuring 1 cm^2 area were fixed over the brim with the help of an adhesive. The cells were weighed accurately and initial weight was recorded, and then kept in a closed desiccators containing saturated solution of potassium chloride. The humidity inside the desiccators was set to be between 80 and 90% RH. The cells were taken out and weighed after 18, 36, 54 and 72 hours. From the increase in weights, the amount of water vapor transmitted and the rate at which water vapor transmitted (Q) were calculated by using the formula:[13]

$$Q = WL/S$$

where W is water vapor transmitted in grams, L is thickness of the film in centimeters, S is the exposed surface area in square centimeters.

Drug content

A film was cut into three pieces of equal diameter and they were taken separately and 100 ml of pH 6.8 phosphate buffer solution was added to each of them and continuously stirred for 24 hours and the solutions were filtered, suitably diluted and analyzed at 272 nm in a UV spectrophotometer. The average of drug content of three films was taken as the final reading.

Stability study in human saliva

The stability study of buccal films was performed in natural human saliva.[14] Samples of human saliva were collected from 10 humans (age 18–40 years) and filtered. The films were placed in separate Petri dishes containing 5 ml of human saliva and kept in a temperature controlled oven at 37±0.2°C for 6 hours. At regular time intervals, the films were examined for changes in color, shape, collapse and physical stability.

Measurement of buccoadhesive strength

A modified balance method was used for determining the *ex vivo* buccoadhesive strength.[15] Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with IPB pH 6.8 as moistening fluid. Sheep buccal mucosa was fixed on the plane surface of glass slide attached (with adhesive tape) to the bottom of smaller beaker, kept inverted in a 500 ml beaker attached to the bigger beaker. IPB pH 6.8 was added to the beaker up to the upper surface inverted beaker with buccal mucosa. The buccal film was stuck to the lower side of the upper clamp using cyanoacrylate adhesive. The exposed film surface was moistened with IPB and left for 5 minutes for initial hydration and swelling. Then, the platform was slowly raised until the film surface came in contact with mucosa. Two sides of the balance were made equal before the study by keeping a weight on the right-hand pan. A weight of 5 g was removed from the right-hand pan, which lowered the pan along with the film over the mucosa. The balance was kept in this position for 5 minutes contact time. Then, weights were slowly added to the right-hand pan until the film detached from the mucosal surface. This detachment force gave the buccoadhesive strength of the buccal film in grams. The results are shown in Table 2 and Figure 3.

Force of adhesion (N) = (Bioadhesive strength (g) × 9.8)/1000

Bond strength (N/m^2) = Force of adhesion/surface area.

Table 2: Buccoadhesive strength of formulations F1–F11

Formulation code	Buccoadhesive strength (g)
F1	15.4
F2	15.5
F3	16.6
F4	20.5
F5	27.8
F6	32.5
F7	15.3
F8	17.4
F9	19.8
F10	24.8
F11	26.7

In vitro drug release studies

The *in vitro* release studies were performed in pH 6.8 phosphate buffer solution at 37°C using a modified dissolution apparatus.[16] The modified dissolution apparatus consisted of a 250 ml beaker as a receptor compartment and an open end tube as a donor tube. The magnetic stirrer assembly with an attached hot plate was adopted for the study. The dissolution medium consisted of 100 ml of phosphate buffer maintained at 37±1°C by means of a thermoregulated hot plate. Film was placed into the donor chamber of the assembly separated from the medium by a semi-permeable membrane. The donor tube was then dipped into the receptor compartment containing dissolution medium, which was maintained at 37±1°C and stirred at a constant speed of 100 rpm using a magnetic bead. One milliliter samples were withdrawn at predetermined time intervals for all the batches. For each sample withdrawn, an equivalent volume of phosphate buffer was replaced to the dissolution medium to maintain constant volume and sink condition. A 10-fold dilution of each of the withdrawn sample was made and the diluted solutions were thereafter analyzed spectrophotometrically at 272 nm.

Ex vivo permeation studies

An *ex vivo* diffusion study of famotidine was carried out using fresh sheep buccal mucosa with a modified diffusion cell at 37±1°C.[14] Fresh sheep buccal mucosa was mounted between the donor and receptor compartments. Sheep buccal mucosa was tied to one end of an open ended cylinder, which acts as a donor compartment. The film

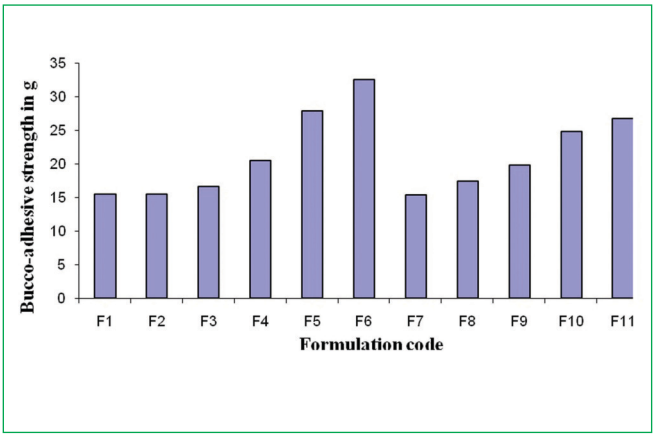

Figure 3: Buccoadhesive strength of formulations F1–F11

should be placed in such a way that it should be stuck on the mucous membrane. The receptor compartment was filled with IPB pH 6.8. The assembly was maintained at 37°C and stirred magnetically. Samples were withdrawn at predetermined time intervals and analyzed by UV spectrophotometer at 272 nm.

In vivo drug release study

Six male New Zealand white rabbits (2–2.5 kg) were selected for the *in vivo* study. The dose of famotidine was adjusted based on the rabbit weight and the optimized formulations were cut and placed in the buccal membrane with the help of a clip. Dextrose solution was transfused continuously throughout the period of study. Periodically, 1 ml of blood sample was taken by syringe containing 1 ml of heparin solution to prevent blood clotting. These blood samples were centrifuged at 2500 rpm for about 30 minutes. One milliliter of the supernatant was taken, and after suitable dilution, analyzed at 272 nm spectrophotometrically by the method described under *in vitro* analysis.

RESULTS AND DISCUSSION

The FTIR spectra of famotidine, HPMC, CP, PVP and the combination of drug and polymers showed no significant interaction between drug and polymer. The prepared famotidine buccal films were characterized based upon their physicochemical characteristics like surface pH, PMA, PML, swelling percentage, Q, thickness, weight and drug content. The results are shown in Table 3.

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the rate of hydration of the polymers, the surface pH of the films was determined. The observed surface pH of the formulations was found to be in the range of 6.52±0.03 to 6.81±0.01. The results show that there is no significant difference in the surface pH of all the formulations and the pH range lies within the range of salivary pH, i.e. 6.5–6.8, thereby not causing irritation in the site of administration.

By checking the physical stability of the film at high humid conditions and integrity of the film at dry conditions, the films were evaluated for PMA and PML.

The swelling behavior of the polymer is reported to be crucial for its bioadhesive character. The adhesion occurs shortly after swelling but the bond formed is not very strong. The adhesion increases with the degree of hydration till the point of disentanglement at the polymer tissue surface, which leads to abrupt drop in adhesive strength due to overhydration. The formulation F6 shows high swelling percentage (138±0.85) which is due to the presence of higher concentration of CP.

Water vapor transmission studies indicate that all the films were permeable to water vapor. The amount of water vapor transmission through the films followed zero order kinetics. The water vapor transmission values were less in the case of HPMC film and more in the case of composition of CP and PVP with HPMC film.

The folding endurance was found to be greater than 300 times in the case of all the formulations. This makes the system acceptable for movement of mouth, indicating good strength and elasticity. Folding endurance test results indicate that the films would maintain the integrity with buccal mucosa when applied.

The observed results of content uniformity indicate that the drug was uniformly dispersed, with minimum intra-batch variability. Recovery was possible to the tune of 18.1–19.9 mg. The stability study of the optimized formulation was done in natural human saliva. The films did not exhibit any significant changes in their color, shape and had satisfactory physical stability.

Table 3: Physiochemical characteristics of formulations F1–F11

Formulation code	Surface pH±SD	PMA±SD	PML±SD	Swelling index±SD	Q±SD	Thickness (mm)±SD	Weight of films (mg)±SD	Drug content (mg)±SD
F1	6.73±0.005	5.21±0.07	4.14±0.12	69.4±1.04	5.98±0.08	0.24±0.01	180.93±1.55	19.7±0.1
F2	6.79±0.005	7.32±0.04	7.13±0.08	99.67±0.69	12.44±0.48	0.62±0.01	163.18±0.9	18.9±0.2
F3	6.71±0.015	9.24±0.09	9.12±0.07	118.4±0.72	10.87±0.35	0.47±0.01	171.53±0.81	18.1±0.26
F4	6.64±0.050	10.32±0.11	4.84±0.08	124.15±0.99	11.1±0.26	0.59±0.01	186.31±0.58	19.76±0.15
F5	6.6±0.015	12.13±0.09	4.08±0.03	132.36±0.61	11.58±0.43	0.85±0.02	191.37±0.85	18.76±0.15
F6	6.52±0.03	14.21±0.06	11.21±0.06	138±0.85	17.17±0.34	0.31±0.01	210.12±1.06	18.43±0.2
F7	6.7±0.03	16.34±0.12	10.06±0.06	67.53±0.65	13.48±0.4	0.22±0.02	181.17±1.79	19.7±0.05
F8	6.8±0.015	7.86±0.27	6.44±0.1	69.7±0.72	12.3±0.59	0.2±0.01	172.35±1.11	18.6±0.2
F9	6.77±0.005	4.12±0.13	1.38±0.03	71.6±0.62	10.58±0.44	0.23±0.01	172.31±1.11	19.1±0.11
F10	6.8±0.001	6.18±0.13	1.18±0.05	78.6±1.07	10.51±0.52	0.25±0.01	174.37±1.11	18.2±0.3
F11	6.81±0.001	2.56±0.25	0.86±0.1	82.6±1.1	13.23±0.55	0.31±0.01	174.94±1.66	19±0.1

SD, $n=3$

CP, being an anionic polymer, gives the highest buccoadhesive force. The buccoadhesive strength exhibited by famotidine buccal films was satisfactory for maintaining them in oral cavity. The combination of HPMC and CP shows good adhesion. Upon addition of PVP, the buccoadhesive strength increases which may be due to hydrogen bond formation and Vander Waals forces.

Distinguishable difference was observed in the release of famotidine in all formulations. The *in vitro* drug release and Higuchi's plot have shown that the drug release followed zero order kinetics, which was known from the regression value (R). CP is present in an ionized state, and as a result, the polymeric network gets loosened comparatively, attributing for the higher drug release. The addition of PVP decreases the famotidine release which may be due to enhancement in swelling of the polymer, which in turn increases the barrier effect and decreases the drug release, thereby controlling the drug release.

Data of *in vitro* release were fit into different equations and kinetic models to explain the release kinetics of famotidine from the buccal films. The kinetic models used were a zero order equation, Higuchi's model and Peppas models. The obtained results in these formulations were plotted in various model treatments as cumulative percentage release of drug versus square root of time (Higuchi's) and log cumulative percentage release versus log time (Peppas).

To find out the mechanism of drug release from hydrophilic matrices, the *in vitro* dissolution data of each formulation were calculated with different kinetic drug release equations, namely, zero order: $Q = K_0 t$; [Figure 4] Higuchi's square rate at time: $Q = K_H t^{1/2}$ [Figure 5] and Peppas $F = K_m t^n$ [Figure 6], where Q is the amount of drug released at time t, F is the fraction of drug released at time t, K_0 is zero order kinetic drug release constant, K_H is Higuchi's square root of time kinetic drug release constant, K_m is constant incorporating geometric and structural characteristic of the films and n is the diffusion exponent indicative of the release mechanism. The correlation coefficient values (R) indicate that the kinetic of drug release was of zero order. The mechanism of drug release by Peppas model indicates the super case II transport evidenced with diffusion exponent values (n).

The oral mucosa represents a barrier to drug permeation and it is intermediate between skin epidermis and the gut in its permeability characteristics. The effectiveness of the buccal barrier and whether buccal absorption could provide means for famotidine administration can be determined by *ex vivo* permeation studies. Permeation studies were carried out on optimized formulation.

In vivo buccal diffusion studies that were conducted for the optimized formulation in rabbits showed zero order release pattern. The *in vivo* studies of buccal films of famotidine in rabbits did not show any inflammation or any other sensitization reactions at the administration site. *In vitro* and *in vivo* correlations were carried out for the therapeutic efficacy of a pharmaceutical formulation and

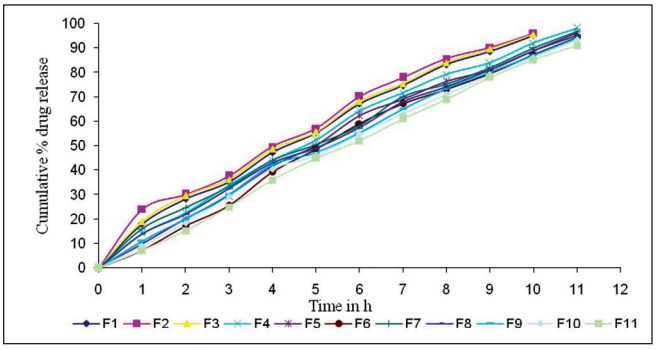

Figure 4: Cumulative % release of formulations F1–F11

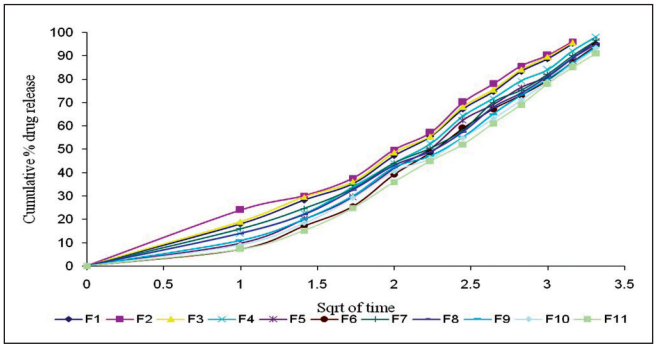

Figure 5: Higuchi's plot of formulations F1–F11

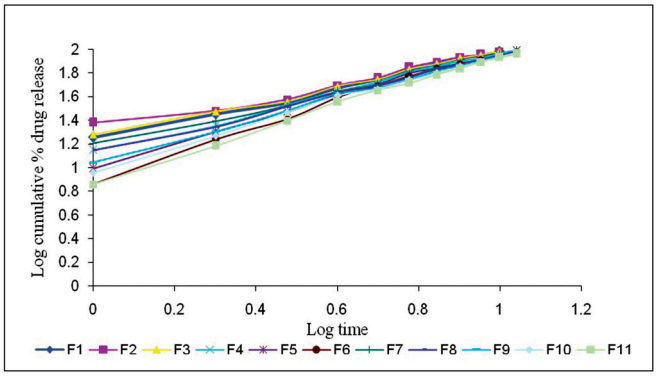

Figure 6: Peppas plot of formulations F1–F11

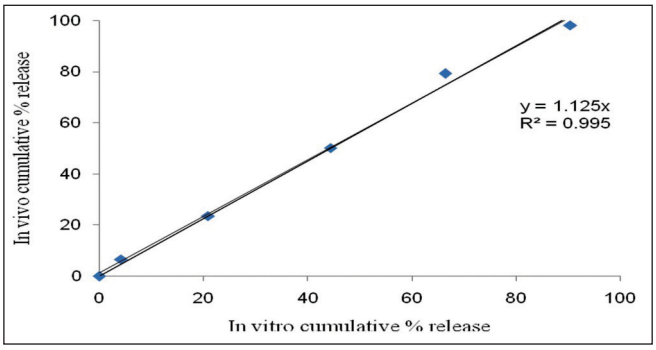

Figure 7: *In vitro* and *in vivo* correlation plot of optimized formulation

are governed by the factors related to both *in vitro* and *in vivo* characteristics of the drug. A graph was plotted by taking cumulative % *in vitro* release and cumulative % *in vivo* drug release for the same period of time and the release rate followed zero order, showing the correlation coefficient value to be 0.995, as shown in Figure 7.

CONCLUSION

The novel trans-buccoadhesive films of famotidine were prepared by solvent casting technique by employing the polymers of HPMC, CP and PVP. Drug–polymer interaction studies by FTIR show that there is no significant interaction between drug and polymers. All the physicochemical characteristics were evaluated, which showed satisfactory results with good buccoadhesive strength. The formulations were showing good stability in natural human saliva. Good correlation was observed between the *in vitro* drug release and *in vivo* drug release, with satisfactory drug permeation across the sheep buccal mucosa. These formulations were found to be suitable candidates for the development of controlled drug delivery for therapeutic use of famotidine.

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How to cite this article: Alagusundaram M, Chetty CM, Dhachinamoorthi D. Development and evaluation of novel-trans-buccoadhesive films of famotidine. J Adv Pharm Tech Res 2011;2:17-23.

Source of Support: Nil, **Conflict of Interest:** Nil.