RESEARCH ARTICLE

Development and evaluation of novel trans-buccoadhesive bilayer tablets of Famotidine

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The present investigation highlights the novel trans-buccoadhesive tablets of Famotidine, an H2-receptor antagonist used as an antiulcerative agent. The buccoadhesive tablets were prepared by direct compression method using bioadhesive polymers like sodium alginate, SCMC, HPMC-K100M, PVP-K30 either alone or in combinations with EC as a backing layer. The prepared formulations were evaluated for their physicochemical characteristics, swelling index, surface pH, *ex vivo* buccoadhesive strength, *in vitro, in vivo* drug release and *ex vivo* permeation studies. The distinguishable differences in the results were shown to be dependent on characteristics and composition of bioadhesive materials used. Stability studies were performed in natural human saliva and accelerated conditions showed no significant difference in physical appearance, drug content, buccoadhesive strength and the *P*-value statistically significant at <0.05. *Ex vivo* mucous irritation by histological examination reveals, the administration site of buccal tablet over the buccal mucosa did not cause any irritation, ulceration, inflammation and redness, and it resembles to controlled buccal mucosa. Good correlations were observed between *in vitro* and *in vivo* drug release, with a correlation coefficient of 0.996. Drug diffusion from buccal tablets showed apparently zero order kinetics and release mechanism was diffusion controlled after considerable swelling.

Key words: *Buccal tablet, buccoadhesive strength, Famotidine, histological examination, zero order*

INTRODUCTION

Famotidine is a histamine H2-receptor antagonist.[1] It is the drug of choice used in the treatment of Zollinger-Ellison syndrome and gastro-esophageal reflux disease, widely prescribed in gastric ulcers, duodenal ulcers. The bioavailability of Famotidine following oral administration is 40-45%, and has a shorter plasma half life (2.5-4.0 hours) due to first pass metabolism.[2,3] Following oral administration, peak plasma concentration is attained in 1-3 h and the duration of therapeutic effect is less. Thus, the development of a buccal bioadhesive formulation with controlled release patterns could provide a single dosing and ensure good patient compliance.

Nowadays considerable interest has been focused on buccal drug delivery systems using the buccal mucosa as an attractive administration route. Hence the advantages such as relative permeability, robustness, and sudden recovery after damage are related to mucous membrane.[4,5] Bioadhesive polymer can notably improve the performance of many drugs, as they are having prolonged contact time with these tissues. Furthermore, there is good potential for prolonged delivery through the mucosal membrane within the oral mucosal cavity.[6] The present research investigate the development and evaluation of novel trans-buccoadhesive bilayer tablets 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 bilayer tablets by direct compression method using the polymers of sodium alginate, sodium carboxy methyl cellulose (SCMC), hydroxy propyl methyl cellulose-K100M (HPMC), polyvinyl pyrrolidone-K30 (PVP) and ethyl cellulose (EC) as a backing layer.

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MATERIALS AND METHODS

Famotidine was obtained as gift from Aurobindo Labs Ltd. (Hyderabad, India); sodium alginate, SCMC, Eudragit RL100, HPMC K100M, PVP K30 and EC 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 materials used and received were of analytical grade. The buccoadhesive bilayer tablets were prepared by direct compression method.

Preparation of buccoadhesive bilayered tablets of famotidine

All the ingredients of the formulation were passed through a sieve # 85 and were blended in a glass mortar with a pestle to obtain uniform mixing. The blended powder of the core was compressed into tablets on a pilot press, nine station tablet punching machine (Chamunda Pharma pvt Ltd, Ahmedabad), the upper punch was then removed and ethyl cellulose as backing material was added over it and finally compressed at a constant compression force 60 kN. The composition of buccoadhesive bilayer tablets of Famotidine are given in Table 1.

Physicochemical evaluation of buccoadhesive bilayered tablets

All the prepared formulation were evaluated for thickness, weight variation, hardness, friability and drug content were determined in a procedure as stated for conventional oral tablets in the accredited pharmacopoeia.[7]

Surface pH

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in buccal environment. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible, The tablet was allowed to swell by keeping it in contact with 5 ml of phosphate buffer containing 2% w/v agar medium (pH 6.8±0.01) for 2 h at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablets and allowing it to equilibrate for 1 minute. A mean of three readings were recorded.[8,9]

Swelling index

Three tablets from each batch were weighed individually and placed separately in a thoroughly cleaned Petri dish containing 5 ml of pH 6.8 phosphate buffer. At regular intervals the tablets were removed and weight was noted. The swollen tablets were reweighed and swelling index was calculated by using the formula:[10,11]

$$S.I = [(W2-W1)/W1] \times 100$$

Where, S.I–swelling index, W1-initial weight of Tablet, W2-weight of swollen tablet at time (t)

Stability study in human saliva

Samples of human saliva were collected from 10 humans (age 18-40 years) and filtered. The tablets from best batch 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 stability of the buccoadhesive tablets were evaluated for its appearance, such as color and shape, and concentration of Famotidine.[12]

Ex vivo buccoadhesive strength

A modified physical balance method was used for determining the *ex vivo* buccoadhesive strength.[13,14] Fresh sheep buccal

Table 1: Composition of buccoadhesive bilayer tablets of Famotidine

Formulation code	Ingredients (mg)								Total weight (mg)
	Famotidine	Sodium alginate	SCMC	Eudragit RL 100	HPMC K100	PVP K30	Mg. Stearate	Ethyl cellulose	
F1	20	70	-	-	-	8	2	50	150
F2	20	-	70	-	-	8	2	50	150
F3	20	-	-	70	-	8	2	50	150
F4	20	-	-	-	70	8	2	50	150
F5	20	35	35	-	-	8	2	50	150
F6	20	35	-	-	35	8	2	50	150
F7	20	-	35	35	-	8	2	50	150
F8	20	-	-	35	35	8	2	50	150
F9	20	35	17.5	17.5	-	8	2	50	150
F10	20	-	35	17.5	17.5	8	2	50	150
F11	20	17.5	-	35	17.5	8	2	50	150
F12	20	17.5	17.5	-	35	8	2	50	150
F13	20	35	-	17.5	17.5	8	2	50	150
F14	20	17.5	35	17.5	-	8	2	50	150
F15	20	-	17.5	35	17.5	8	2	50	150
F16	20	17.5	17.5	17.5	17.5	8	2	50	150

mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. The mucosal membrane was separated by removing underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8 and two sides of the balance were made equal before the study. The sheep buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the glass vial, which was filled with phosphate buffer. The glass vial was tightly fitted into a glass beaker (filled with phosphate buffer pH 6.8 at 37°C±1°C) so that it just touched the mucosal surface. The buccal tablet was stuck to the lower side of a rubber stopper with cyanoacrylate adhesive and adds 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 tablet over the mucosa. The balance was kept in this position for 5 minutes contact time. The water (equivalent to weight) was added slowly with an infusion set (100 drops/min). To the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of then buccal tablet in grams.

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

Bond strength (Nm^{-2}) = Force of adhesion / surface area

In vitro drug release study

The USP type II rotating paddle method was used to study the drug release from the bilayer tablet. The dissolution medium consisted of 900 ml of phosphate buffer pH 6.8. The release study was performed at 37±0.5°C, with a rotation speed of 50 rpm. The backing layer of the buccal tablet was attached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of the dissolution vessel. Aliquots were withdrawn at regular time intervals and replaced with fresh medium to maintain sink conditions. The samples were filtered, made appropriate dilutions with phosphate buffer and were thereafter analyzed spectrophotometrically at 272 nm.[15,16]

Ex vivo permeation studies

An *ex-vivo* diffusion study of Famotidine buccal tablets was carried out using a fresh sheep buccal mucosa using modified diffusion cell at 37°±1°C. 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 tablet should be placed in such a way that it should be stuck on the mucous membrane. The receptor compartment was filled with isotonic phosphate buffer pH 6.8. The assembly was maintained at 37°C and stirred magnetically. Samples were withdrawn at predetermined time intervals and analyzed using UV Spectrophotometer at 272 nm.[17]

Ex vivo muco irritation by histological examination

Ex vivo muco irritation of Famotidine buccal tablets (F5) were performed by using a fresh sheep buccal mucosa was purchased from local slaughter house immediately after slaughter and the sheep buccal mucosa was used for histological examination within 2 h. Histological examination was performed to evaluate the pathological changes in cell morphology and tissue structure during administration of buccoadhesive tablets. The epithelial tissues of mucosa were fixed in 10% neutral buffered formalin for 2 h, washed with distilled water upto 1 h and dehydrated with graded ethanol (60, 80, 90, 95 and 100%). Then it is treated with xylene for permeation and embedded with liquid paraffin using the standard procedures. After 8 h formalin-fixed, paraffin-embedded samples were cut in 4-μm thick sections on a microtome with a disposable blade and conveniently stained with eosin.[18]

In vivo drug-release study

Six male Newzealand white rabbits (2-2.5 kg) were selected. The dose of Famotidine was adjusted based on the rabbit weight and the best formulations (F5) were placed in the buccal membrane with the adhesive layer. Dextrose solution was transfused continuously throughout the period of the 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 as like *in vitro* analysis.[19]

Stability study

The formulation F5 was selected and the stability studies were carried out at accelerated condition of 40±2°C, 75±5% RH conditions, stored in desiccators, the tablets were packed in amber color screw cap container and kept in above-said condition for period of 3 months. The tablets were analyzed periodically for their physical appearance, buccoadhesive strength and *in vitro* drug release. Results were analyzed by one-way ANOVA followed by Tukey's test. Differences were considered statistically significant at $P<0.05$.[20]

RESULTS AND DISCUSSION

The main objective of this research was to develop novel trans-buccoadhesive bilayer tablets to release the Famotidine at site of administration in unidirectional pattern for extended period of time without wash of drug by saliva. The bilayer tablets were prepared by direct compression method using sodium alginate, SCMC, HPMC-K100M, PVP-K30. EC was chosen as a backing layer because of its low water permeability and flexibility in the buccal environment. The prepared buccoadhesive bilayer tablets were characterized for thickness, weight variation, hardness, friability and drug content. The results are shown in Table 2. All the formulation passes test for weight variation, showed acceptable drug content and friability.

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the rate of hydration of polymers, the surface pH of the tablets was determined. The observed surface pH of the formulations was found to be in the range of 6.51±0.061 to 6.79±0.04. The results are shown in Table 2. The results show that there is no significant difference in the surface pH of all the formulations that indicates no irritation in the buccal mucosa.

The swelling behavior of the polymer is reported to be crucial for its bioadhesive character and drug release profile. The adhesion occurs shortly after swelling but the bond formed is not very strong. Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration. Swelling index was calculated with respect to time up to 6 h. The results are shown in Table 3 and Figure 1. The formulation F5 shows high swelling index (78.6±1.04) which is due to equal concentrations of sodium alginate and SCMC by the reaction between alginic acid and sodium ion.

The stability of Famotidine buccoadhesive tablets in human saliva was evaluated by their appearance, color, shape and concentration of Famotidine. The buccoadhesive strength exhibited by Famotidine buccoadhesive tablets was satisfactory for maintaining them in buccal cavity. The combination of sodium alginate and SCMC shows high buccoadhesive strength in formulation F5 (34.6 g) which may

Table 2: Physicochemical evaluation of formulations F1-F16

Formulation code	Thickness (mm)±SD	Weight variation (mg)±SD	Hardness (Kg/cm^2)±SD	Friability (%)±SD	Drug content (mg)±SD	Surface pH±SD
F1	2.23±0.03	149±1.55	4.2±0.15	0.43±0.025	19.77±0.42	6.51±0.061
F2	2.29±0.02	147±0.94	4.1±0.25	0.54±0.03	19.85±0.21	6.73±0.03
F3	2.19±0.03	150±0.81	4.3±0.31	0.60±0.042	19.82±0.38	6.62±0.026
F4	2.28±0.05	148±0.72	3.9±0.21	0.48±0.036	19.76±0.31	6.79±0.040
F5	2.31±0.03	150±0.19	4.3±0.2	0.48±0.01	19.99±0.01	6.76±0.065
F6	2.29±0.04	147±0.84	4.2±0.26	0.51±0.02	19.89±0.04	6.77±0.066
F7	2.23±0.07	149±0.38	4.2±0.31	0.61±0.038	19.86±0.05	6.77±0.061
F8	2.26±0.02	148±0.52	4.5±0.25	0.54±0.025	19.87±0.25	6.56±0.066
F9	2.23±0.02	148±0.76	4.3±0.45	0.44±0.01	19.85±0.19	6.76±0.045
F10	2.25±0.02	150±0.41	4.2±0.41	0.44±0.026	19.86±0.15	6.72±0.04
F11	2.26±0.03	149±0.82	4.4±0.21	0.48±0.03	19.56±0.47	6.67±0.045
F12	2.27±0.03	147±0.48	4.1±0.15	0.69±0.025	19.58±0.56	6.64±0.077
F13	2.25±0.02	149±0.65	4.2±0.31	0.47±0.015	19.89±0.31	6.75±0.049
F14	2.28±0.01	150±0.23	4.0±0.41	0.44±0.036	19.79±0.24	6.60±0.056
F15	2.26±0.02	149±0.57	3.7±0.15	0.52±0.041	19.76±0.23	6.76±0.080
F16	2.24±0.03	151±0.75	4.1±0.23	0.58±0.03	19.78±0.25	6.78±0.041

Table 3: Swelling index of formulations F1-F16

Formulation code	Swelling index±SD					
	Time in h					
	1	2	3	4	5	6
F1	26.09±0.76	38.61±1.08	55.58±0.80	64.96±0.70	71.27±0.76	74.84±0.27
F2	22.23±0.72	32.15±0.91	40.75±0.46	50.71±0.54	60.04±0.61	65.21±0.53
F3	19.19±0.64	24.48±0.63	37.81±0.67	45.84±0.68	51.8±0.66	55.77±0.51
F4	23.73±1.08	33.97±0.48	46.13±0.93	51.81±0.69	63.84±0.28	68.91±0.93
F5	27.39±1.03	41.62±0.90	57.67±0.53	66.68±0.75	71.25±0.61	78.6±1.04
F6	19.81±0.67	31.39±0.98	39.81±0.67	51.12±0.62	57.52±1.08	62.76±0.43
F7	16.01±0.84	25.64±0.75	32.76±0.54	41.10±0.88	46.46±0.87	51.76±0.64
F8	26.65±0.72	40.98±0.79	56.93±0.86	65.29±0.97	71.28±0.30	74.84±0.60
F9	23.35±1.12	31.43±0.64	41.91±0.93	51.66±0.57	61.44±0.63	65.69±0.64
F10	31.47±0.93	42.62±0.77	58.41±0.79	67.45±0.96	73.17±0.61	76.85±0.65
F11	24.72±0.38	33.98±0.81	44.19±0.91	51.81±0.67	61.52±1.06	67.85±0.51
F12	17.13±0.55	27.77±0.61	35.96±0.86	41.92±0.88	48.72±0.65	53.93±0.75
F13	21.48±0.94	32.18±0.82	42.18±0.37	50.91±0.82	57.80±0.99	64.26±0.78
F14	22.3±0.65	31.96±0.49	43.34±0.48	51.67±0.49	59.15±0.70	66.04±0.83
F15	20.47±0.76	31.11±0.75	42.01±0.86	48.12±0.62	57.2±0.40	64.08±0.63
F16	25.82±0.37	32.88±0.72	45.25±0.85	52.72±0.58	62.63±0.95	68.77±0.43

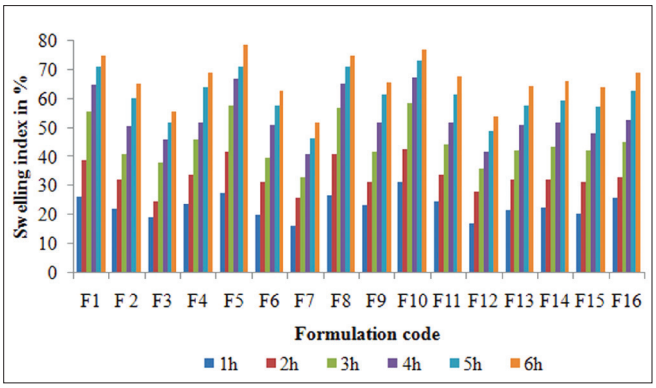

Figure 1: Swelling index of formulations F1-F16

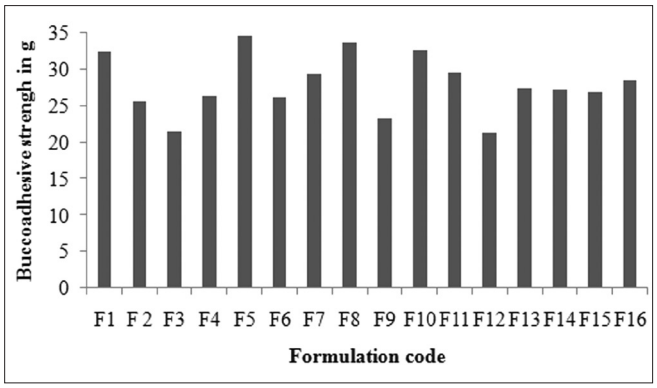

Figure 2: Buccoadhesive strength of formulations F1-F16

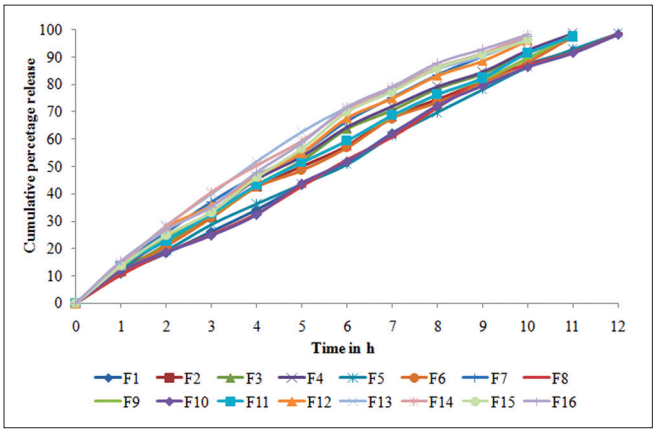

Figure 3: Cumulative % release of formulations F1-F16

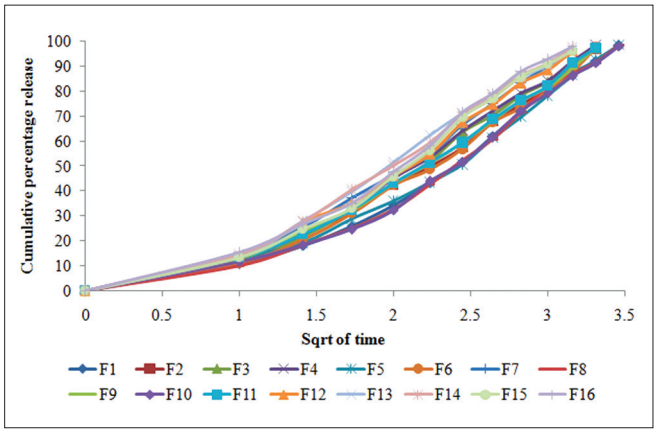

Figure 4: Higuchi's plot of formulations F1-F16

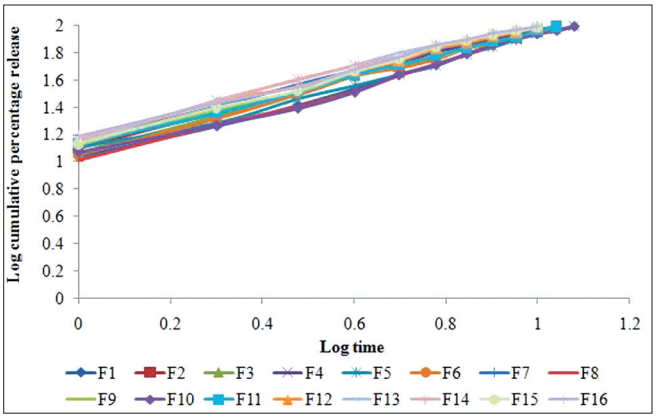

Figure 5: Peppa's plot of formulations F1-F16

be due to ionic gelation of Na+ ions and alginic acid. The results are shown in Table 4 and Figure 2.

Distinguishable difference was observed in the release of Famotidine in all formulations which may be due to the varying proportions of polymeric substances. The formulations are producing reasonable release of Famotidine at the end of 12 h. The release rate of Famotidine depends on the swelling index and buccoadhesive strength, which may varies with characteristics and composition of matrix forming polymers

Table 4: Buccoadhesive strength of formulations F1-F16

Formulation code	Buccoadhesive strength in g
F1	32.4
F2	25.6
F3	21.5
F4	26.4
F5	34.6
F6	26.2
F7	29.5
F8	33.8
F9	23.4
F10	32.7
F11	29.6
F12	21.3
F13	27.4
F14	27.2
F15	26.9
F16	28.6

in the formulations. In general the rate of drug release was increased by increasing proportions of hydrophilic polymer. The maximum cumulative percentage release of Famotidine from formulation F5 could be recognized to the proportions of sodium alginate and SCMC due to increases in swelling index and buccoadhesive strength.

Data of *in vitro* release were fit into different equations and kinetic models to explain the release kinetics of Famotidine from the buccal tablets. The kinetic models used were a zero-order equation, Higuchi's model and Peppa's models. The obtained results in these formulations were plotted in various model treatments as Cumulative percentage release of drug vs Square root of time (Higuchi's) and Log cumulative percentage release vs 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: $Q=K_0t$; [Figure 3] Higuchi's square rate at time: $Q=K_Ht^{1/2}$ [Figure 4] and Peppas: $F=K_mt^n$ [Figure 5], where Q is amount of drug release at time t, F is Fraction of drug release 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 the kinetic of drug release was zero order. The mechanism of drug release was by Peppas model indicates the non-Fickian release kinetics, 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 performed in best formulation F5.

Histological examination was performed to evaluate the pathological changes in cell morphology and tissue organization during administration of buccoadhesive tablets. The administration site of buccal tablet over the buccal mucosa should not cause any irritation, ulceration, inflammation and redness, and it resembles to controlled buccal mucosa. The resulted images for control and test were shown in the Figures 6 and 7.

In vivo buccal diffusion studies that were conducted for the formulation F5 in rabbits showed zero-order release pattern. The *in vivo* studies of buccoadhesive tablets of Famotidine in rabbits did not show any inflammation, irritation or any other sensitization reactions at the administration site. *In vitro* and *in vivo* correlation was performed for the therapeutic efficacy of Famotidine from buccal tablets is 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 on x-axis and cumulative % *in vivo* drug release on y-axis for the same period of time and the release rate followed zero order with correlation coefficient value to be 0.996 shown in Figure 8.

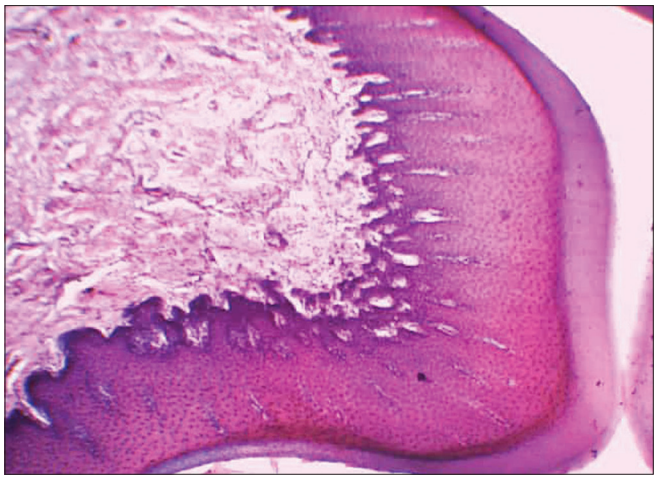

Figure 6: Controlled untreated sheep buccal mucosa

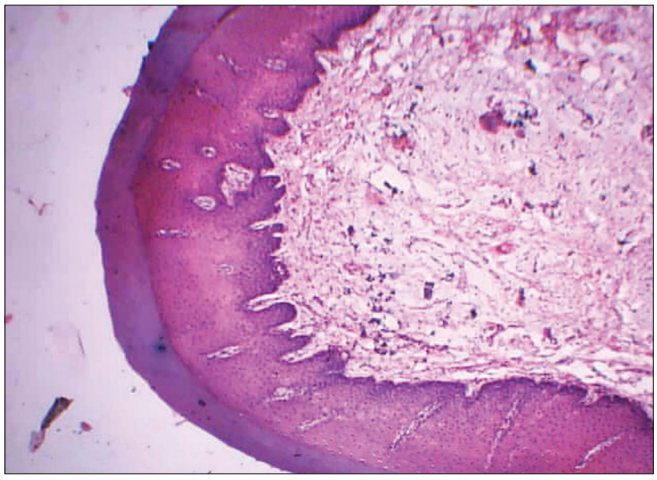

Figure 7: Famotidine buccoadhesive tablet subjected to simple diffusion in sheep buccal mucosa

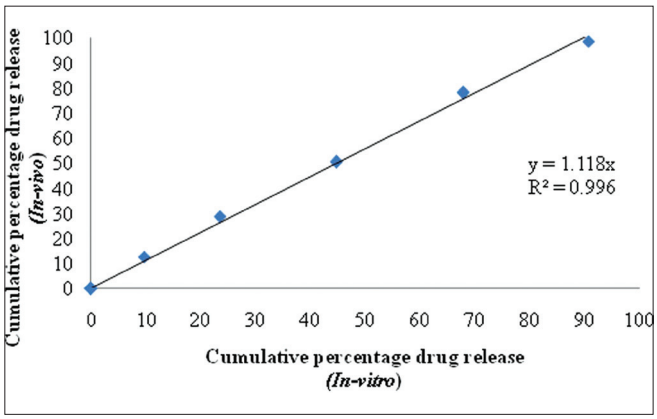

Figure 8: *In vitro* and *in vivo* correlation plot of optimized formulation

CONCLUSIONS

The novel trans-buccoadhesive tablets of Famotidine were prepared by direct compression method by employing bioadhesive polymers like sodium alginate, SCMC, HPMC-

K100M, PVP-K30 either alone or in combinations with EC as a backing layer. All the parameters were evaluated for the formulations showed satisfactory results with good swelling index and buccoadhesive strength. The administration site of buccal tablets did not show any inflammation and any other sensitization reaction, which is revealed by histological examination. The best formulation was showing good stability in natural human saliva and accelerated conditions. Good correlation was observed between *in vitro* and *in vivo* drug release, with satisfactory drug permeation across the sheep buccal mucosa. Buccoadhesive bilayer tablets of Famotidine could be promising one as they, increase bioavailability, minimize the dose, reduces the side effects and improves patient compliance hence, Famotidine might be a right and suitable candidate for oral controlled drug delivery via buccoadhesive bilayer tablets for the therapeutic use.

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