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FORMULATION AND EVALUATION OF BUCCOADHESIVE FILMS OF FAMOTIDINE

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Abstract

The buccal region offers an attractive route of administration for systemic drug delivery. The aim of this study is to develop an innovative fast dissolving oral film (FDOF) of Famotidine . A buccal film for systemic administration of famotidine in the oral cavity has been developed using hydroxy propyl methyl cellulose -15cps (HPMC), carbopal(CP) and poly vinyl pyrrolidine (PVP) by solvent casting method. The physicochemical interactions between and polymers were investigated by Fourier transform infrared (FTIR)Spectroscopy. According to FTIR the drug did not show any evidence of an interaction with the polymers used and was present in an unchanged state.

The films were evaluated for their physical characteristics like weight variation, thickness, drug content uniformity, surface pH, folding endurance, swelling percentage, percentage moisture absorption (PMA), percentage moisture loss (PML), water vapour transmission rate (WVT), mucoadhesion strength, Ex-vitro permeation studies. *In vitro* release studies were conducted for famotidine films in phosphate buffer (pH, 6.8) solution and the withdrawn solutions were thereafter analysed spectrophotometrically at 289 nm.

A Total number of 8 formulations were prepared and In vitro drug release study of all the formulations showed that, from the formulation F8 the drug was released approximately upto 99.8% in 45 minutes. Hence formulation F8 was the best obtained formulation in the above study. Data of invitro 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, First order equation, Higuchi's model and Peppa's models. The correlation coefficient values (R^2) indicate that the drug release was following zero order release kinetics. The mechanism of drug release was by peppas model indicates the super case II transport evidenced with diffusion exponent values (n) i.e > 0.89.

Keywords: Famotidine, Buccal films, Solvent casting method, Hpmc, cp, pvp, zero order

1. Introduction

Bioadhesive formulations have a wide scope of applications, for both systemic and local effects of drugs. The mucosa is relativelypermeable with a rich bloodsupply. Theoral transmucosal drugdelivery bypasses liver and avoids pre-systemic elimination in the GI tract and liver. These factors make the oral mucosa a very attractive and feasible site for systemic drug delivery. A few drugs,such as buprenorphine ropranolol salbutamol sulphate diclofenac sodium, flurbiprofen, and fexofenadine. Famotine is a histamine H2-receptor antagonist (also called H2-blocker) which decreases the amount of acid produced by the stomach and is used to treat gastric and duodenal ulcers by blocking the H2 subtype of histamine receptors. The prescribed dose of the drug should be low. Any drug with a daily requirement of 40g or less would be a candidate suitablefor buccal delivery. Though the prescribed dose of famotidine is 20 mg twice daily, selected dose for film formulation is 10 mg. Therefore, it is possible for the drugt o get absorbed in a short time. It is available in the form of tablets and parenteral. The bioavailability of the drug shou ld be low or variable The F value of famotidine is about 40-45 %. Therefore, this drug is suitable for buccal absorptio n. The pKa of the drug should be greater than 2 for an acid and less than 10 for a base thefrom above points, it is clear that famotidine is suitable drug for buccal absorptionand may provide a better therapeutic profile than that of the oral route.

Unlike the sublingual mucosa, the buccal mucosa offers many advantages because of its smooth and relatively immobile surface and its suitability for the placement of controlled-release system which is well accepted by patients. The buccal mucosa is relatively permeable, robust in comparison to the other mucosal tissues and is more tolerant to potential allergens which have a reduced tendency to irreversible irritation or damage. The buccal mucosa is a useful route for the treatment of either local or systemic therapies overcoming the drawbacks of conventional administration routes. Buccal route is well vascularized draining to the heart directly via the internal jugular vein. So, it has been largely investigated as a potential site for controlled drug delivery in various chronic systemic therapies.. Bioadhesive polymer can significantly improve the performance of many drugs, as they have prolonged contact time with these tissues. These patient compliance controlled drug delivery products have improved drug bioavailability.

2. Materials and Methods

2.1) Materials: FAMOTIDINE drug IS obtained from Aurobindo Pharma Ltd, Hyderabad. hydroxy propyl methyl cellulose -15cps (HPMC), carbopal (CP) and poly vinyl pyrrolidine (PVP)were received from MYLAN Chemicals Mumbai . Other materials were purchased from S.D Fine chem. Ltd.

2.2) Preformulation Studies:

2.2.1) Analytical method for Estimation of Famotidine:

Construction of calibration curve

An accurately weighed 100 mg of Famotidine was dissolved in pH 6.8 phosphate buffer as per I.P and make up the volume up to 100 ml in a volumetric flask, (Stock Solution: I, 1000 µg/ml) . From this 5 ml of solution were pipette out and make up the volume up to 100 ml (Stock Solution: II, 50 µg/ml). Then the aliquots were prepared, whose concentration ranging from 0 to 30µg/ml and the absorbance were measured at 289 nm by using UV Spectrophotometer Elico, PG instruments. Ltd. (Model No: T60 UV) against the reagent blank.

2.3) Formulation Development

2.3.1) Fabrication of Drug Free Buccal Films

The buccal mucoadhesive films were prepared by the method of solvent casting technique[43] employing 'O' shape ring placed on a glass surface as substrate by using different polymers like Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC), Carbopol(CP) and Poly vinyl pyrrolidone (PVP).

The calculated quantities of polymers were dispersed in ethanol (70 %). The carbopol polymeric solution was neutralized using triethanolamine. The polymeric solutions are 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 semisolid consistency. Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles Then this were casted on a glass surface employing 'O' shape ring having 3.6 cm in diameter is covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature over night. The dried films were separated and the backing membrane used was aluminium foil. Then the formulations were stored in desiccators until further use.

2.3.2) Fabrication of Famotidine Buccal Films

The buccal mucoadhesive films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different polymers like Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC), carbopol(CP) and The calculated quantities of polymers were dispersed in ethanol (70 % v/v). The carbopol 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 semisolid consistency. Then the solution was subjected to sonication in a bath sonicator to remove the air bubbles Then this were casted on a glass surface employing 'O' shape ring having 3.6 cm in diameter is covered with funnel to controlling the evaporation of solvent and allowed to dry at room temperature over night. The dried films were separated and the backing membrane used was aluminium foil. Then the formulations were stored in desiccators until further use.

Table 1: The composition of buccal films prepared using Famotidine.

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
Famotidine (mg)	20	20	20	20	20	20	20	20
HPMC K4M (mg)	200	180	160	150	100	140	150	150
carbopol (mg)	--	20	40	50	100	45	35	25
pvp (mg)	--	--	--	--	--	15	15	25
Sodium saccharine (%)	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Ethanol (70% v/v) (ml)	9.5	9.5	9.5	9.5	9.5	9.5	9.5	9.5
Propylene glycol (ml)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total weight (mg)	250	250	250	250	250	250	250	250

2.4) Physico - Chemical Evaluations

a) Surface pH

Buccal films were left to swell for 2 h on the surface of an agar plate, prepared by dissolving 2 % (w/v) agar in warmed isotonic phosphate buffer of pH 6.8 under stirring and then pouring the solution into a petridish till gellig at room temperature. The surface pH was measured by means of a pH paper placed on the surface of the swollen patch. The mean of two reading was recorded.

b) Percentage Moisture Absorption (PMA)

The percent moisture absorption test was carried out to check the physical stability of the buccal films at high humid conditions. In the present study the moisture absorption capacity of the films were determined as follows. Three 1cm diameter films were cut out and weighed accurately then the films were placed in desiccators containing saturated solution of aluminium chloride, keeping the humidity inside the desiccators 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.

$$\text{Percentage Moisture Absorption} = \frac{\text{Final weight} - \text{Initial weight}}{\text{Initial weight}} \text{X100}$$

C) Percentage Moisture Loss (PML)

This test was also carried to check the integrity of films at dry condition. Three 1cm diameter films was 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 out.

$$\text{Percentage Moisture Loss} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \text{X100}$$

d) Swelling Percentage (%S)

A drug loaded films were placed in a thoroughly cleaned petridish having 50 ml of pH 6.8 phosphate buffer. An increase in the weight of the patch was noted in 15 min intervals for 60 min and the weight was calculated. The swelling percentage was calculated by using the following formula,

$$\% \text{ S} = \frac{\text{X}_t - \text{X}_0}{\text{X}_0} \text{X100}$$

Where, % S - swelling percentage

X_t - the weight of swollen film after time t,

X_0 -weight of film at zero time.

e) Water Vapour Transmission Rate (WVT)

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 found in between 80 – 90 % RH. The cells were taken out and weighed after 18, 36, 54 and 72 hrs. From increase in weights the amount of water vapour transmitted and the rate at which water vapour transmitted were calculated by using the following formula.

W V T = WL/S

Where, W is water vapour transmitted in mg, L is thickness of the film in mm, S is exposed surface area in cm^2.

f) Thickness

The thickness of each film was measured by using a digital vernier caliper at six different positions of the film and the average thickness was calculated.

g) Weight of Films

The weights of three films were taken and the weight variation was calculated.

h) Folding Endurance

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

i) Drug Content Estimation

A film was cut into three pieces of equal diameter were taken in separate 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, suitably diluted and analyzed at 289 nm in a UV Spectro photometer. The average of drug content of three films was taken as final reading.

j) Measurement of Buccoadhesive Strength

A modified balance method was used for determining the *ex-vivo* buccoadhesive strength. Fresh sheep buccal mucosa was obtained from a local slaughterhouse and used within 2 h 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 isotonic phosphate buffer (IPB) pH 6.8 as moistening fluid. Sheep Buccal mucosa was fixed on the plane surface of glass slide attached (with adhesive tape) to bottom of smaller beaker, kept inverted in 500 ml beaker attached to the bigger beaker. Isotonic phosphate buffer 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 with cyanoacrylate adhesive.

The exposed patch surface was moistened with IPB and left for 30 s 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 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 patch 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 following parameters were calculated from the bioadhesive strength.

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

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

k) In-Vitro Drug Release Studies

The *in-vitro* release studies were performed in phosphate buffer solution (pH 6.8, 100 ml) at 37 ºC using a modified dissolution apparatus. 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 (pH 6.8) maintained at 37 ± 1°C by means of a thermo-regulated 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 ten-fold dilution of each of the withdrawn sample was made and the diluted solutions were thereafter analyzed spectrophotometrically at 289 nm.

l) Ex-Vivo Permeation Studies

An *ex-vivo* diffusion study of Famotidine 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.

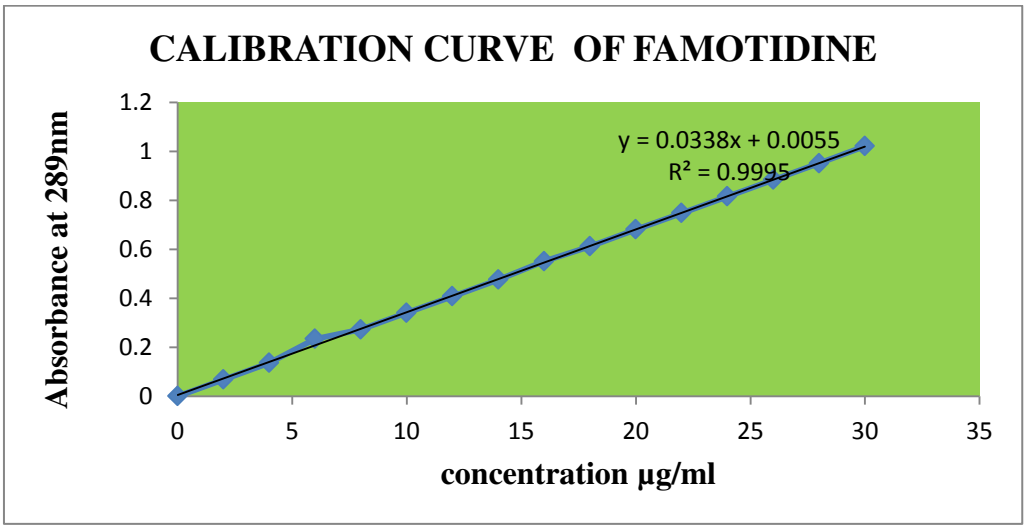
The film should be placed in such a way that it should be stuck on the mucous membrane. The receptor compartment was filled with isotonic phosphate buffer pH 6.8.

The assembly was maintained at 37ºC and stirred magnetically. Samples were withdrawn at predetermined time intervals and analyzed using UV - Spectrophotometer at 289 nm.

3. Results and Discussion

3.1 Preformulation characteristics:

Figure 1: standard graph of Famotidine.



3.2 Drug: Excipient Compatibility studies- FTIR

Figure 2 : F.T.I.R graph of pure drug of Famotidine.

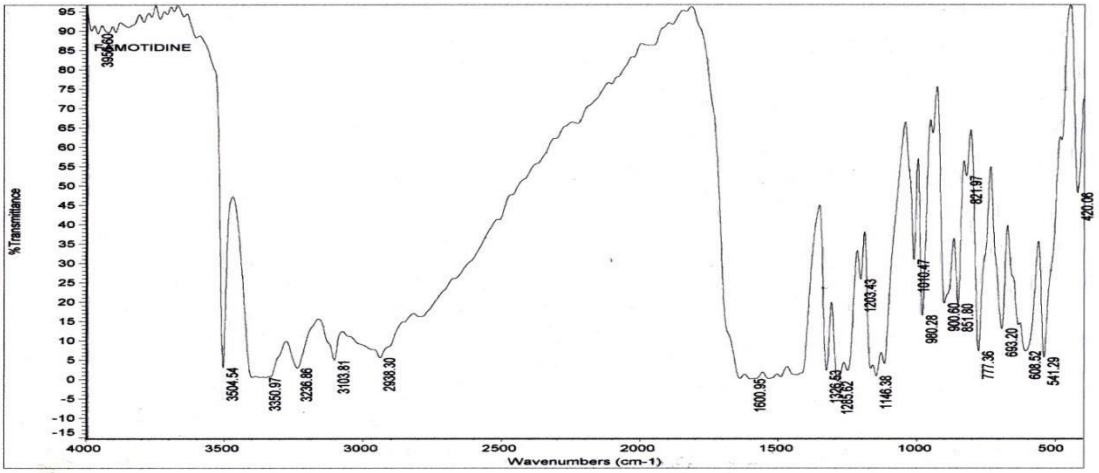
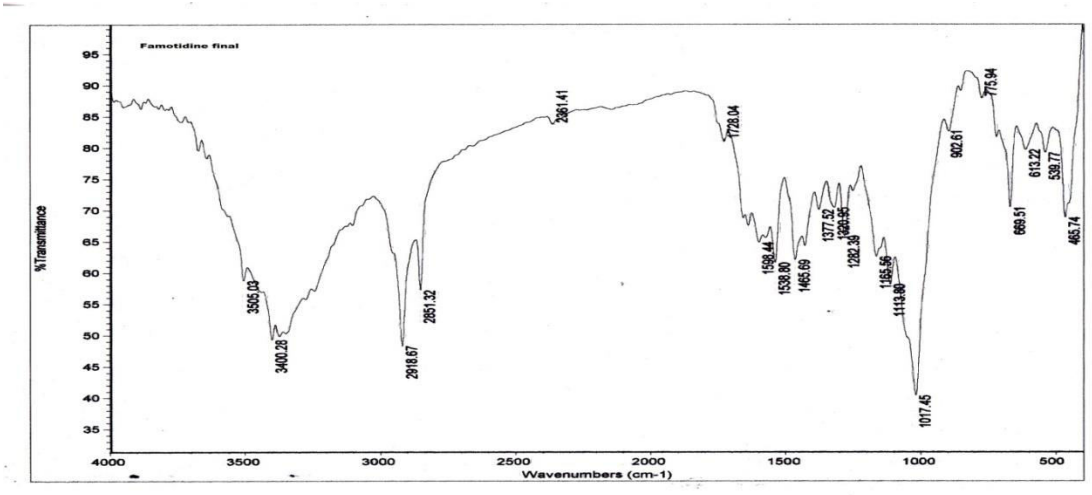


Figure 3: F.T.I.R graph of Famotidine with excipients (HPMC + CP + PVP)



Inference: There is no significant change in the shift of major peaks of drug in the above graphs, hence there were no drug and excipient interactions found.

Table 2: Physicochemical evaluation data of buccal films of famotidine

Formulation Code	Weight of the film (mg)*	Thickness (mm)*	Surface pH*	Folding Endrance (times)*
F1	180.93±1.55	0.24±0.01	6.73±0.005	301±2.0
F2	169.18±0.9	0.62±0.01	6.80±0.005	303±3.0
F3	171.53±0.81	0.47±0.01	6.71±0.015	300±1.0
F4	186.31±0.58	0.59±0.01	6.64±0.050	305±6.0
F5	191.37±0.85	0.65±0.02	6.6±0.015	307±4.0
F6	212.12±1.06	0.31±0.01	6.52±0.03	309±5.0
F7	173.9±0.65	0.44±0.01	6.57±0.004	312±6.0
F8	172.37±0.92	0.39±0.01	6.65±0.005	320±5.0

Table 3: Physicochemical evaluation data of buccal films of famotidine

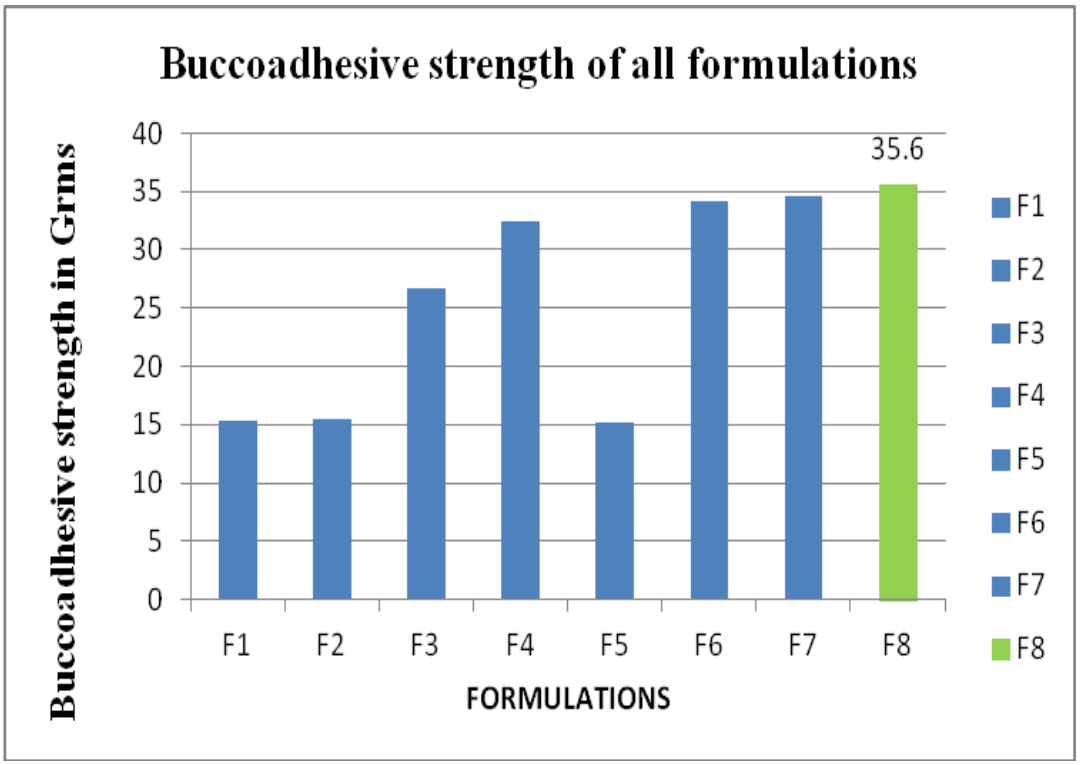
Formulation Code	Swelling Index (%)*	PMA ± SD (%)*	Drug content per film (2 x 2cm) (mg)*	PML± SD (%)*
F1	69.4±1.04	5.21±0.07	19.7	5.97±0.12
F2	99.67±0.69	7.32±0.04	18.9	5.14±0.72
F3	118.4±0.72	9.24±0.09	18.1	4.74±0.1
F4	124.15±0.99	10.32±0.11	18.76	4.14±0.2
F5	132.36±0.61	12.13±0.09	18.76	4.08±0.03
F6	138±0.85	14.21±0.06	18.43	3.88±0.02
F7	77.9±0.5	11.23±0.23	18.7	5.71±0.02
F8	73.4±0.6	10.26±0.23	19.7	6.71±0.01

Discussion: All the formulations of famotidine fims were evaluated for various physicochemical parameters and they were found to within limits. The optimised formula is F8.

Table-4: Data of Buccoadhesive strength of the famotidine films.

Formulation code	Buccoadhesive strength in gms
F1	15.4
F2	15.5
F3	26.7
F4	32.5
F5	15.2
F6	34.2
F7	34.6
F8	35.6

Figure 4: Profile of Buccoahesive strength of all formulations (F1-F8).



Discussion: Among all the formulations, the buccoadhesive strength of formulation F8 was found to be highest i.e 35.6gms.

Table 5: Comparative In-vitro drug release study data of Famotidine films (F1-F8)

TIME (Min)	Cumulative % Drug Release							
	F1	**F2**	**F3**	F4	**F5**	**F6**	**F7**	**F8**
0	0	0	0	0	0	0	0	0
5	3.9	5.6	7.8	6.2	15	9.9	25	18
10	11.5	12.6	17.6	16.3	26.5	25.6	34.5	26.2
15	14	17	25.6	26.2	36	28.4	48.6	49.1
20	26.3	30.5	32.5	38.3	47	44.8	58.6	58.2
25	42.6	42.9	45	47.6	55	59.1	71.6	66.4
30	45.6	48.6	50	57	59.5	65	78.9	83.2
35	58	57.6	62.6	68.6	73	74.4	83.6	89.4
40	69	67	74.9	74.6	75.2	85.2	91.9	96.2
45	75.6	75.4	80	78.6	84	87	96.6	99.8

Discussion: Among all the formulations, F8 formulation showed highest % of drug release i.e. 99.8% in 45 mins highest among all formulation. Hence F8 was optimized.

Figure 5 : Comparative study of in-vitro drug release profile of all formulations (F1-F8).

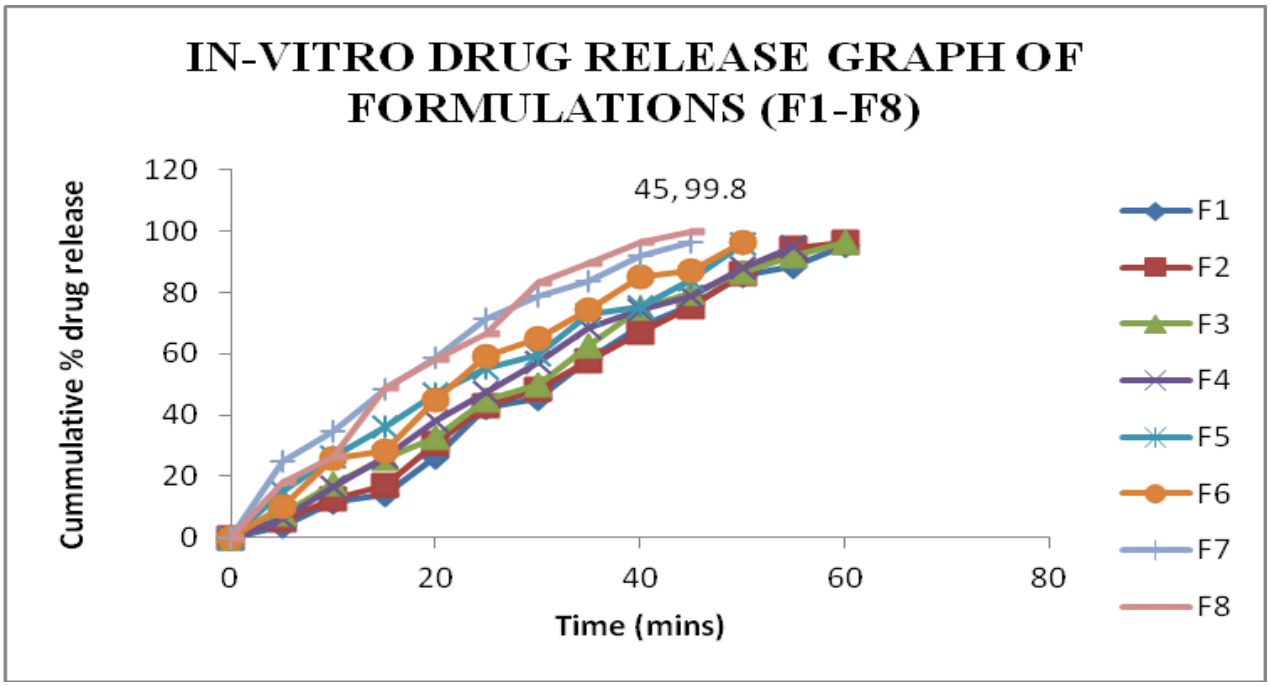


Table-6: In-vitro drug release data for optimised Famotidine fim formulation (F8).

TIME (MINS)	%CDR
0	0
5	18
10	26.2
15	49.1
20	58.2
25	66.4
30	83.2
35	89.4
40	96.2
45	99.8

Discussion: The dissolution profile of optimised film of Famotidine showed a % drug release of 99.8% in 45 mins.

Figure 6 : In-vitro drug release profile of optimised Famotidine film formulation (F8).

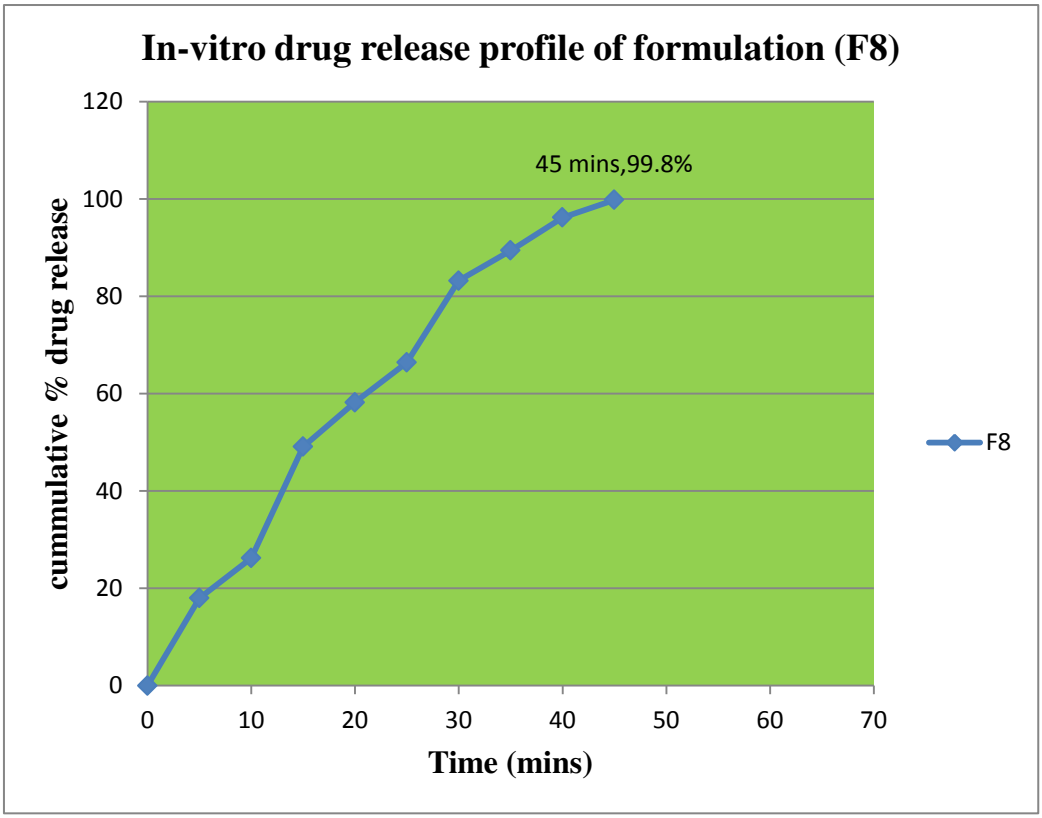
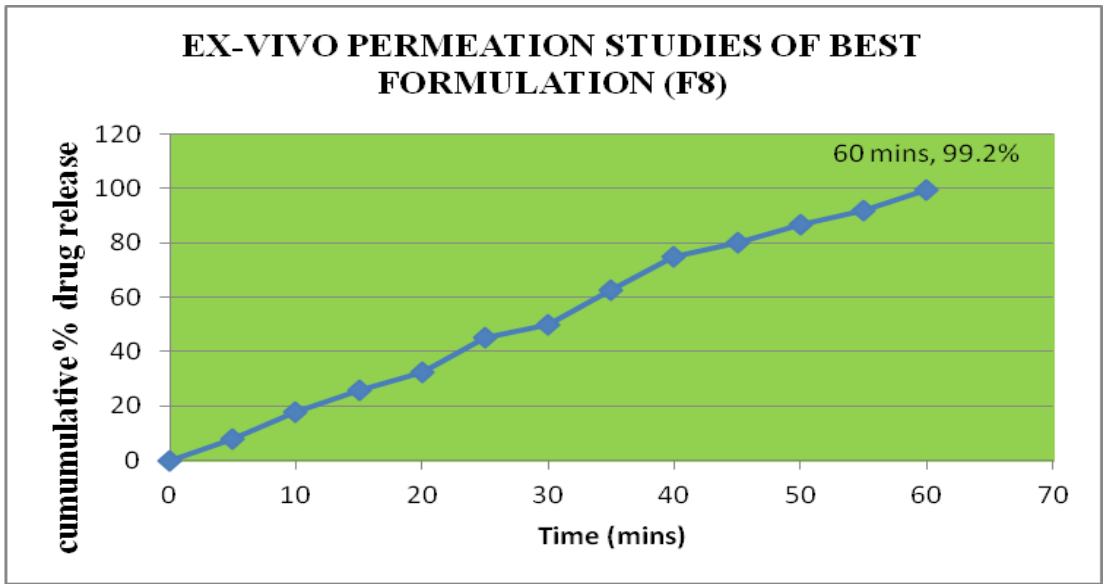


Table-7: Ex-vivo permeation studies data of optimsed formulation (F8).

TIME	%CDR
0	0
5	7.8
10	17.6
15	25.6
20	32.5
25	45
30	50
35	62.6
40	74.9
45	80
50	86.8
55	92
60	99.2

Discussion: The Ex-vivo permeation studies data of optimised film of Famotidine showed a % drug release of 99.2% in 60 mins.

Figure 7 : Ex-vivo permeation profile of optimised Famotidine film formulation (F8).



3.3) Release Kinetics of optimized formulation:

Discussion: The optimised formula followed zero order and super case II transport release.

Table-8: Drug release Kinetic data of optimsed formulation.

	ZERO	FIRST	HIGUCHI	PEPPAS
	% CDR Vs T	Log % Remain Vs T	%CDR Vs √T	Log C Vs Log T
Slope	2.269212121	-0.04773546	16.46395172	1.545042397
Intercept	7.592727273	2.350801143	-12.4241050	-0.68686566
Correlation	0.984914723	-0.87779199	0.978080375	0.798251103
R^2	0.970057012	0.770518781	0.95664122	0.637204823

Figure-8: Zero Order Plot.

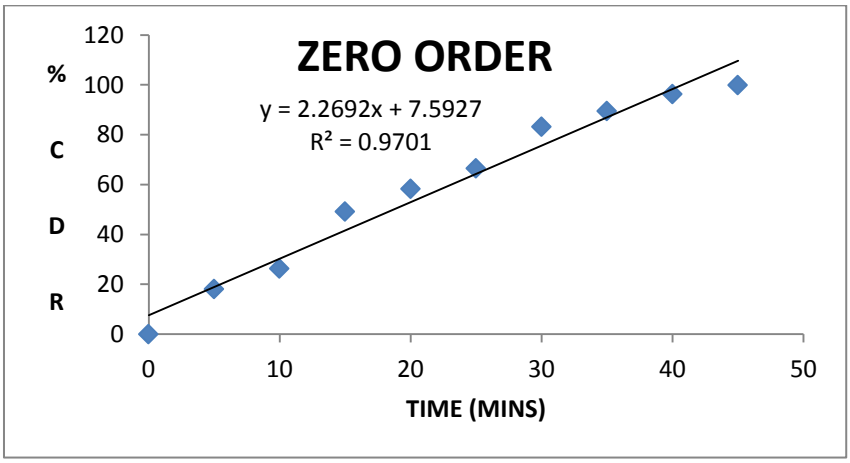


Figure-9: First Order Plot.

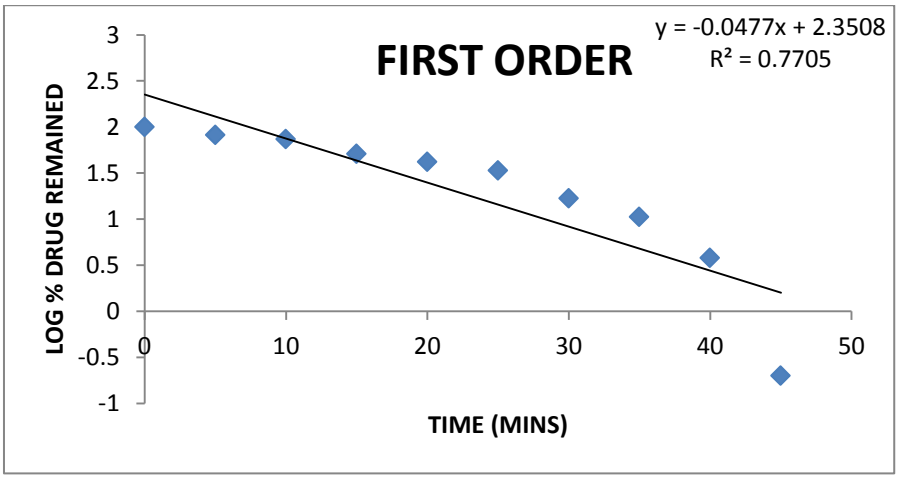


Figure-10: Higuchi's Model Plot.

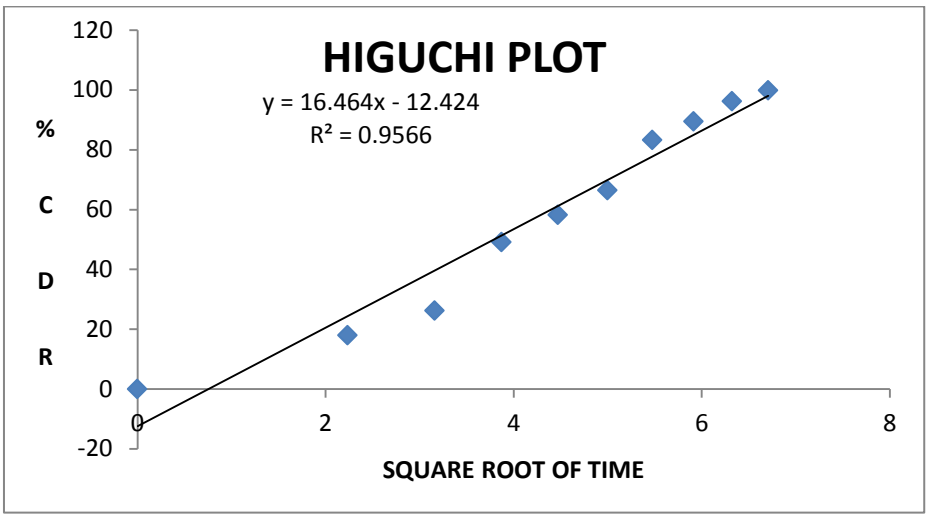
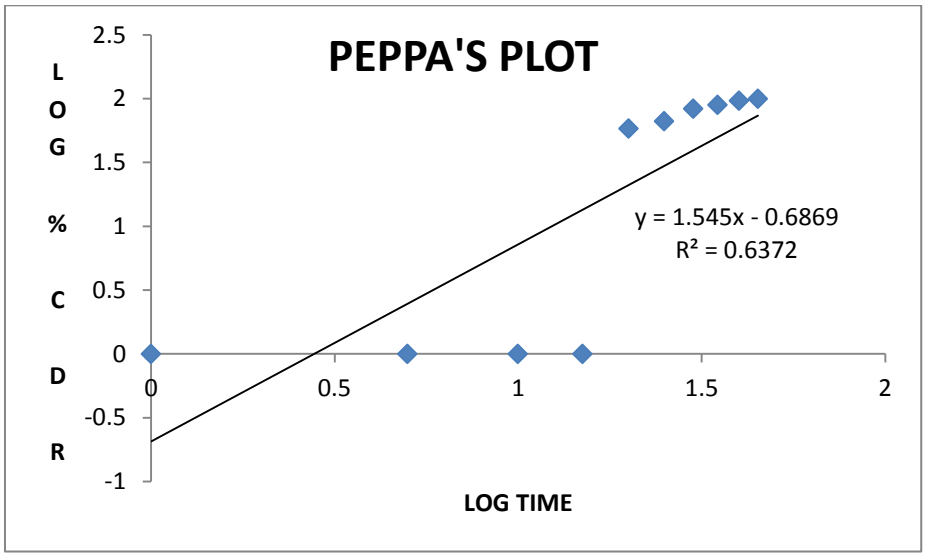


Figure-11: Peppa's Model Plot.



4. Conclusion

The Famotidine buccal mucoadhesive films were prepared by the method of solvent casting technique employing 'O' shape ring placed on a glass surface as substrate by using different polymers such as Hydroxy Propyl Methyl Cellulose - 15 cps (HPMC), Carbopol-P 934 (CP) and Poly vinyl pyrrolidone (PVP). Ethanol (70 % v/v) is used as the solvents. Propylene glycol serves as the plasticizer as well as penetration enhancer. The prepared famotidine mucoadhesive buccalfilms were characterized based upon their physico-chemical characteristics like surface pH, swelling percentage, thickness, weight variation, drug content, percentage moisture absorption(PMA), percentage moisture loss(PML), Folding endurance, measurement of *Ex-vivo* buccoadhesive strength, *in-vitro* release studies, stability in human saliva, *Ex-vivo* permeation studies .Based on the results of evaluation tests, the formulation coded "F8" was concluded as best formulation.

Finally it may be concluded that the successful formation and optimization of fast dissolving films of FAMOTIDINE was done using HPMC CP and PVP. Hence Famotidine can be conveniently administered orally in the form of films.

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