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Formulation and *In Vitro* Evaluation of Mucoadhesive Buccal Tablet of Venlafaxine Hydrochloride

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ABSTRACT

The present study involves the formulation and evaluation of buccal tablets of venlafaxine hydrochloride, an antidepressant drug belongs to class SNRI(serotonin-nonepinephrine reuptake inhibitor)has high first pass metabolism, So buccal drug delivery has been considered an alternative to the oral dosing for compound subjected to degradation in the gastrointestinal tract or to first pass metabolism. An attempt has been made to developed muccoadhesive buccal tablets comprising of drug containing mucoadhesive layers and drug free backing layer ethyl cellulose of to release the drug for extended period of time with reduction in dosing frequency, dose related side effects and improve bioavaibility of drug. Tablets of Venlafaxine Hydrochloride were prepared by direct compression using muccoadhesive polymers Carbopol 934-P and HPMC K4M.Buccal tablets were evaluated by different parameters such as thickness, hardness, weight uniformity, content uniformity, swelling index, surface pH, *ex vivo* bioadhesive strength, in vitro drug release, *ex vivo* drug permeation and FTIR studies. The modified in vitro assembly was used to measure the bioadhesive strength of tablets with fresh goat buccal mucosa as model tissue. In order to determine the mode of release, the data was subjected to Krosmeyer and Peppas diffusion model. All the formulations followed Fickian release mechanism. Tablet containing Carbopol 934P and HPMC K4M in the ratio of 1:1(25%) had maximum *in vitro* drug release for 8 hrs.

Keywords: Buccal tablets, Venlafaxine hydrochloride, *in vitro* drug release, *ex vivo* studies, kinetic model.

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INTRODUCTION

The oral cavity is an attractive site for drug delivery due to ease of administration, avoidance of possible drug degradation in the gastrointestinal tract, and first-pass metabolism. The buccal region of the oral cavity is an attractive target for administration of the drug of choice. Buccal delivery involves the administration of the desired drug through the buccal mucosal membrane lining of the oral cavity. Moreover buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage from the buccal cavity therefore mucoadhesive dosage forms were suggested for oral drug delivery which include adhesive tablets ,adhesive gels and adhesive patches[1].

In the, oral cavity the delivery of drugs are classified into three categories: 1.)Sublingual delivery, which is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth; 2.)buccal delivery it is the drug administration through mucosal membranes lining the cheeks (buccal mucosa); and 3.) Local delivery it is the drug delivery into the oral cavity.[2] Among these routes, buccal delivery is suitable for administration of retentive dosage forms because of an excellent accessibility, an expanse of smooth muscle and immobile mucosa**.**Venlafaxine is a representative of new class of antidepressants. It acts by inhibiting selectively the uptake of serotonin and noradrenaline but shows no affinity for neurotransmitter receptors. Hence it lacks the adverse anticholinergic, sedative and cardiovascular effects of tricyclic antidepressants, However, the main limitation to therapeutic effectiveness of venlafaxine is its poor bioavailability (45%), molecular weight (313.87 gm/mol),basic nature of drug and short biological half life (5hr) necessitating the administration, two or three times daily so as to maintain adequate plasma levels of drug. This necessitates the development of sustained delivery system which permits direct access of the active constituent to the systemic circulation thereby by-passing first- pass metabolism. Buccal delivery is one such system which has been attracting much attention in the recent years. The potential pharmacokinetic benefits of such systems such as lower peak plasma drug concentration and smaller fluctuations between peak and through plasma drug concentration makes it suitable for the treatment of depression. Moreover, it offers easy administration and increases patient compliance. In present study, the mucoadhesive tablets were developed using HPMC K4M and Carbopol 934P in different concentration to get controlled order drug release[3].

MATERIALS AND METHODS

Materials

Venlafaxine hydrochloride was gift sample from Intas pharmaceuticals, Ahmedabad, India. Methocel K4M and Ethyl cellulose from Colorcon, India and Carbopol 934 by zydus cadila, India, Mannitol from Libraw pharma ltd, New Delhi, india.

Mucoadhesive Tablets Preparation

Bilayered buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Venlafaxine hydrochloride was mixed geometrically with different ratios of HPMC K4M, Carbopol 934-P and mannitol as diluent for 10 min. The blends were lubricated with magnesium stearate for 3-5min. The mixture is compressed in rotary tablet compression machine using 8 mm flat faced punches. Then upper punch was raised and the pre-compressed tablet was placed on backing layer of ethyl cellulose then two layers were compressed again to get bilayered buccal tablets.

Optimization of variables using full factorial design

It is desirable to develop an acceptable pharmaceutical formulation in shortest possible time using minimum number of man-hours and raw materials. Traditionally pharmaceutical formulations after developed by changing one variable at a time approach. The method is time consuming in nature and requires a lot of imaginative efforts. Moreover, it may be difficult to develop an ideal formulation using this classical technique since the joint effects of independent variables are not considered. It is therefore very essential to understand the complexity of pharmaceutical formulations by using established statistical tools such as factorial design. In addition to the art of formulation, the technique of factorial design is an effective method of indicating the relative significance of a number of variables and their interactions.

A statistical model incorporating interactive and polynomial terms was used to evaluate the responses. The number of experiments required for these studies is dependent on the number of independent variables selected. The response (Y) is measured for each trial.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2$$

Where Y is the dependent variable,

b0 is the arithmetic mean response of the nine runs and

bi is the estimated coefficient for the factor Xi.

The main effects (X1 and X2) represent the average result of changing one factor at a time from its low to high value. The interaction terms (X1X2) show how the response

Changes when two factors are simultaneously changed.

A 3^2 randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible

combinations. The coded value and design layout of independent factor is shown in table 1 and table 2 respectively and composition shown in table 3. The total content of polymer (X1) and ratio of polymer carbopol 934-P to HPMC K4M (X2) were selected as independent variables while % drug release at 8 hr(Q_8), mucoadhesive strength, swelling index, diffusion coefficient (n) and release rate constant (K) were taken as dependent variables.

Table 1: Coding of variable

Coded Values	Actual Values	
	X_1 Total Polymer(mg)	X_2 Ratio of polymer (Carbopol :HPMC K4M)
-1	20	1:1
0	25	1:2
1	30	1:3

Table 2: Formulation layout for factorial batches

Batch	Coded value		Un-coded value	
	X_1	X_2	X_1 (mg)	X_2 (mg)
F_1	-1	-1	20	10:10
F_2	-1	0	20	6.66:13.34
F_3	-1	1	20	5:15
F_4	0	-1	25	12.5:12.5
F_5	0	0	25	8.33:16.67
F_6	0	1	25	6.25:18.75
F_7	1	-1	30	15:15
F_8	1	0	30	10:20
F_9	1	1	30	7.5:22.5

Table 3: Composition of buccal tablet

Ingredients (mg)	Formulations								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
VenlafaxineHCL	33.75	33.75	33.75	33.75	33.75	33.75	33.75	33.75	33.75
Carbopol 934-P	10	6.66	5	12.5	8.33	6.25	15	10	7.5
HPMC K4M	10	13.34	15	12.5	16.67	18.75	15	20	22.5
Mannitol	41.25	41.25	41.25	36.25	36.25	36.25	31.25	31.25	31.25
Magnesium stearate	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2
Backing layer (EC)	50	50	50	50	50	50	50	50	50
Total weight	150	150	150	150	150	150	150	150	150

EVALUATION OF BUCCAL TABLETS

Drug and polymer compatibility studies:

This can be confirmed by carrying out with Infrared light absorption scanning spectroscopy (IR) studies. Infrared spectra of pure drug, polymer and physical mixture of formulations were recorded by dispersing them in a suitable solvent (KBR) using Fourier Transform Infrared spectrophotometer. A base line correction was made using dried potassium bromide and the spectra of the pure drug, polymer and the formulation mixture were recorded on FTIR.

Thickness

The thickness of three randomly selected buccal tablets from every batch was determined using vernier callipers. The average thickness was calculated.

Weight variation

For the evaluation of weight uniformity, ten tablets from every batch were taken and weighed individually on electronic balance. The average weight was calculated and compared with deviation permitted for buccal tablet i.e.±7.5%.

Hardness

Hardness was conducted for 3 tablets from each batch using Monsanto hardness tester and average values were calculated.

Assay[4]

Ten tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of one tablet was dissolved in 6.8 pH phosphate buffer by sonication for 30 min and filtered through filter paper. The drug content was analyzed spectrophotometrically at 226 nm using an UV spectrophotometer.

Friability test:

For each formulation, pre weighed tablet sample (20 tablets) were placed in the Roche friabilator which is then operated for 100 revolutions. The tablets were deducted and reweighed. Conventional compressed tablets that loose < 0.5 to 1% of their weight are considered acceptable.

Surface pH Study

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. 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. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute. The average pH of three determinants was reported.

Ex vivo mucoadhesion time[5]

The ex-vivo mucoadhesion time was examined after application of the buccal tablet on freshly cut goat buccal mucosa. The fresh goat buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the goat buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8 and kept at 37 ± 1°C. After 2 minutes, stirring was applied slowly to simulate the buccal cavity environment, and tablet adhesion was monitored for 8 h. The time for the tablet to detach from the goat buccal mucosa was recorded as the mucoadhesion time.

Ex Vivo Mucoadhesive Strength

A modified balance was used for determining the ex vivo mucoadhesive strength. Fresh goat buccal mucosa was obtained from a local slaughterhouse and used within 2 hours 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 6.8 solutions at 37°C. The goat buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the cork, the cork 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 glass stopper with cyanoacrylate adhesive. The two sides of the balance were made equal before the study, by keeping a 5-g 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. Different weight was put slowly to the right-hand pan until the tablet detached from the mucosal surface. This detachment force gave the mucoadhesive strength of the buccal tablet in grams.

Swelling Index[6]

Buccal tablets were weighed individually (designated as W1) and placed separately in Petri dishes containing 5 ml of phosphate buffer (pH 6.8) solution. At regular intervals (1, 2, 4, 6 and8hr), the buccal tablets were removed from the Petri dishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W2) .This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following Eq[8].

%Swelling index= (W2-W1)/W1 X 100

W1---initial weight of tablet,

W2--- weight of swollen tablet

In Vitro drug Release[7]

USP dissolution apparatus type 2 (paddle method) was used to study drug release from tablet formulation under sink conditions at 37± 0.5^0C and stirred at rate of 50 rpm. Each tablet was fixed on a glass slide with the help of cyanoacrylate adhesive so that the drug could be release only from upper surface. Then the slide was immersed in the vessel containing 500 ml of pH 6.8 phosphate buffer solution. The aliquots of 5 ml were withdrawn at the time interval of 1hour up to 8 hrs and replaced with equal volume of fresh dissolution medium. The sink condition was maintained throughout the study[9]. The amounts of Venlafaxine hydrochloride was determined by UV Spectrophotometer at 226nm and amount of drug release at various time intervals was calculated.

Permeation studies[10, 11]

The in vitro study of Venlafaxine hydrochloride permeation through the goat buccal mucosa was performed using a franz diffusion cell. Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments so that the smooth surface of the mucosa faced the donor compartment. The tablet was placed on the mucosa and the compartments clamped together. The donor compartment was filled with 1 ml of phosphate buffer pH 6.8. The receptor compartment contained isotonic phosphate buffer pH 6.8. The hydrodynamics in the receptor compartment was maintained by stirring with a magnetic bead at 50 rpm and maintaining the temperature at 37±0.5ºC. 5 ml sample was withdrawn at predetermined time intervals and analyzed for drug content at 226 nm. The graph of % drug permeated v/s time was plotted.

Statistical Analysis

The statistical analysis of the factorial design batches was performed by multiple regression analysis using Microsoft Excel. To evaluate the contribution of each factor with different levels on responses 2-way analysis of variance (ANOVA) was performed. Influence of each factor on responses, the response surface plots were generated using Sigma Plot software Version 8.0, (Jandel Scientific Software, San Rafael, CA). The $P < .05$ was considered to be significant

Kinetic modeling of dissolution data[12]

The dissolution profile of all batches were subjected to various models such as zero order, first order, Higuchi, Korsmeyer and Peppas to ascertain the kinetic of drug release.

Stability study

To determine the change in physical properties and *in vitro* release profile on storage, optimized batch tablets were stored at 40ºC ± 5ºC and 75% ± 5% relative humidity. Samples were evaluated at 1 month time for physical evaluation, assay and dissolution.

RESULTS AND DISCUSSION

Drug Excipient Compatibility Study

Drug polymer compatibility studies were carried out using Fourier Transform Infra Red spectroscopy to establish any possible interaction of Venlafaxine HCL with the polymers used in the formulation. The FT-IR spectra of the formulations were compared with the FT-IR spectra of the pure drug .The results indicated that the characteristic absorption peaks due to pure Venlafaxine HCL have appeared in the formulations, without any significant change in their position, indicating no chemical interaction between Venlafaxine HCL and Polymers as shown in figure1 and 2

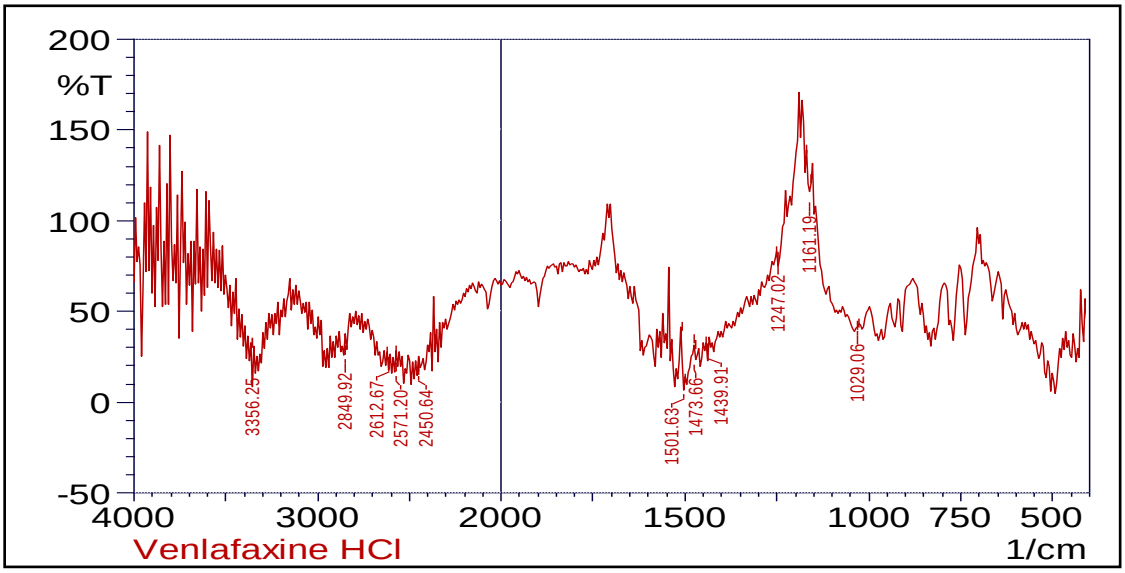

Figure 1: FTIR spectrum of Venlafaxine HCL

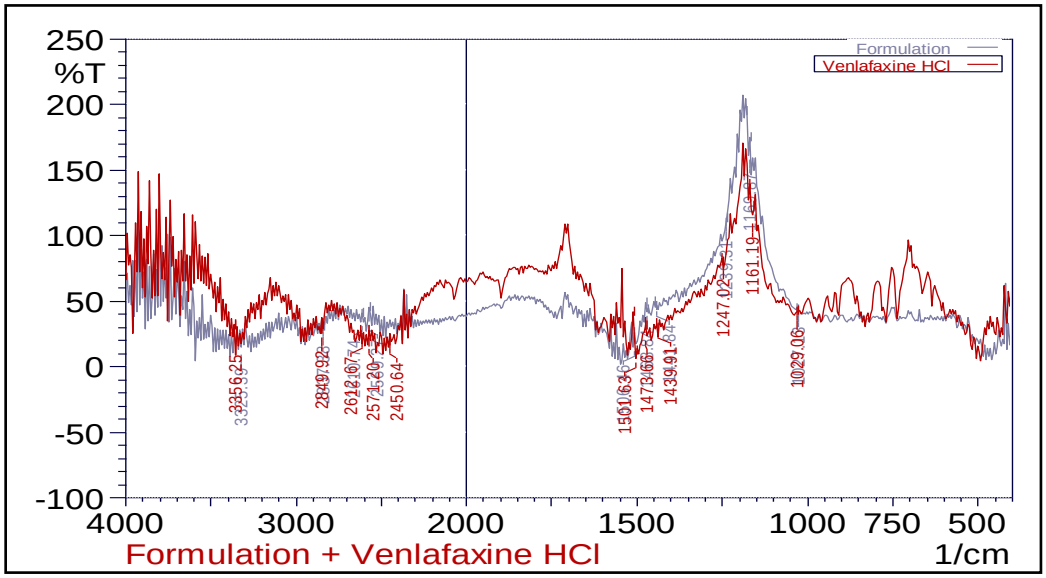

Figure 2: Overlay FTIR Spectrum of formulation and pure drug

Hardness

The hardness of tablets of different formulation (F1 to F9) was determined as per standard procedure. The average hardness of tablets was found to be 4.3 to 5.9 Kg/cm2.

Thickness of Tablets:

The average thickness of tablets (F1 to F9) determined and results are presented in Table 4. The maximum and minimum average thickness of tablet was found to 2.6 mm and 2.23 mm respectively.

Table 4: Evaluation of Physical parameter of factorial batches

Batches code	Thickness (mm)	Weight Variation	Friability (%)	Hardness (Kg/cm^2)	Drug content
F_1	2.23±0.010	151.5±0.22	0.17	5.3±0.13	100.17
F_2	2.43±0.035	152.1±0.25	0.24	4.8±0.13	99.20
F_3	2.6±0.010	149.1±0.49	0.17	4.3±0.33	99.37
F_4	2.56±0.035	152.1±0.71	0.31	5.6±0.05	100.38
F_5	2.51±0.042	147.1±0.49	0.36	4.9±0.10	100.01
F_6	2.44±0.030	153.1±0.71	0.42	4.7±0.10	101.19
F_7	2.56±0.010	153.1±0.31	0.08	5.9±0.10	100.38
F_8	2.34±0.035	148.1±0.49	0.26	5.6±0.10	99.02
F_9	2.6±0.030	154.2±0.31	0.08	4.6±0.90	99.38

Content uniformity:

The content uniformity of the entire tablet (F1 to F9) was evaluated and the results are presented in Table 4. The maximum percentage of drug content from the different formulations was found to be 101.19 and minimum percentage of drug content was found to be 99.02%. Hence it is concluded that all the formulations are falling within the pharmacopoeia limits.

Surface pH:

The prepared formulations were subjected to surface pH measurement. Tablets of all formulation showed a surface pH values in range of 5.8±0.07 to 6.34±0.14 that indicates no risk of mucosa damage or irritation.

Mucoadhesion strength

Bioadhesion strength depends on molecular weight and swelling behavior of the polymers and contact time with mucus. The bilayered tablets containing higher proportions of Carbopol showed good bioadhesion strength. Bioadhesion characteristics were found to be affected by the nature and proportion of bioadhesive polymers used. As the concentration of Carbopol increased the bioadhesive strength was also increased, the reason for such findings might be ionization of Carbopol at salivary pH, which leads to the formation of secondary bioadhesion bonds with mucin and interpenetration of the polymer chains in the interfacial region. The highest

Mucoadhesion strength was observed with formulation F_7 containing higher amount of carbopol as shown in Table 5

Table 5: Evaluation Parameters for factorial Batches

Formulation code	Mucoadhesion strength (gm)	Surface pH	*Ex vivo* residence time(hr)
F_1	26.12±0.14	5.8±0.07	7.30
F_2	25.69±0.6	5.9±0.07	6.35
F_3	24.36±0.07	6.15±0.6	6.24
F_4	28.16±0.19	6.13±0.06	>8
F_5	27.89±0.6	6.34±0.14	>8
F_6	26.56±0.06	5.9±0.24	>8
F_7	31.11±0.14	6.12±0.16	>8
F_8	30.32±0.07	6.25±0.19	>8
F_9	29.96±0.09	6.13±0.6	>8

Surface pH

The prepared formulations were subjected to surface pH measurement. Tablets of all formulation showed a surface pH values in range of 5.8±0.07 to 6.34±0.14 (Table 5) that indicates no risk of mucosal damage or irritation.

Ex vivo residence time

Ex vivo residence time of tested tablets shown in Table 5. The difference could be due to the combination of various amounts of polymers that might have affected mucoadhesion. In fact with bilayered tablets containing higher proportion of Carbopol, mucoadhesion time was found to be increased. This is because of the high mucoadhesive nature of the Carbopol and inter-penetration of polymeric chains in to the mucus membrane.

Swelling index

The swelling index was determined for prepared tablets, swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration as shown in table 6 and figure 3. The swelling ratio of tablet increased with increasing amount of carbopol, the maximum swelling was seen in formulation F_7 containing higher amount of carbopol.

Table 6: Swelling index of factorial batches

Time (hr)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1	15.17	15.06	14.69	16.66	12.43	16.18	19.07	16.47	14.72
2	20.68	18.49	16.33	25	19.21	21.25	29.60	27.06	30.06
4	29.65	28.77	28.12	38.11	27.12	31.25	44.73	40	31.29
6	38.62	31.50	31.11	46.52	36.15	39.38	57.89	51.76	44.78
8	44.83	38.35	37.89	50.69	46.89	45	77.63	65.88	56.44

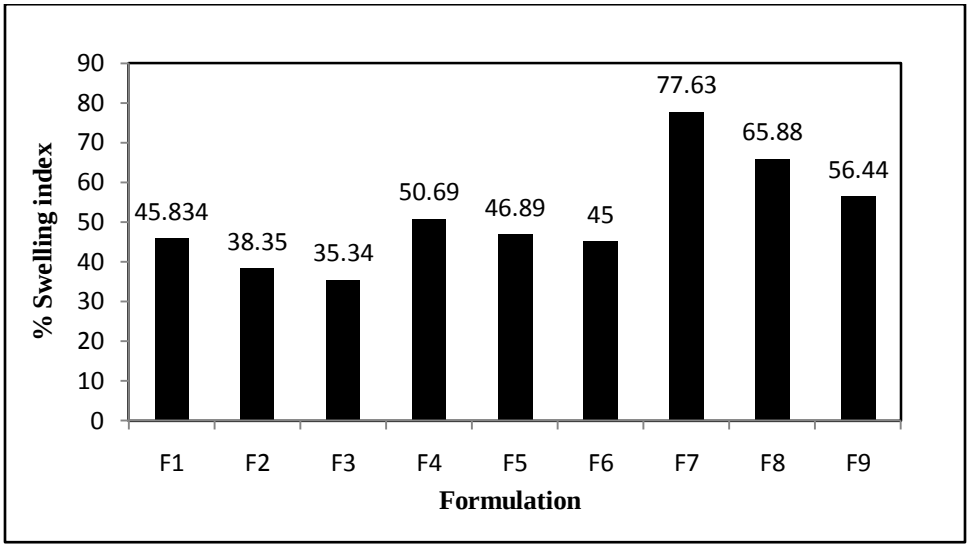

Figure 3: Swelling index of factorial batches F_1-F_9

Table 7: *In vitro* Dissolution Data of factorial Batches

Time (hr)	CPR								
	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
1.00	39.08	29.95	28.13	37.34	39.04	33.19	38.31	36.53	32.87
2.00	55.40	40.85	39.04	50.87	55.60	47.38	59.16	51.30	47.21
3.00	67.17	59.22	55.59	59.72	63.31	56.79	68.87	62.68	58.20
4.00	75.37	67.99	67.26	67.48	70.77	64.75	76.33	70.76	67.14
5.00	82.21	74.86	74.79	75.09	78.78	74.82	85.79	77.59	75.05
6.00	85.76	81.18	82.21	84.59	81.84	80.53	90.92	81.49	79.61
7.00	91.01	84.08	85.21	92.25	86.11	86.96	93.25	90.26	84.84
8.00	95.03	89.65	87.73	99.31	89.97	90.09	97.59	93.64	94.68

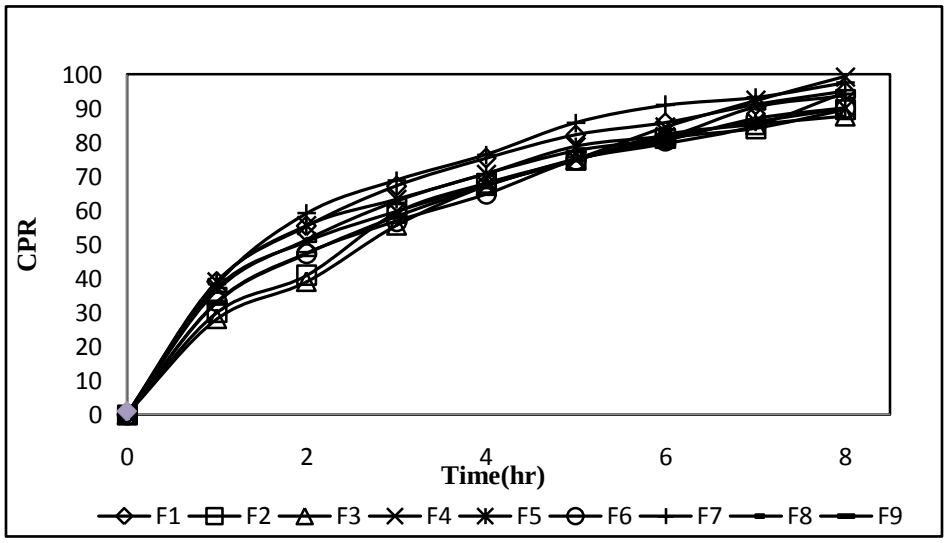

Figure 4: Comparative dissolution profile of factorial batches F_1-F_9

***In vitro* dissolution study**

Release of drug from the buccal mucoadhesive tablets varied according to the type and ratio of matrix-forming polymer. Carbopol 934P has excellent mucoadhesive, gelling properties and also helps in sustaining effect. Carbopol is more hydrophilic. It can swell rapidly, therefore decrease of carbopol content delays the drug release from tablet core. The maximum cumulative percent of drug release i.e. 99.31% from formulation F4 (Table7) could be attributed to the presence of considerable amount of carbopol which will ionizes at pH environment of the dissolution medium. Ionization of Carbopol 934P leads to the development of negative charges along the backbone of the polymer. Repulsion of like charges uncoils the polymer into an extended structure. The counter ion diffusion inside the gel creates an additional osmotic pressure difference across the gel leading to the considerable swelling of the polymer. The continued swelling of polymer matrix causes the drug to diffuse out from the formulation at a faster rate. The higher the uptake of water by polymer, the more the amount of drug diffused out from the polymer matrix. F9 formulation contain higher amount of carbopol having lower drug release due the higher amount of HPMCK4M which retard the drug release due the formation of complex polymeric matrix as shown in figure 4.

Statistical Analysis

A statistical model incorporating interactive and poly nominal terms was used to evaluate the responses.

$$\mathbf{Y= b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2}$$

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high values. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed.. The dissolution profile for 9 batches showed a variation at 8 hr ranging from 87.73 % to 99.31% as shown in Table 8. The fitted equations (full and reduced) relating the responses, Q_8, mucoadhesive strength, swelling index, diffusion coefficient(n) and release rate constant (K) to the transformed factor are shown in the Table 9.

The polynomial equations can be used to draw conclusions after considering the magnitude of coefficient and the mathematical sign it carries (i.e., negative or positive). Table 10 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. The high values of correlation coefficient for all variables (Table 10) indicate a good fit, i.e., good agreement between the dependent and independent variables.

Table 8: Result of dependent variables of factorial design batches

Batch Code	Variable Levels in Coded Form		Q_8	Mucoadhesive strength(gm)	Swelling index (%)	n	k
	X_1	X_2					
F1	-1	-1	95.03	26.12±0.14	44.83	0.409	0.415
F2	-1	0	89.65	25.69±0.6	38.35	0.417	0.391
F3	-1	1	87.73	24.36±0.07	37.89	0.488	0.324
F4	0	-1	99.31	28.16±0.19	50.69	0.433	0.383
F5	0	0	89.97	27.89±0.6	46.89	0.417	0.391
F6	0	1	90.09	26.56±0.06	45	0.468	0.344
F7	1	-1	97.59	31.11±0.14	77.63	0.456	0.399
F8	1	0	93.64	30.32±0.07	65.88	0.452	0.371

Table 9: Multiple Regression Analysis of dependent variables

Q_8						
Response	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{12}**	**b_{22}**
FM	91.133	2.25	-3.238	-0.07	1.0975	2.985
RM	93.0766	2.25	-3.23833	-	-	-
Mucoadhesive strength						
Response	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{12}**	**b_{22}**
FM	27.706	2.536667	-0.75167	0.39	0.1525	-0.255
RM	27.7966	2.536667	-0.75167	-	-	-
Swelling index						
Response	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{12}**	**b_{22}**
FM	46.3888	13.14667	-5.63667	5.976667	-3.5625	1.70666
RM	51.5111	13.1466	-5.63667	-	-	-
n						
Response(n)	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{12}**	**b_{22}**
FM	0.422	0.011333	0.022	0.01	-0.01525	0.026
RM	0.42866	0.011333	0.022	-	-0.01525	0.026
K						
Response(k)	**b_0**	**b_1**	**b_2**	**b_{11}**	**b_{12}**	**b_{22}**
FM	0.38344	-0.00267	-0.03083	0.001333	0.009	-0.01617
RM	0.37844	-	-0.02217	-	-	-

Table 10: Result of two ways ANOVA for measured response.

Q_8							
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	**Fcalc.**	**F_{Crit} DF(3,3)**
FM	5	115.9441	23.18882	7.830085	0.928826	2.54	9.276
RM	2	93.29582	46.64791	8.876078	0.747391		
Error							
FM	3	8.884508	2.961503				
RM	6	31.53278	5.255464				

Mucoadhesive strength							
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	**Fcalc.**	**F_{Crit} DF(3,3)**
FM	5	42.52536	8.505072	110.9156	0.9946	2.2920	9.276
RM	2	41.99808	20.99904	166.3693	0.9822		
Error							
FM	3	0.230042	0.076681				
RM	6	0.757317	20.99904				
Swelling index							
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	**Fcalc.**	**F_{Crit} DF(3,3)**
FM	5	1355.673	271.1347	32.41658	0.981827	5.10	9.276
RM	2	1227.641	613.8206	24.05185	0.889102		
Error							
FM	3	25.09222	8.364073				
RM	6	153.1244	25.52073				
n							
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	**Fcalc.**	**F_{Crit} DF(1,3)**
FM	5	0.006157	0.001231	15.98622	0.963825	2.85	10.127
RM	4	0.005957	0.001489	13.81848	0.932517		
Error							
FM	3	0.000231	0.00007				
RM	4	0.000431	0.000108				
k							
Regression	**DF**	**SS**	**MS**	**F**	**R^2**	**Fcalc**	**F_{Crit} DF(4,3)**
FM	**5**	**0.006597**	**0.001319**	**5.863134**	**0.907166**	**1.176**	9.117
RM	**1**	**0.002948**	**0.002948**	**11.9011**	**0.629651**		
Error							
FM	**3**	**0.000675**	**0.000225**				
RM	**7**	**0.001734**	**0.000248**				

Full and Reduced Model for Q_8

The critical value of F for $\alpha = 0.05$ is equal to 9.276 (df = 3, 3). Since the calculated value (F = 2.54) is less than critical value, it may be concluded that the interaction term b_{11}, b_{12} and b_{22} do not contribute significantly to the prediction of Q_8 and can be omitted from the full model to generate the reduced model.

Full model:

$91.13333 + 2.25X_1 - 3.23833X_2 + 1.0975X_1X_2 - 0.07\ X_1^2 + 2.985X_2^2$

Reduced model:

$93.07667 + 2.25X_1 - 3.23833X_2$

Full and Reduced Model for mucoadhesive strength

The critical value of F for α = 0.05 is equal to 9.276 (df = 3, 3). Since the calculated value (F = 2.292) is less than critical value, it may be concluded that the interaction term b_{11}, b_{12} and b_{22} do not contribute significantly to the prediction of mucoadhesive strength and can be omitted from the full model to generate the reduced model.

Full model:

$27.70667+ 2.5366X_1 -0.75167X_2+ 0.1525X_1X_2 +0.39X_1^2 -0.255X_2^2$

Reduced model:

$27.79667+ 2.536667X_1 -0.75167X_2$

Full and Reduced Model for Swelling index

The critical value of F for α = 0.05 is equal to 9.276 (df = 3, 3). Since the calculated value (F = 5.10) is less than critical value, it may be concluded that the interaction term b_{11}, b_{12} and b_{22} do not contribute significantly to the prediction of swelling index and can be omitted from the full model to generate the reduced model.

Full model:

$46.38889+ 13.14667X_1 -5.63667X_2-3.5625X_1X_{2+} 5.9766X_1^2+ 1.70X_2^2$

Reduced model:

$51.11+13.143X_1-5.636X_2$

Full and Reduced Model for Diffusion Coefficient (n)

The critical value of F for α = 0.05 is equal to 10.127 (df = 1, 3). Since the calculated value (F = 2.85) is less than critical value, it may be concluded that the interaction term b_{11} do not contribute significantly to the prediction of diffusion coefficient (n) and can be omitted from the full model to generate the reduced model.

Full model:

$0.422+ 0.011333X_1 + 0.022X_2-0.015X_1X_{2+} 0.01X_1^2+ 0.026X_2^2$

Reduced model:

$0.4286+0.01133X_1+0.022X_2-0.01525X_1X_2+0.026X^2$

Full and Reduced Model for Release Rate Constant (K)

The critical value of F for α = 0.05 is equal to 9.117 (df = 4, 3). Since the calculated value (F = 1.176) is less than critical value, it may be concluded that the interaction term b_{11} do not contribute significantly to the prediction of release rate constant (K) and can be omitted from the full model to generate the reduced model.

Full model:

$0.3834 -0.00267X_1 -0.0308X2+0.009X1X2+0.0013X_1^2-0.0161X_2^2$

Reduced model:

$0.378444-0.02217X_2$

Kinetic modeling of dissolution data

The kinetics of the dissolution data were well fitted to zero order, Higuchi model and Krossmayer-Peppas model as evident from regression coefficients (Table11). In case of the controlled release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms. Formulation containing swelling polymers show swelling as well as diffusion mechanism because the kinetic of swelling include relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to rubbery state. The value of diffusion exponent n for most factorial formulations is between 0.4097-0.4887 (Table 11) indicating Fickian drug release from the formulations.

Table 11:Kinetic treatment of dissolution data

	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Zero order									
B	8.270	7.759	8.934	9.0115	7.7593	8.6261	8.9121	8.5964	8.800
A	35.695	34.445	24.555	29.746	34.445	27.264	34.804	30.848	27.12
R^2	0.9675	0.9596	0.975	0.9947	0.9596	0.9844	0.9564	0.9765	0.985
First order									
B	0.0587	0.0587	0.0729	0.0647	0.0587	0.0682	0.0639	0.0649	0.069
A	1.5763	1.5544	1.4496	1.5290	1.5544	1.4837	1.5606	1.5235	1.483
R^2	0.9270	0.9084	0.9465	0.9643	0.9084	0.9445	0.9037	0.9300	0.943
Higuchi									
B	11.371	11.313	-0.773	4.8290	11.313	2.6951	8.1391	5.9321	2.126
A	30.610	28.884	32.566	32.515	28.884	31.503	33.226	31.623	32.10
R^2	0.9949	0.9921	0.9914	0.9971	0.9924	0.9988	0.9906	0.9980	0.998
Korsmeyer and Peppas									
k	0.4155	0.3916	0.3248	0.3839	0.3916	0.3440	0.3996	0.3719	0.344
n	0.4097	0.4177	0.4887	0.4339	0.4177	0.456	0.452	0.4523	0.474
R^2	0.9968	0.9963	0.9776	0.9959	0.9963	0.9987	0.9945	0.9991	0.998

B = slope, A= intercept, R^2= Square of correlation coefficient, n= diffusion exponent

***Ex vivo* drug release of optimise batch F4**

Formulation F4 containing Carbopol-934P and HPMCK4M showed good mucoadhesive strength, a convenient residence time as well as promising drug release pattern.

On the basis of above result formulation F4 was optimised and subjected to ex vivo permeation study. The result of drug permeation from the buccal tablet through goat buccal mucosa shown in table 12. The drug permeation was slow and steady (Figure 5) and 91.97% of Venlafaxine HCL could permeate through the buccal membrane in 8 hr.

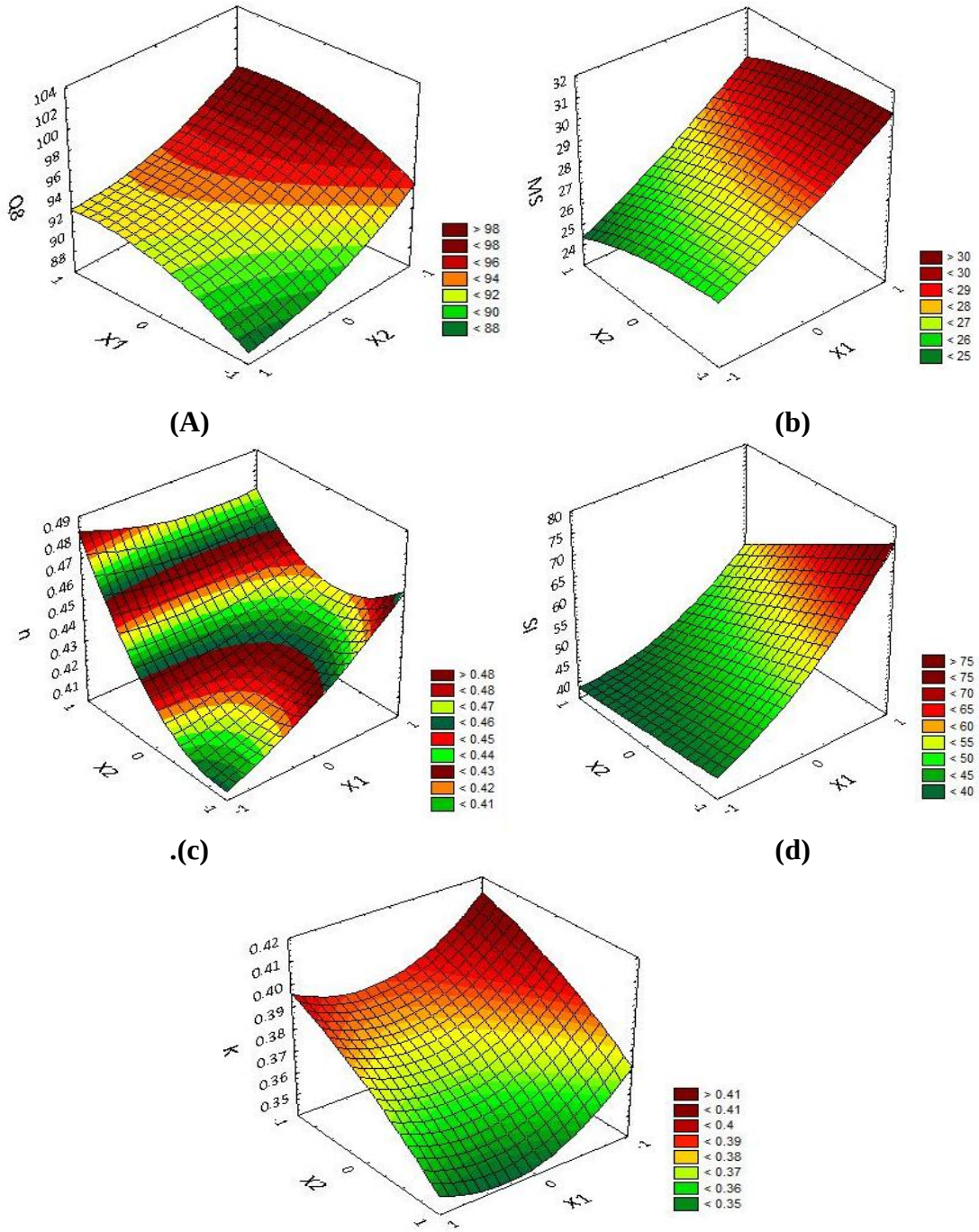

Figure 5: Surface response plot to depict the total polymer concentration (X1) and polymer ratio (X2) on (a) Q_8 (b) mucoadhesive strength (c) Swelling index (d) Diffusion Coefficient (n) (e) Release Rate Constant (K)

Table 12: *Ex vivo* drug release of optimize batch F4

Time(hr)	CPR
0	0
1	29.38
2	43.45
3	56.41
4	64.05
5	69.18
6	75.76
7	83.56
8	91.97

Stability Study

The samples of optimized batch (F4) were kept in accelerated condition (40˚ ± 2˚C/75% ± 5% RH) for one month. Then samples were analyzed for physical evaluation, assay and dissolution. The results are given in table 13 and 14.

Table 13: *In vitro* Dissolution Data of Batch F4 after Accelerated Stability Study

Time (hr)	CPR (Initial)	CPR (After storage at 40^{o} C for 1month)
0	0	0
1	37.34	40.09
2	50.87	52.6
3	59.72	60.24
4	67.48	70.86
5	75.09	78.56
6	84.59	86.44
7	92.25	92.78
8	99.31	96.66

Table 14: Physical evaluation and assay of samples drawn from stability study

Parameters	Zero time	After 1 month
Assay (%)	100.38	99..81
Friability (%)	0.31	0.41
Hardness (kg/cm^2)	5.6±0.05	5.4±0.09

The results showed that there was no change in physicochemical parameter of tablets. Drug content and Friability were found in acceptable limit, and similar drug release profile (figure 6). Hence the prepared mucoadhesive buccal tablets of Venlafaxine HCL were found stable at 40˚C/75% RH.

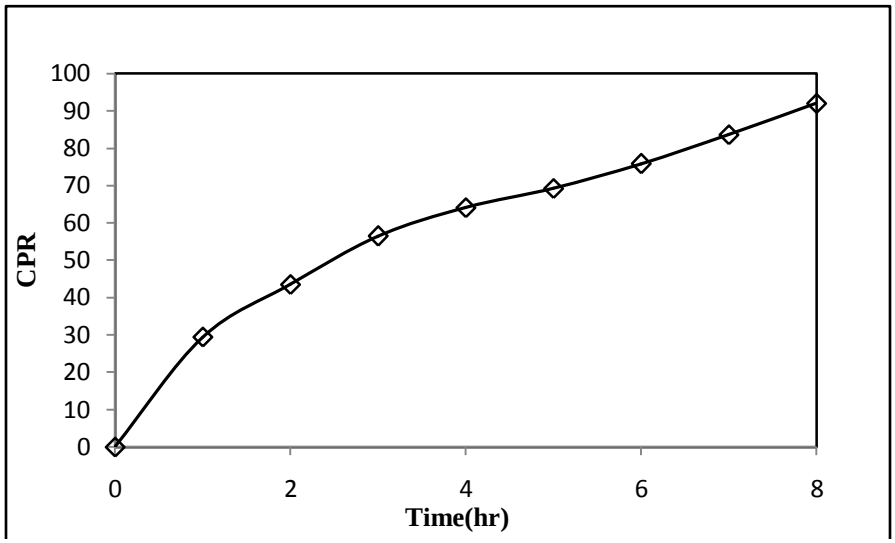

Figure 6 *Ex vivo* drug release of optimize batch F_4

CONCLUSION

The prepared mucoadhesive buccal tablets of Venlafaxine HCL can help bypass extensive hepatic first-pass metabolism and improve bioavailability. The buccal bilayer tablets showed a mucoadhesion time of more than 8 h. Similarly, *in-vitro* permeation studies showed 99.31% drug release of the sustained dosage form. It can be concluded that formulation F4 could be used to release the drug unidirectionally in buccal cavity without the risk of mucosal irritation.

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