DEVELOPMENT AND EVALAUATION OF FROVATRIPTAN BIOADHESIVE FILMS

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ABSTRACT

Formulation development for new drugs, an extension of formulations, finding an alternative to conventional dosage forms for better therapeutic response are some of the research impetus in Pharmaceutical F and D. The new -untried routes of administration are also an avenue that can be explored. Under this research frovatriptan, an antimigraine, BCS class II drug is formulated into mucoadhesive films. Frovatriptan shows 40 to 50% oral bioavailability owing to its low solubility and degradation in GIT. Mucoadhesive films can be an effective formulation for this drug owing to its good permeability. Direct absorption in blood and preventing GIT degradation by mucoadhesion on buccal mucosa can be two rationales stated for the improvement of bioavailability of frovatriptan *via* mucoadhesive films. Migraine strikes as abrupt and disturbing health situation and needs immediate treatment. Thus, the mucoadhesive film can be more promising than oral tablets for frovatriptan in the treatment of migraine. Blank mucoadhesive films were prepared using various combinations of. HPMC K15, Eudragit L 100, whereas concentrations of chitosan, PVA, beta-cyclodextrin, Na CMC were selected from the literature survey. Later 2.5 mg per 2 × 2 cm^2 drug-loaded formulations were developed and optimized. Factorial design of 3^2 models suggested F1 be optimized batch. Evaluation of films for mechanical and drug release studies along with stability study suggested that mucoadhesive films can be a successful formulation for frovatriptan for the management of migraine. Such formulation can have commercial applications, too, as no such formulation is yet available.

Keywords: Mucoadhesive films, Frovatriptan, Migraine, HPMC K15, Beta-cyclodextrin, Eudragit L 100, Chitosan

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INTRODUCTION: During the last few years, mucoadhesive systems have become promising drug delivery systems, rendering effective and safe treatment in topical disorders as well as systemic problems. The lack of efficacy of certain drugs is due to various reasons like low bioavailability, unpredictable and erratic absorption, GI intolerance, or pre-systemic elimination due to the selected route of administration.

The oral mucosa has many properties, which makes it an attractive site for drug delivery but also poses several challenges for researchers leading to investigating novel delivery techniques to overcome these challenges. Mucoadhesive buccal films share a number of unique advantages like tiny thickness, ease of application, direct systemic absorption followed by a sustained effect, local as well as systemic effects [1].

Due to the versatility of the manufacturing processes, the release from mucoadhesive films can be oriented either towards the buccal mucosa or towards the oral cavity; in the latter case, it can provide controlled release of the drug via gastrointestinal (GI) tract administration or absorption in blood *via* mucosa.

As buccal mucosa is highly permeable and usually rich in blood supply, it allows provides rapid uptake of drugs in the systemic circulation, leading to the quick onset of action and, in most cases, avoids degradation by first-pass hepatic metabolism hence leading to higher bioavailability [2]. Frovatriptan is a serotonin (5-HT1) agonist used for the treatment of migraine. Its absolute oral bioavailability is about 40 to 50%, the half-life is 2.5 to 3 h, and it undergoes hepatic metabolism. So, in order to tackle these challenges and improve the bioavailability and efficacy, under this research buccal patch of frovatriptan was developed.

Presently frovatriptan is available in the market in the form of a conventional oral tablet (2.5 mg, 5 mg), mouth dissolving tablet (2.5 mg), and nasal spray (5 mg). It has been investigated earlier that the nasal route has its limitations, such as rapid mucociliary clearance and low permeability of the nasal mucosa to the drugs [3]. The aim of this work was to develop and evaluate the Frovatriptan mucoadhesive patch that will initially demonstrate fast release and later prolonged release of the drug, satisfying the need for an anti-migraine effect. This was achieved using different mucoadhesive polymers and drug release modifiers.

MATERIALS AND METHODS: Frovatriptan was obtained as a gift sample from Ajanta Ltd. (Paithan, Maharashtra, India). HPMC K15 and Eudragit L100, chitosan, B-cyclodextrin, propylene glycol (PG), polyvinyl alcohol (PVA) were obtained commercially from Research-Lab Fine Chem (Mumbai). Na CMC, Acetone, and Alcohol were purchased from Analab, Mumbai [4].

Preformulation Study: Pre-formulation studies to generate supportive data were performed to understand the physicochemical behavior of a drug and the necessary modifications needed to design, develop, and evaluate dosage forms. The preformulation studies performed were

1. U.V. spectroscopy of frovatriptan
2. DSC
3. Excipient compatibility with the drug by using FTIR. Results are discussed in result and discussion.

Formulation Development: Frovatriptan mucoadhesive films were prepared by solvent casting method. The drug is soluble in the ethanol so, the formulation of the film was made in ethanol as main solvent along with acetone as co-solvent. It produced thin and clear blank as well as drug-loaded films.

Formulation of Blank Films: As per the literature survey it was found that in the development of mucoadhesive films various polymers like chitosan, ethylcellulose, beta cyclodextrin, polyvinyl alcohol, Na CMC and plasticizer as propylene glycol, are used in concentrations range mentioned below. With this reference, the blank films were prepared using film formers and excipients at concentrations mentioned in **Table 1**. The two polymers HPMC K15 as major mucoadhesive polymer and Eudragit as controlled release polymer were varied in order to get the optimized mucoadhesive and controlled release drug release behavior from the film. The polymeric mixture was prepared in 10 ml of the solvent mixture of ethanol and acetone (10:8). Polymers were mixed in this solvent mixture with constant stirring on magnetic stirrer.

TABLE 1: COMPOSITION OF BLANK FILMS EXCEPT, HPMC K15 AND EUDRAGIT L-100

Name of excipient	All quantities are in mg for 2 × 2 cm patch
Chitosan	10
Ethylcellulose	50
Beta cyclodextrin	08
Propylene glycol	0.05
Polyvinyl alcohol	08
Na CMC	30
Aspartame	02
Acetone	08
Ethanol	10

Formulation of Drug Loaded Films: 3^2 factorial design is used in order to optimize quantities of HPMC K15 and Eudragit L-100.

Procedure Followed for Drug Loaded Films: 2.5 mg drug was dissolved in 5 ml ethanol and was lowly added in the polymeric solution (made using a remaining quantity of ethanol and acetone and all polymers) for the uniform distribution. This mixture was stirred using a magnetic stirrer for the net 6 h. The beaker was sealed using aluminum foil to avoid evaporation. Weight was made up of for the lost solvent using a vehicle mixture of ethanol and acetone. The casting mixture containing drug was poured in the mould and kept at the room temperature overnight for evaporation of casting solvent. The dried film was removed from the mould carefully and kept in the in the desiccator for the further drying. The thickness of film was found to be between the 0.04 mm to 0.06 mm (average of 10 film thickness for a fixed size mould).

The loading of the drug was optimized at the 2.5mg/cm^2 of the film formulation. The films were removed easily from the moulds as the mould had Teflon coating. The films were further cut to the required size [5].

TABLE 2: COMPOSITION OF FROVATRIPTAN MUCOADHESIVE BUCCAL PATCHES

Name of excipient	F1	F2	F3	F4	F5	F6	F7	F8	F9
HPMC K15	130	130	130	150	150	150	170	170	170
Eudragit L-100	70	80	90	70	80	90	70	80	90
Chitosan	10	10	10	10	10	10	10	10	10
Ethyl cellulose	50	50	50	50	50	50	50	50	50
β-cyclodextrin	08	08	08	08	08	08	08	08	08
Propylene glycol	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Polyvinyl alcohol	08	08	08	08	08	08	08	08	08
Na CMC	30	30	30	30	30	30	30	30	30
Aspartame	02	02	02	02	02	02	02	02	02
Acetone	08	08	08	08	08	08	08	08	08
Ethanol	10	10	10	10	10	10	10	10	10
Frovatriptan	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

* All quantities are in mg for 2 × 2 cm patch

Optimization of the Drug Loaded film Formulation:

Factorial Design: A two factor & three levels (3^2) full factorial design was opted for the optimization of the quantities of HPMCK15 and Eudragit L100. A factorial design is an efficient method of finding the relative significance of a number of variables and there interaction on the response or outcome of the study. A two factor and three levels (3^2) full factorial designs was used and nine experimental runs were performed. Statistical models with interaction terms were derived to evaluate the influence of HPMC K15 (X_1) and Eudragit L100 (X_2) on mucoadhesion and drug release shown as independent variables. The mucoadhesion (Y_1), Percentage cumulative drug release (Y_2) selected as the dependent variables. The coding was +1, 0, and −1, respectively, for higher, middle, and lower levels of HPMC K15 and Eudragit L100.

TABLE 3: INDEPENDENT VARIABLES AND LEVELS USED FOR FACTORIAL DESIGN

Independent variable factor	Level used		
HPMC K15	130 (-1)	150 (0)	170 (+1)
Eudragit L100	70 (-1)	80 (0)	90 (+1)

TABLE 4: FACTORIAL DESIGN

STD	Run	Factor 1 A: HPMCK15	Factor 2 B: Eudragit	Response 1 Mucoadhesion (N)	Response 2 Drug Release (%)
4	1	-1	0	57.22	83.20
1	2	-1	-1	56.35	85.15
6	3	1	0	64.32	78.70

2	4	0	-1	61.20	83.35
9	5	1	1	66.85	73.45
3	6	1	-1	66.45	81.00
7	7	-1	1	56.00	81.24
8	8	0	1	61.25	78.65
5	9	0	0	60	80.75

Evaluation of Drug Loaded Films: The prepared buccal films were evaluated for the following properties like weight uniformity, thickness, folding endurance, surface pH, swelling index, *in-vitro* residence time, tensile strength, drug content, *in-vitro* drug release study and stability study [6, 7].

Thickness: Three films of each formulation were taken, and the film thickness was measured using (Aerospace-0-150 Digital Caliper) at three different places, and the mean value was calculated. The average of such 10 reading was obtained as the average thickness of the films.

Surface pH of Films: [8, 9] The film to be tested was placed in petri dish and moistened with 0.5ml of distilled water and kept for 30 sec. The pH was noted by using an electrode, which was directly placed on the film surface that displayed the pH. The average of three readings was obtained for each formulation.

Folding Endurance: [10] Three films of each formulation of size (2 × 2 cm) were cut by using sharp blade. Folding endurance was measured by folding a small portion of the film at the same place till it broke. The count of the film folding at the same place without a break at folded line was considered as the value of folding endurance.

Percent Swelling: **[11]** For determination of percent swelling, the film was allowed to swell on the surface of agar plate and was kept in an incubator maintained at 37 °C. The original film weight of the sample was noted and an increase in the weight of the patches (n=3) was determined at time interval of 1 h (1-5 h).

The percent swelling, % S, was calculated after 5 h of swelling time using the following equation:

$\% S = X_1\text{-}X_0 \times 100 / X_r$

Where, X_r is the weight of the swollen patch after time t, and Xo is the dry weight at zero time.

Drug Content Uniformity: [12] The percentage of drug content was determined by UV spectrophotometer at 222 nm (Jasco V-630, Japan) using the standard calibration curve of frovatriptan in methanol. The procedure was repeated for three patches of each formulation. The results are shown in **Table 4**. As the drug content values of the same formulation did not show a significant difference, it can be concluded that the drug was uniformly dispersed in the buccal patches.

***In-vitro* Dissolution:** **[13]** *In-vitro* release study was carried out by using the USP Type-II dissolution apparatus. One film of each formulation was fixed to the central shaft of the paddle using a cyanoacrylate adhesive. 250 ml of phosphate buffer, pH 6.8, was used as a dissolution medium. The rotation speed was 50 rpm at 37 °C. The drug release was analyzed spectrophotometrically at 222 nm.

Tensile Strength: [14] The films of size 20 × 40 mm dimensions were taken and fixed in the fixed jaw and movable jaw of the tensile strength apparatus. Stress was applied to the films with a movable jaw. Force at which the film broke was calculated as the tensile strength using the formula:

F = M * A

F = M * 9.8

F = Force, M= mass of water, A= acceleration due to gravity.

The maximum increase in the length of the film during the applied load was measured as the percent elongation of the film.

Mucoadhesive Strength: [15] Mucoadhesion tester was designed and fabricated as the second part of this project. The apparatus is shown in **Fig. 1**.

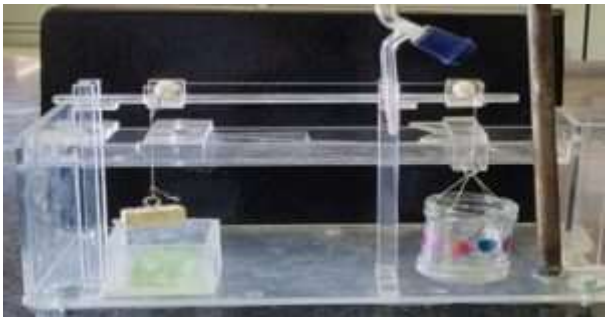

FIG. 1A: SIDE VIEW OF MUCOADHESION TESTER

FIG. 1B: TOP VIEW OF MUCOADHESION TESTER

The porcine buccal mucosal membrane was used for the determination of mucoadhesive strength. The fresh porcine mucosal membrane was purchased from the local slaughterhouse and was washed using the isotonic phosphate buffer pH 6.8. The piece of the fresh membrane was glued to support (glass block) with the cyanoacrylate adhesive in mucoadhesion tester.

The glass block was lowered into the container, which was filled with isotonic buffer pH 6.8 maintained at 37 ± 1 °C, such that the buffer just reaches the surface of the mucosal membrane to keep it moist. This block was put below the left-hand side of the assembly.

The test film was glued with the adhesive to this block. The rubber block was lowered along with the film over the mucosa with the weight. The attachment of the film to the mucosal membrane was kept in this position for 3 min, and then slowly, water was added to the container on the right-hand side by using a burette. The force of detachment of the two surfaces was obtained. The weight of the water was measured. The mucoadhesive strength of the film was obtained using the following formula

$F = M * A$

$F = M * 9.8$

F = Force, M = mass of water, A = acceleration due to gravity.

Three films were tested on each mucosal membrane. After each measurement, the tissues were thoroughly but gently washed with the phosphate buffer (pH 6.8) and left in it for 5 min before the experiment. Three readings were obtained for each batch of the film. The fresh membrane was used for each batch of the film.

Stability Testing For Humid Conditions: [16] (Exposing films in an open container at room temperature and normal uncontrolled humidity)

The films were exposed in the open container to observe the effect of room temperature and normal uncontrolled humidity conditions. The change in the appearance of the films was observed for 1 month.

Stability Studies: During the stability studies, the product was exposed to accelerated conditions of temperature and humidity. Ten films from optimized batch were packed in aluminum wrapping foil and were subjected to the stability for one month as per the ICH guidelines. Stability conditions used were: t 25-30 °C-75 % RH, >30 °C -65% RH and 40 °C - 75% RH.

RESULTS AND DISCUSSION:

Preparation of Standard Calibration Curve of Frovatriptan: 10 mg of frovatriptan was weighed accurately and dissolved in pH 6.8 buffer, and volume was made up to 100 ml with pH 6.8 phosphate buffer. This solution was treated as the stock solution, which was 100 µg/ml.

From this stock solution 0.1. 0.2, 0.4, 0.5 ml of aliquots were diluted up to 10 ml with pH 6.8 buffer to obtain concentrations of 1 to 5 µg/ml. The absorbance of these solutions was measured at 222 nm to get standard curve.

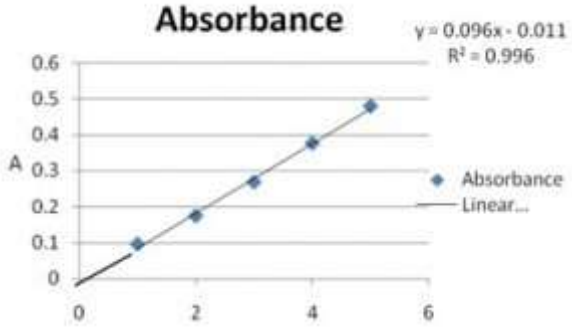

FIG. 2: CALIBRATION CURVE OF FROVATRIPTAN

Here, Y = 0.1008x + 0.0277 and R^2 = 0.9994

Where, Y = Absorbance, m = slope, x = Concentration, C = Constant, R^2 = coefficient of correlation.

TABLE 5: CALIBRATION CURVE OF FROVATRIPTAN

Conc. ppm	Absorbance
1	0.0959
2	0.1743
3	0.2681
4	0.3758
5	0.4789

FTIR Spectroscopy: The FTIR spectrum is shown in **Fig. 3** and **4,** along with interpretation. FTIR spectrum of frovatriptan showed all the peaks corresponding to the functional groups present in the structure of frovatriptan.

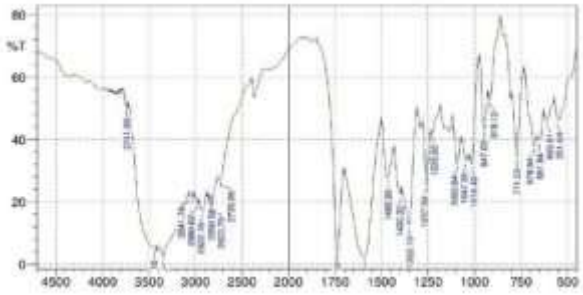

FIG. 3: FTIR OF FROVATRIPTAN

Fig. 3 shows an IR spectrum of the pure drug and physical mixture of formulations. The IR spectrum of the pure drug frovatriptan has indicated the presence of absorption peak due to the presence of N-H of the lactam, as well as secondary amine absorption, suggesting that these functionalities are present in the drug molecule. The aromatic and aliphatic C-H absorption is noticed from 2850 cm^{-1} to 3100 cm^{-1}. The characteristics O-C= O of the drug exhibited an absorption peak at 1750 $cm^{-1,}$ which is in cyclic form. These are the characteristics of the frovatriptan.

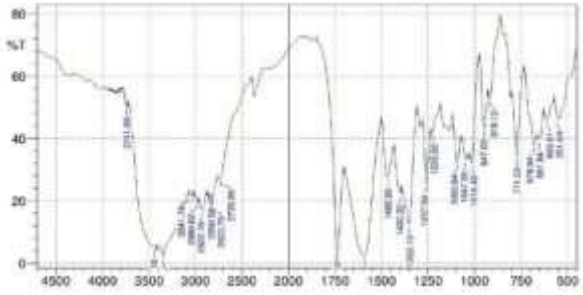

FIG. 4: FROVATRIPTAN WITH EXCIPIENTS

Fig. 4 shows FTIR spectra with excipients (HPMCK15, Chitosan, PVA). The IR spectra did not show any difference in wavelength from those obtained for frovatriptan, indicates that there was no interaction between excipients and frovatriptan.

Differential Scanning Calorimetry Studies: Differential scanning calorimetry studies indicated a sharp peak at 137.86 °C, corresponding to the melting of pure frovatriptan. It was concluded that the given sample of the drug was pure. The DSC thermograms confirmed that there is no interaction between drug and polymers, as shown in **Fig. 5.**

The enthalpy of fusion of frovatriptan was found to be 107.48j/g, which was close to the reported value. The DSC thermogram of formulation showed in **Fig. 6** has a characteristic sharp endothermic peak at 137.86 °C with an enthalpy value of 107.48j/g.

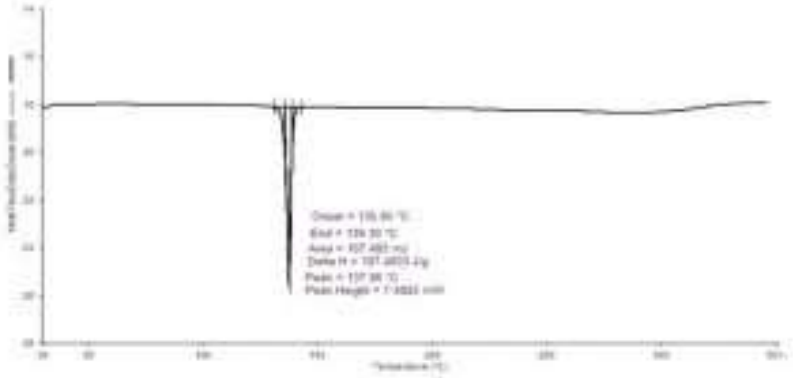

FIG. 5: DSC OF FROVATRIPTAN

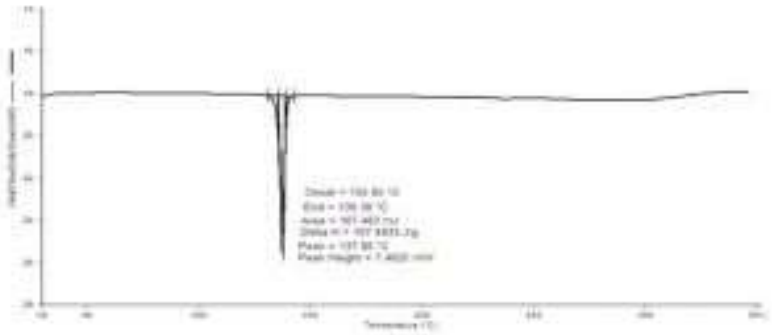

FIG. 6: DSC OF DRUG AND EXCIPIENTS

There was no significant change in the position of this peak in the thermograms of drug and excipients mixture. So, it can be concluded that the excipients and drugs do not interact with each other.

Evaluation of Frovatriptan Loaded Films:

TABLE 6: EVALUATION OF FROVATRIPTAN LOADED FILM

Formulation no.	Thickness	Folding endurance	Percentage swelling	pH	Weight mg	Mucoadhesive strength (N)	Tensile strength (kg/mm^2)	Drug assay
F1	0.1mm	210	89.25	7.4	100	56.24	5.0	92
F2	0.1mm	251	71.05	7.1	128	57.00	4.8	91
F3	0.2mm	270	94.00	6.5	115	56.23	5.2	95
F4	0.2mm	255	92.01	7.3	128	61.80	4.9	92
F5	0.1mm	210	86.20	7.1	109	60.12	5.6	88

F6	0.2mm	215	90.02	6.5	100	61.54	4.8	90
F7	0.2mm	250	90.05	6.5	112	66.35	4.2	92
F8	0.2mm	235	89.06	7.2	122	64.23	4.4	87
F9	0.1mm	205	91.00	6.8	125	66.50	5.6	86

The Drug Delivery System: Mucoadhesive films of frovatriptan were designed as a matrix. All the films showed a smooth surface and elegant texture.

Thickness: The thicknesses of the film was in between 0.1 and 0.2 mm. The thickness of the film directly affected the time of adhesion and swelling index. It also affects patient compliance in terms of comfort after mucoadhesion. The films were found uniform in weight and thickness.

Surface pH of Films: Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymer, the surface pH of the buccal films were determined. Attempts should be made to keep the surface pH as close to salivary pH as possible. The surface pH of all the films was within the range of 6.5 to 7.4. No significant difference was found in the surface pH of different films.

Folding Endurance: The folding endurance was measured manually, the film sample was folded repeatedly till it broke, and it was considered as the endpoint. Folding endurance was found to be in the range of 205 to 270 count of folds. The folding endurance was found to be highest for F3 and the lowest for F9 formulation.

Swelling Index: The comparative percentage swelling of various formulations was in order of F2 > F5 > F1 > F8 > F6 > F7 > F9 > F3. Percentage swelling was highest for F3 and the lowest for F2 formulation.

Eudragit L100 is freely soluble in water, which enhanced the water uptake capacity in the finished dosage form. The swelling behavior and *in-vitro* residence time of the mucoadhesive polymers were observed.

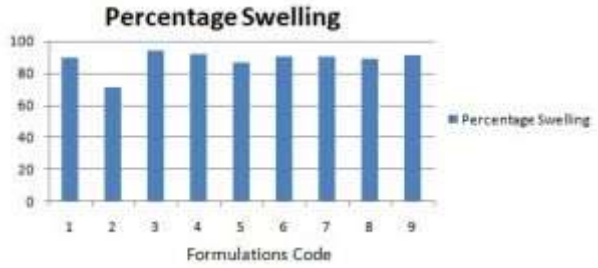

FIG. 7: COMPARATIVE SWELLING INDEX OF FORMULATION F1 TO F9

Drug Content (Assay): The drug content results are shown in **Table 6**. In all formulations, the drug was uniformly dispersed in the patches and content of drug was in the range of 86.45 to 95.20%.

Cumulative Drug Release: Fig. 8 shows the *in-vitro* drug release studies performed for F1 to F9 formulations by using pH 6.8 phosphate buffer as dissolution medium and measuring drug concen-tration UV spectrophotometrically at 222 nm. The studies were performed for 2 h (anticipated residence time of the mucoadhesive film in the buccal cavity).

TABLE 7: CUMULATIVE DRUG RELEASE

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
2	0.0072	0.0072	0.0072	0.072	0.072	0.072	0.072	0.07	0.075
5	32.62	32.8	32.62	35.75	33.18	29.51	28.23	30.03	25.12
10	39.65	37.03	36.85	36.91	40.13	39.91	37.02	35.21	30.21
15	57.42	45.17	44.89	57.45	45.21	48.08	44.08	46.09	35.25
20	59.84	53.67	53.49	59.87	53.69	53.51	50.28	53.12	43.38
30	65.36	56.03	58.49	62.41	56.37	55.87	54.20	56.45	50.46

45	66.51	62.19	65.03	63.41	61.15	56.93	61.05	60.41	56.84
60	74.15	69.89	72.22	77.22	70.13	63.22	68.30	67.58	63.45
90	80.15	76.46	79.85	78.15	71.75	70.75	75.21	74.54	68.10
120	85.74	83.28	81.85	83.84	80.84	78.54	81.08	78.65	73.06

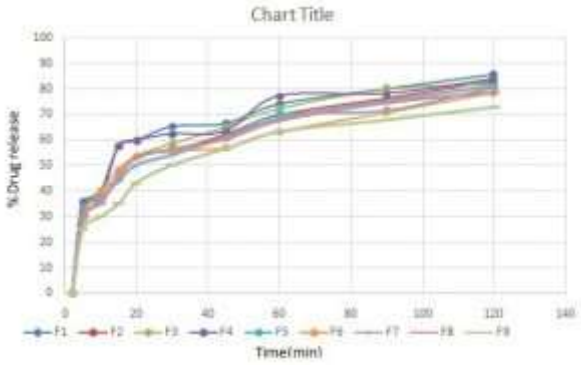

FIG. 8: FROVATRIPTAN % DRUG RELEASE

Fig. 8 are graphs of the percent cumulative drug release and time. The release study was performed using the Franz cell diffusion apparatus. F9 and F8 showed slower drug release.

The concentration of Eudragit L100 is responsible for variation in the drug release rate. The higher the concentration of Eudragit L100 lower is the rate of drug release, so can help in sustained drug release.

Tensile Strengths: The tensile strength of films were in the order of F7>F8>F6>F2>F4>F1>F5>F9. Among all the films studied, F9 showed the highest tensile strength, and F7 showed the lowest tensile strength. This must be due to the hydrogen bonding between drug-polymer and polymer-polymer molecules. The tensile strength of films is in the range of 4.2 to 5.6 Kg/cm^2.

Mucoadhesion of Films: Mucoadhesion is dependent on the amount of HPMC K15 present in the formulation. HPMC K15 helped to improve the adhesion between the mucin and film by hydrogen bonding. In this formulation, F9 showed the highest mucoadhesion, and F1 showed the lowest.

Stability Study for Humidity: The optimized films F1 and F3 were subjected to the open environment for one month and were evaluated for the parameters mentioned in **Table 8**.

TABLE 8: STABILITY STUDY OBSERVATIONS AFTER 1 MONTH

S. no.	Parameters	F1	F3
1	Appearance	Hard	Hard and Brittle
2	Folding Endurance	90	52
3	Surface pH	6.5	6.8
4	Tensile strength	6.2	7.1
5	Mucoadhesive strength (N)	53.8	37.5

It was observed that when the films were exposed in the open container at room temperature, some changes were observed into mechanical parameters and surface pH. It could have happened because of loss of water and thus changes in the polymer matrix properties.

Optimization of Formulation: Development of formulation based on the dependent and independent factors: HPMC K15 and Eudragit L100 concen-trations were independent factor and Mucoadhesion and % Drug release were a dependent factor. As per the requirement, Factorial model 3^2 was tried.

TABLE 9: RESPONSE SUMMARY FOR RESPONSE Y1 (MUCOADHESION)

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
2FI	0.0427		0.9437	0.9064	Suggested

The linear model suggests that excipient do not show any interaction, its suggested batches.

TABLE 10: RESPONSE 1- MUCOADHESION ANOVA FOR RESPONSE SURFACE LINEAR MODEL ANALYSIS OF VARIANCE TABLE [PARTIAL SUM OF SQUARES - TYPE III

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	131.14	2	65.64	68.06	<0.0001	Significant

The model F-value of 68.06 implies the linear model is significant. There is only a 0.01% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant.
Mucoadhesion ranges from 55.00 to 65.85 for the taken quantity of polymers is significant though linear.

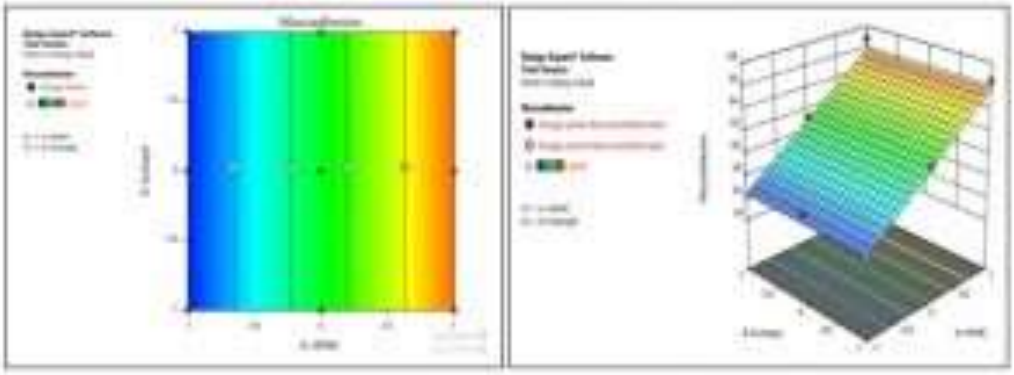

FIG. 9: THE RESPONSE SURFACE GRAPH FOR MUCOADHESION Y1

TABLE 11: RESPONSE SUMMARY FOR Y2 (% DRUG RELEASE)

Source	Sequential p-value	Lack of Fit p-value	Adjusted R^2	Predicted R^2	
2FI	0.0427		0.9614	0.8607	Suggested

Model suggests the taken concentration HPMCK15 and Eudragit does not show interaction. Linear polynomial where the additional terms are significant is selected. Here Adjusted R^2 and Predicted R^2 are optimum

TABLE 12: ANOVA FOR LINEAR MODEL RESPONSE Y2 (%): R2

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	91.88	3	30.63	37.49	0.0002	Significant

The model F-value of 37.49 implies the model is significant. There is only a 0.02% chance that an F-value this large could occur due to noise. P-values less than 0.0500 indicate model terms are significant.

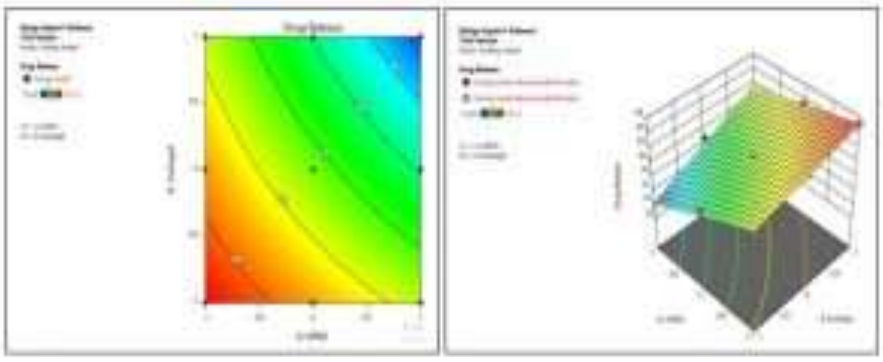

FIG. 10: THE RESPONSE SURFACE GRAPH FOR % DRUG RELEASE PRODUCT Y2

As per the results, the taken formulation confidence is near to 95.00%.

Thus, the mucoadhesive films of frovatriptan are successfully prepared and evaluated. During this study effect of various polymers and other excipients having different mucoadhesion, film-forming, drug release, and plasticity properties were studied and optimized. The optimization of formulations after the trial batches suggested that formulations F1 and F3 can be considered better, and formulation F1 is concluded to be the best batch. Evaluation of films for mechanical and drug release studies along with stability study suggest that mucoadhesive films can be a successful formulation for frovatriptan for the management of migraine. Such formulation can have commercial applications as no such formulation is yet available in the market.

CONCLUSION: Aim of this research, formulation development, and evaluation of mucoadhesive films of frovatriptan was divided into sequential studies and the set objectives were sequentially met. The studies included:

1. Preformulation of frovatriptan and excipients used in mucoadhesive film formulation.
2. Formulation and evaluation of preliminary batches.
3. Optimization of formulation of mucoadhesive films containing 2.5 mg per 2 × 2 cmusing 3^2 factorial design. Batch F1 was considered optimum at the end of this study.
4. Evaluations carried out were: - % Drug release, film thickness, mucoadhesive strength (using *in-situ* developed apparatus), swelling index, folding endurance, and tensile strength of the film.
5. All the evaluations lead to the conclusion that F1 could be optimum formulation. That was further confirmed by the stability study of F1 films. Mucoadhesive films of frovatriptan could be the successful formulation for the management of migraine as compared with formulations available in the market.

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