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Original Article

FORMULATION AND EVALUATION OF BILAYER BUCCAL TABLET OF SUMATRIPTAN SUCCINATE

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ABSTRACT

Objective: To develop mucoadhesive bilayer buccal tablet of sumatriptan succinate to enhance its bioavailability and reduce its dosing frequency.

Method: A batch prepared with ratio of HPMC K15: HPMC K100LV as 1:3, 4% Penetration enhancer, 40mg backing layer, compressed at 2 tons/cm2 for 10 s was identified as an ideal batch based on its buccal residence time and optimum mucoadhesive strength of 13.99 g. The formulated tablets were stable with respect to their physicochemical and in vitro drug release behaviour over a period of 60 days at different temperatures and relative humidity.

Results: The Optimised buccal tablet batch shows the drug release up to 90% in 8hr, good mucoadhesive time as 470 Min.

Conclusion: Mucoadhesive bilayered buccal tablet of sumatriptan succinate may have enhanced bioavailability. A combination of polymer HPMC K15: HPMC K100LV in the ratio of 1:3 shows good mucoadhesive strength, ex-vivo drug release, and good mucoadhesive time.

Keywords: Bilayer buccal tablet, Sumatriptan succinate, mucoadhesive strength, HPMC K100LV.

INTRODUCTION

Buccal delivery of drug, as an alternative to the oral route of drug administration, is a subject of growing interest because of its numerous advantages such as good accessibility, robustness of epithelium, facile removal of dosage form in case of need, relatively low enzymatic activity, prevent drug degradation in gastrointestinal tract and avoid hepatic first-pass metabolism. There are various dosage forms for buccal drug delivery like buccal tablets, buccal patch, adhesive gels etc.[1,2] A suitable buccal drug delivery system should possess good bioadhesive properties, so that it can be retained in the oral cavity for desired duration. Bioadhesive polymers have been used extensively for use in buccal drug delivery systems like polyacrylic acid, polycyanoacrylate, various grades of Hydroxypropyl methyl cellulose, etc. The development of newer excipients for potential use as mucoadhesive polymers continues to be of interest. In addition, it should release the drug in a unidirectional way towards the mucosa, in controlled and predictable manner, to elicit the required therapeutic response. This unidirectional drug release can be achieved by using bilayer devices using polymers like Ethyl cellulose, carbopol, magnesium separate, polycarbophil, etc. [3,4,5.]

Sumatriptan succinate is 5-HT1receptor agonist used in the treatment of migraine. Sumatriptan succinate is chemically designated as 3-[2-(dimethylamino) ethyl]-N-methyl-indole-5-methanesulfonamide succinate. The physiochemical properties of sumatriptan succinate include its half life about 2.5 hours, molecular weight about 413, bioavailability 15%(oral), 96%(subcutaneous), metabolism by MAO-A enzyme.[6]

Migraine is a mysterious disorder characterised by pulsating headache, usually restricted to one side, which comes in attacks lasting 4-48 hours and is often associated with nausea, vomiting, sensitivity to light and sound, vertigo, loose motion and other symptoms.[7]

The oral formulation offers convenience and ease of use but produces unreliable blood levels and inconsistent response. Recurrence (rebound) occurs with these formulations. This common problem with recurrence is likely due to persistence of the original event with a time course exceeding the duration of action from the currently available formulations. Buccal drug delivery system has the potential to fill an unmet need in migraine care by providing direct access to the systemic circulation through the internal jugular vein bypassing the first pass metabolism leading to high bioavailability. Other advantages are non-invasive administration, rapid-onset of action, convenient and easily accessible site, self administrable, low enzymatic activity, etc. [7,8,9.]

The rationale of this research work is to develop a new mucoadhesive bilayer buccal tablet of sumatriptan succinate to counteract the problems associated with the conventional available marketed preparation of sumatriptan succinate that they have low bioavailability, frequent dosing as a limitation.

MATERIAL AND METHODS

Sumatriptan succinate (Wockhardt limited MIDC, Waluj, Aurangabad), HPMC K15M and HPMC K100LV (Colorcon PVT limited, Goa) were obtained as gift sample. All other chemicals and reagents used in the work were of analytical grades.

METHODS

Drug identification and drug- excipients compatibility study

Melting Point

Melting point of Sumatriptan Succinate was determined by taking a small amount of sample in a capillary tube closed at one end and placed in Digital melting point apparatus. (Veego Digital Melting point apparatus) The melting point was recorded.

UV Spectrum and Calibration curve of Sumatriptan Succinate

The UV spectrum of Sumatriptan succinate was obtained using Shimadzu UV1700. Accurately weighed 100 mg of the drug was dissolved in sufficient quantity of buffer pH 6.8 and volume made upto100 ml known as stock solution (1000 µg/ml). 1ml of aliquot was withdrawn and volume was made up to 100 ml using buffer pH 6.8 to obtain the concentration of 10µg/ml (stock 2). Subsequently aliquots were removed from stock 2 to give 2-10µg/ml. The resultant solution was scanned from 400 to 200 nm.

Fourier transforms infra-red spectra (FTIR)

The drug sample was placed in FTIR cuvette. The drug sample was scanned over the range of 4000-400 cm^{-1} on an FTIR (Prestige 21 SHIMADZU). The FTIR spectra of drug sample were recorded. Similarly, the procedure repeated by dispersing a sample {drug, drug and polymer (1:1) as well as mixture of drug and polymers (1:1:1:1) in FTIR cuvette.

Differential Scanning Calorimetry (DSC)

The thermal behaviour of Sumatriptan succinate was studied using Shimadzu DSC TA60 WS Thermal Analyzer. Accurately weighed samples of (For drug 6.06 mg) were hermetically sealed in aluminium pan and heated at a constant rate of 20°C/min over temperature range of 100 to 300°C. The DSC thermo gram was recorded. The physical mixtures of drug with polymers for compatibility studies were prepared by triturating drug and drug and polymers (1:1) in a dried mortar for 5 min and kept as it is for 24 hrs.

Preparation of BBT of sumatriptan succinate

Core tablet

Various batches of BBT were prepared by changing the ratio of HPMC K15M, and HPMC K100LV. The drug-polymer combination was mixed and triturated for 15min (Table 1) in a glass mortar to obtain homogeneous mixture. The powder mixture equivalent to 150mg was then compressed directly using an 11mm diameter die in a single-stroke multistation tablet machine (Karnavati mini press, India). Upper punch was raised and the backing layer of ethyl cellulose was placed on the above compact. Then 2 layers were compressed into a mucoadhesive bilayer tablet with a total weight of 200 mg/tablet. [10,11.]

Backing Layer

Ethyl cellulose granules were prepared by wet granulation using isopropyl alcohol as the granulating solvent. The wet mass was passed through mesh #8 and dried at 40°C for 1 h. The granules were then passed through mesh #22 and retained on mesh #44. The core tablet was transferred to the die cavity fitted with 10-mm flat punch. Ethyl cellulose granules (50 mg) were added and subsequently compressed at constant maximum compression force. The tablets were coated from the sides and bottom with ethyl cellulose as backing membrane such that only the top surface remained uncoated. [12].

Table 1: Formulation of 3^2Factorial Design Batches

Ingredients (mg) / batch	F1	F2	F3	F4	F5	F6	F7	F8	F9
Sumatriptan succinate	10	10	10	10	10	10	10	10	10
HPMC K15M	25	20	25	30	20	30	30	25	20
HPMC K100LV	80	75	70	75	80	70	80	75	70
SLS	4	4	4	4	4	4	4	4	4
MCC 102	29	39	39	29	34	34	24	44	44
Mg. Stearate	2	2	2	2	2	2	2	2	2
Ethyl cellulose(backing layer)	50	50	50	50	50	50	50	50	50
Total	200	200	200	200	200	200	200	200	200

Evaluation of Tablets

Tablets are evaluated for following official and non official tests.

Weight variation test

Twenty tablets were selected at random and weighed individually. The individual weights were compared with the average weight for determination of weight variation. [2,5]

Hardness

Tablet hardness is defined as force required to crushing the tablet in diametric compression test. The hardness was measured with Monsanto hardness tester. [2,5]

Friability

Twenty tablets were weighed and subjected to friability test in Roche friabilator. The pre-weighed sample was placed in friabilator which revolves at 25 rpm for 4 min. dropping the tablets through a distance of 6 inch with each revolution. This process was repeated for all formulations and the percentage friability was calculated. [5]

Drug content

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 ethyl alcohol and filtered through a 0.45-µm filter paper. The filtrate was diluted with phosphate buffer (pH 6.8).The drug content was analyzed spectrophotometrically at 227 nm using an UV spectrophotometer using a reference to a standard calibration curve of the sumatriptan succinate**.** [13]

Thickness

The thickness of buccal tablets was determined using a digital Vernier calliper.

***In vitro* Drug release studies**

USP dissolution apparatus with paddle was used for the in vitro dissolution studies of mucoadhesive tablets with a simple modification. A two-end open glass cylinder of 3 cm diameter and 10 cm length was taken. The prepared mucoadhesive tablet was placed by applying a moderate pressure onto a moistened membrane having a thickness of~500µm and this was then tied to one end of the cylinder, taking care to place the tablet inside the cylinder. This cylinder was then placed on the surface of dissolution medium (500 ml of phosphate buffer pH 6.8) maintained at 37 ± 0.5 ◦ C at 50 rpm for 8 h. At specified time intervals, 5 ml samples were withdrawn and immediately replaced with an equal quantity of fresh buffer. The samples were filtered and analysed after appropriate dilution by UV Spectrophotometer at 227 nm. [14, 15.]

Evaluation of mucoadhesive strength

Weight required to pull off the formulation from mucus tissue is recorded as mucoadhesion/bioadhesion strength in g. This parameter for the tablets was measured on a modified physical balance using bovine cheek pouch as model mucosal membrane. [16,3,17]

***In-vitro* swelling studies**

Eight buccal tablets were weighed (W1) and placed separately in Petri dishes with 5ml of phosphate buffer of pH 6.8. At the time interval of 1,2,3,4,5,6,7 and 8 hrs, tablets were removed from the Petri dish and excess water was removed carefully using filter paper. The swollen tablets were then reweighed (W2) and the percentage hydration were calculated using the following formula.[18,19,20]

$$\text{Percentage hydration} = \frac{(W2 - W1)}{W1} \times 100$$

Ex Vivo Mucoadhesion Time

The *ex vivo* mucoadhesion time was performed after application of the buccal tablet on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was tied on the glass slide and a bilayer buccal tablet core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 sec. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8 and was kept at 37 ± 1°C. After 2 min, a 50 rpm stirring rate was applied to simulate the buccal cavity environment and tablet adhesion was monitored for 12 h. The time for the tablet to detach from the sheep buccal mucosa was recorded as the mucoadhesion time. [21,22,23].

Surface pH

A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping them in contact with 2 ml of phosphate buffer pH 6.8 in a test tube for 2hrs.The pH was then noted by bringing the electrode in contact with the surface of the formulation pH and allowing it to equilibrate for 1 min. [24,25,26]

Statistical analysis by Design Expert Software

A 3^2 full factorial design was selected and the 2 factors were evaluated at 3 levels, respectively. The percentages of HPMC K15M (X1), HPMC k100LV (X2) were selected as independent variables and the dependent variables were %dr, Mucoadhesive strength, Mucoadhesive time The data obtained were treated using Stat Ease Design Expert 7.1.6 software and analyzed statistically using analysis of variance (ANOVA) . The data were also subjected to 3-D response surface methodology to study the interaction of HPMC K15M (X1) HPMC K100LV(X2) on dependent variables.

Kinetics analysis of drug release

To analyze the mechanism of drug release from the tablet the *In vitro* dissolution data were fitted to zero order, first order, Higuchi release model, Hixson and Crowell powder dissolution method and Korsmeyer Peppas model by using PCP Disso Version 3 software, and the model with the higher correlation coefficient was considered to be the best model.

RESULTS AND DISCUSSION

Drug Identification and drug-excipients compatibility study

Melting Point

The melting point of Sumatriptan Succinate was determined on Digital melting point apparatus was found to be 169-172ºC which is in good agreement with reported melting point.

UV Spectrum and Calibration curve of Sumatriptan Succinate

The UV spectrum of Sumatriptan Succinate solution (10µg/ml) exhibited wavelength of absorbance maximum at 227 nm which complies with the reported and calibration curve shows r^2=0.999.

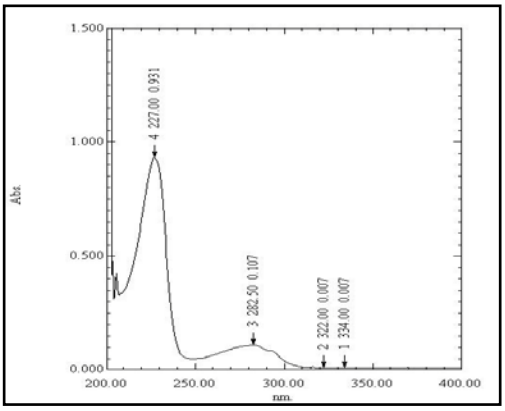

Fig. 1: UV spectrum of Sumatriptan Succinate

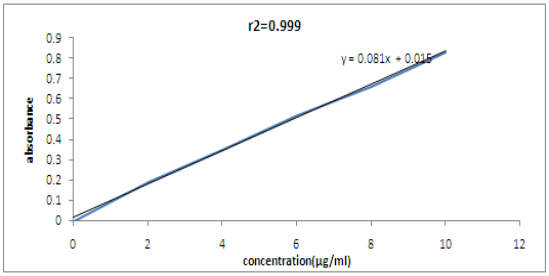

Fig. 2: Calibration curve of Sumatriptan Succinate

Fourier Transform Infra Red Spectrophotometer (FTIR)

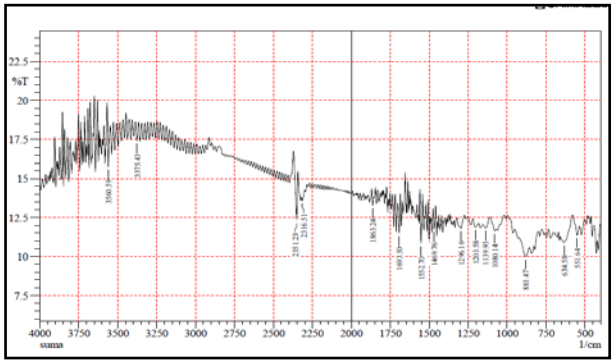

Fig. 3: FTIR spectrum of Sumatriptan Succinate

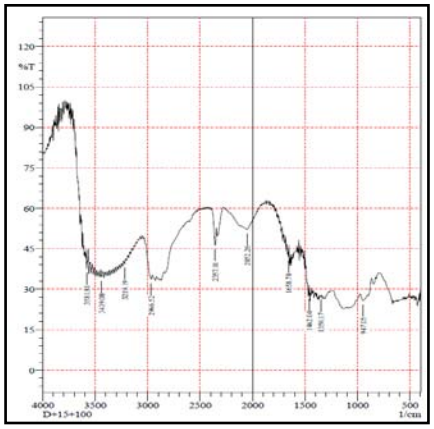

Fig. 4: FTIR spectrum of Factorial tablet

Differential scanning calorimeter (DSC)

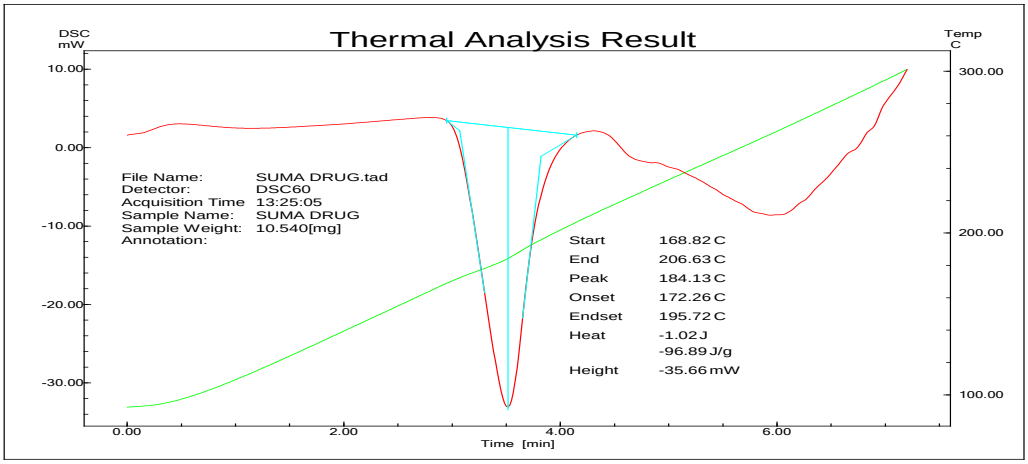

Fig. 5: DSC Thermogram of Sumatriptan Succinate

Evaluation of Tablets:

The tablets from the factorial batches were evaluated for different evaluation parameters of tablets.

Appearance

The tablets from all factorial batches were white, circular. The surface texture was smooth. The thickness of tablets of factorial batches was 3.12 to 3.24 mm and it was found to be within limit of deviation from average value (not more than 5%).

Weight variation

For tablet weighing 300 mg or more, not more than two tablets differ from the average weight by 5% deviation. The weight variation within limits indicates uniformity in tablet compression and consequently content of drug in a unit.

Hardness

The hardness is important characteristics to be evaluated for handling and transportation properties of the tablets. The hardness of tablets was found to be 5.8 to 8.0 Kg/cm^2 which indicate good handling and transportation characteristics.

Friability

The friability is important characteristics to be evaluated for handling and transportation properties of the tablets. The friability of tablets was less than 0.5% which indicates good handling and transportation characteristics.

Drug content

The drug content of the nine formulations was found to be between 97.2 to102 %(i.e. variation of ±4%).

The value ensures good uniformity of the drug content in the tablet.

***In* vitro drug release studies**

In vitro drug release study was carried out using USP dissolution apparatus II in buffer pH 6.8 for a period of 8 Hrs.

Statistical analysis by Design Expert Software

The coefficients of X_1 X_2 were found to be significant at $p < 0.05$, hence confirmed the significant effect of all the variables on the selected responses.

3-D Response surface plot

The response surface plots showed that various combinations of independent variables X_1, X2 may satisfy any specific requirement (i.e. maximum drug release up to 8 hrs and Mucoadhesive strength) while taking into consideration of various factors involved in dosage form.

Kinetics analysis of drug release

The various dissolution Models are applied for the kinetics of drug release study like zero, first, higuchi, peppas model but the best fit model that follows by all the batches is higuchi (matrix) model.

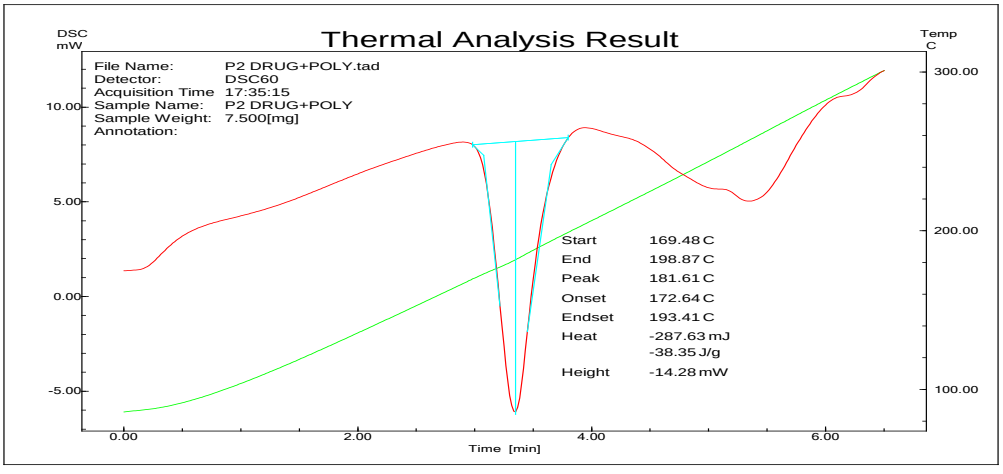

Fig. 6: DSC Thermogram of Tablet blend

Table 2: Evaluation of Bilayer buccal tablet of Sumatriptan Succinate tablets

Batch	Surface pH	Weight variation* mg ± SD	Hardness (Kg/cm²) ±SD	Friability# %	Mucoadhesive time(min)	Thickness (mm) ±SD	Swelling index	Mucoadhesive strength(gm)	Drug content (%mg) ±SD
F1	6.58±0.27	198.66±1.15	6.26±0.05	0.56±0.005	325	2.39±0.02	19±0.8	5±0.3	99.43±1.42
F2	6.66±0.2	199.33±0.57	6.56±0.02	0.72±0.01	350	2.4±0.01	29±1.2	7±0.6	99.1±0.6
F3	6.4±0.2	200±1.0	6.6±0.1	0.65±0.01	380	2.42±0.005	45±1.3	9±0.5	101.33±0.70
F4	6.1±0.1	199.66±0.5	6.6±0.05	0.6±0.1	410	2.38±0.005	52±0.9	7±0.4	99.06±0.30
F5	6.53±0.15	198.66±0.56	6.2±0.1	0.50±0.01	430	2.39±0.01	56±1.4	8±0.5	99.96±1.35
F6	6.1±0.5	200.3±0.57	6.46±0.05	0.56±0.01	460	2.38±0.01	59±1.8	12±0.4	101.2±0.8
F7	5.86±0.11	200±1.0	6.03±0.1	0.71±0.02	470	2.37±0.0	62±1.5	13±0.5	98.5±0.9
F8	6.23±0.05	199.66±0.57	5.93±0.05	0.82±0.02	482	2.35±0.1	61±1.4	15±0.3	99.86±1.25
F9	6.4±0.1	200.33±0.57	5.9±0.1	0.77±0.02	490	2.39±0.005	67±1.1	11±0.4	100.46±1.44

All values are mean ± SD n=3

Table 3: Percent total drug release of formulation F1 to F9

Time (Hrs)	Drug Release (%)								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	F7	**F8**	**F9**
1	29.4 ±0.10	39.1 ±0.03	38.5 ±0.06	24.65 ±0.14	34.4 ±0.12	32.95 ±0.05	32.05 ±0.07	21.1 ±0.04	12.7 ±0.07
2	40.65±0.09	45.95±0.10	46.2±0.09	34.35±0.13	53.3±0.06	49.2±0.11	48.35±0.12	42.6±0.11	19.3±0.14
3	52.55 ±1.44	59.1 ±0.04	56.25 ±1.43	47.9 ±0.01	60 ±0.07	53.5 ±0.15	54.5 ±0.14	49.7 ±0.05	30.2 ±0.13
4	64.35±1.40	65.28±0.02	62.5±1.53	54.65±0.12	62.32±0.19	58.6±0.10	58.8±0.24	55.2±0.05	33.5 ±0.37
5	65.7 ±1.50	71.7 ±0.09	66.45 ±1.37	55.5 ±0.05	64.36 ±0.20	60.9 ±0.22	64.7 ±0.03	60 ±0.19	49.5 ±0.03
6	75.95 ±1.13	75.4 ±0.08	77.77 ±1.27	57.6 ±0.08	68.55 ±0.16	63.4 ±0.11	78.5 ±0.15	62.9 ±0.08	52.02 ±0.07
7	81.2 ±1.32	77.9 ±0.27	84.6±1.20	62.77±0.02	71.40±0.12	66.20±0.38	81.5±0.17	75 ±0.06	62.3 ±0.34
8	87.9 ±1.40	82.4 ±0.35	86.05 ±1.22	75 ±0.24	76.31 ±0.60	72.91 ±0.25	90 ±0.01	77.9 ±0.22	64.2 ±0.25

All values are mean ± SD n=3

Table 4: Analysis of variance for % Drug Release

source	Sum of squares	Df	Mean square	F value	P value Prob>F	
Model	387.54	2	193.77	7.54	0.0231	
A-HPMC K15	207.68	1	207.68	8.08	0.0295	significant
B-HPMC K100LV	179.85	1	179.85	7.00	0.0383	
Residual	154.20	6	25.70			
Core Total	541.74	8				

Table 5: Analysis of variance for Mucoadhesive Strength

source	Sum of squares	df	Mean square	F value	P value Prob>F	
Model	30.17	2	15.08	65.16	< 0.0001	
A-HPMC K15	13.50	1	13.50	58.32	*0.0003*	Significant
B-HPMC K100LV	16.67	1	16.67	72.00		
Residual	1.39	6	0.23			
Core Total	31.56	8				

Table 6: Analysis of variance for Mucoadhesive Time

source	Sum of squares	df	Mean square	F value	P value Prob>F	
Model	27565.67	2	13782.83	85.15	< 0.0001	
A-HPMC K15	*2604.17*	1	*2604.17*	*16.09*	*0.0070*	Significant
B-HPMC K100LV	*24961.50*	1	*24961.50*	*154.21*	*< 0.0001*	
Residual	971.22	6	161.87			
Core Total	28536.89	8				

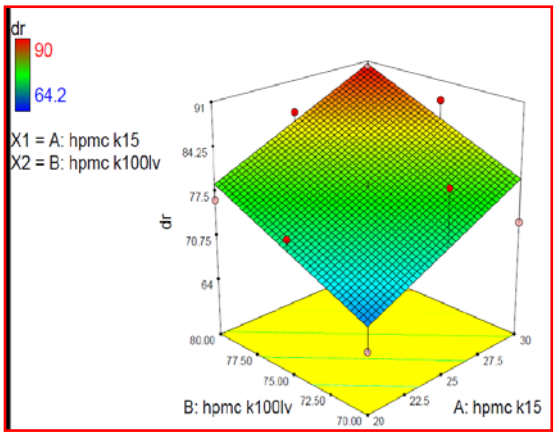

Fig. 7: Response Surface Plot for % Drug Release

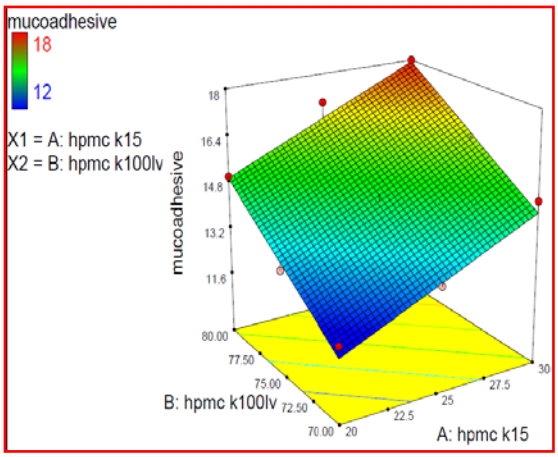

Fig. 8: Response Surface Plot For Mucoadhesive Strength

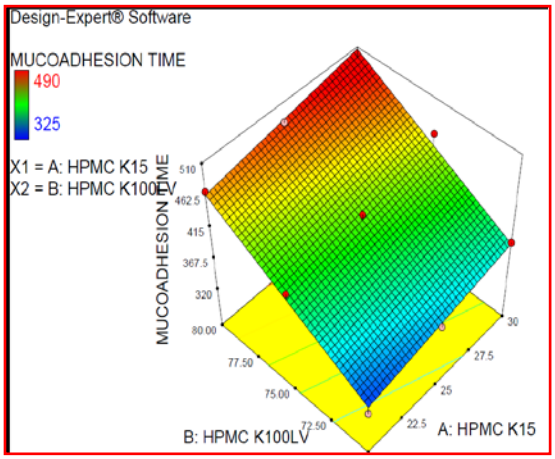

Fig. 9: Response Surface Plot For Mucoadhesive Time

CONCLUSION

The bilayer buccal tablet of sumatriptan succinate was prepared. A combination of polymer HPMC K15: HPMC K100LV in the ratio of 1:3 shows good mucoadhesive strength, ex-vivo drug release, and good mucoadhesive time. Addition of sodium lauryl sulphate is useful for the desired permeation across the buccal mucosa. The preparation of bilayer buccal tablet of sumatriptan succinate shows increase in the bioavailability thus avoiding the hepatic first pass effect. The patients get advantages of the buccal tablet for the treatment of migraine as marketed preparation shows erratic drug absorption.

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