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Research Article

DESIGN AND EVALUATION OF MUCOADHESIVE ATORVASTATIN CALCIUM TABLET USING SURFACE RESPONSE METHODOLOGY

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ABSTRACT

Objective: Study was aimed at to developed mucoadhesive tablet containing inclusion complex of Atorvastatin calcium with β-cyclodextrin and evaluating the effect of two independent variables (X1) HPMCK4M and (X2) Carbopol 934P using central composite Design.

Method: Mucoadhesive tablets were prepared by Kneding method using Factorial design and all prepared tablets were evaluated by for their pre and post compression study, Bioadhesion Studies, Mucoadhesive time, effect of independent variables on dependent variables i.e. (Q_2)- Percentage release at 2 hr ,(Q_8) percentage drug release at 8 hr. The main effects and the interaction terms were quantitatively evaluated by quadratic model.

Results: All the physical parameters for the tablet were within Pharmacopoeial limits. The bioadhesive strength and *in-vitro* release of formulation was found to vary linearly with increasing amount of both polymers. The Q_2 and Q_8, for 9 batches (F1- F9) showed a wide variation (i.e.18.94-27.54, 69.52-91.54% respectively). The effects of all the tested independent variables had P-values < 0.05.

Conclusion: A systemically planed study by using a 3^2 full factorial design revealed that the amount of HPMCK4M (X1) and amount of Carbopol 934P (X2) had a significantly effect on Q_2 and Q_8.The formulation F4 was selected as an optimized formulation because it gave the best results in terms of the required bioadhesion study, and drug release in sustained release manner. Dissolution profiles have shown non-fickian drug release mechanism, which indicated that the drug release was by diffusion and erosion mechanism.

Keywords: Atorvastatin Calcium, Mucoadhesive Tablet, HPMCK4M, Carbopol-934P, Factorial Design.

INTRODUCTION

Among the various routes of drug delivery, oral route is the most suitable and most widely accepted one by the patients for the delivery of the therapeutically active drugs[1]. Atorvastatin Calcium belongs to anti-hyperlipidemic class. It is normally indicated for the treatment of hyperlipidemias and cardiovascular diseases. Atorvastatin is a competitive inhibitor of HMG-CoA reductase, the rate limiting enzyme that convert 3-hydroxy-3-methylglutaryl-coenzyme A to mevalonate, a precursor of sterols, including cholesterol. Sterol synthesis is inhibited 1 to 8 hour after single oral dose of atorvastatin. The oral bioavailability of atorvastatin is approximately 14% because of extensive first pass metabolism. It's having half-live of 11-19 h in humans after single dose of 10 mg of Atorvastatin calcium. These pharmacokinetic parameters make Atorvastatin calcium a suitable candidate for buccal delivery [2-3.] Sustained or controlled release delivery systems can achieve predictable and reproducible release rates, extended duration of activity for short half – life drugs, decreased toxicity, and reduction of required dose, optimized therapy and better patient compliance [4].

The application of an optimization technique consisting of statistical design to pharmaceutical formulation development provides an efficient and economical method to acquire the necessary information to understand the relationship between controllable (independent) variables and performance dependent variables or responses[5-7]. The study was aimed to developed mucoadhesive dosage form containing inclusion complex of Atorvastatin calcium with β-cyclodextrin investigate the effect of two independent variables i.e. amount of two polymer: HPMC K4M and Carbopol 934P (CP) on *in-vitro* release at the end of 2 h and 8 h of mucoadhesive drug delivery system. So an attempt was made by formulating Atorvastatin calcium buccal tablet to reduced dosing frequency and to achieve plasma concentration profile over 10 h.

MATERIAL AND METHOD

Atorvastatin Calcium was obtained as Kind gift sample by Glenmark Pharmaceuticals, Nasik. (Maharashtra) India, HPMC-K4M and Carbopol 934P were obtained as a gift sample from the Zim Labs. Ltd. Nagpur.India. β-Cyclodextrin was obtained as gift from SDFCL, Mumbai. All other materials and solvents used were of analytical grade.

EXPERIMENTAL

Infrared spectra analysis

Infrared spectrum of Atorvastatin calcium was determined on Fourier Transform Infrared Spectrophotometer (FTIR-4100s) using KBr dispersion technique [8-9]. The base line correction was done using dried potassium bromide. IR spectra for drug and mixture were recorded in a Fourier Transform Infra-Red (FTIR) spectrophotometer with KBr.

Formulation of Mucoadhesive Tablets

Formation of Complex

Accurately weighed quantities of drug and β-cyclodextrin were taken in ratio of (1:1). β-cyclodextrin was added to the mortar, add small quantity of 50% methanol and dichloromethane (1:2) with continuous triturating in clockwise direction to get slurry like incorporated into the slurry and trituration continued for one hour. Slurry was air dried at 25^0 C for 24 hours, pulverized and passed through sieve No.100 and stored in desiccators over fused calcium chloride [9].

Formulation of Bilayer Mucoadhesive Tablet

The mucoadhesive tablets were formulated by direct compression method. All the ingredients of the formulation were passed through a sieve # 60 and were blended in a mortar with a pestle to obtain uniform mixing. The blended powder of the core was compressed on 8 mm punch with single stroke multi station tablet punching machine [10-11]. After punching the core layer, upper punch was removed and ethyl cellulose 30 mg was added over it and again compressed. Tablets weighing ≈ 150 mg were obtained. The various compositions of preliminary formulation containing different ratios of polymers were tried are given in the Table 1.

Table 1: **Composition of Preliminary Batches**

Ingredients (mg)	Batches											
	C1	**C2**	**C3**	**C4**	**C5**	**C6**	**C7**	**C8**	**C9**	**C10**	**C11**	**C12**
Inclusion	20	20	20	20	20	20	20	20	20	20	20	20
HPMCK4M	10	30	50	70	--	--	--	--	10	20	30	50
Carbopol934P	--	--	--	--	10	10	30	50	70	60	40	20
Lactose	87	67	47	27	87	67	47	27	27	27	27	87
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Ethyl cellulose	30	30	30	30	30	30	30	30	30	30	30	30

Experimental Design

From the preliminary batches A 3^2 randomized full factorial design was applied, in this design 2 factors were evaluated, each at 3 levels and experimental trials were performed at all 9 possible combinations. The amount of HPMCK4M (X_1) and amount of Carbopol 934P (X_2) were selected as independent variables. The percentage drug release at 2 hours (Q_2) and percentage release at 8 hours (Q_8) were selected as dependent variables [5,12-13].

Evaluation of prepared mucoadhesive tablets

Weight variation

Weigh individually 20 units selected at random or, for single dose preparations in individual containers, the contents of 20 units, and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table and none deviates by more than twice that percentage [14].

Thickness of Tablets

Six tablets were taken and the thickness was measured using a micrometer screw gauge. The tablet thickness should be lie between within a ±5 % variation of a standard value [11].

Hardness

There is a certain requirement of hardness in tablets so as to withstand the mechanical shocks during handling, manufacturing, packaging and shipping. Hardness tester (Monsanto type) was used to measure hardness of tablets[11]. The whole experiment was performed in triplicate. It is expressed in Kg/cm^2 [11].

Friability

An adequate resistance for powdering and friability are the necessary requisites for consumer acceptance. This test was carried out by using tablet friability test apparatus (Roche). Twenty pre-weighed tablets were rotated at 25 rpm for 4 min. The tablets were then de-dusted and reweighed. The percentage friability was measured using following formula [14].

$\% F = w_0 - w / w_0 \times 100$.

Uniformity of Content

Weighed and powdered five tablets accurately. A quantity of powder equivalent to 10mg of Atorvastatin Calcium was weighed accurately and extracted in 100 ml methanol. After shaking for 20 min, sufficient dilution with methanol, samples were analyzed by UV spectrophotometer at 241 nm. This procedure repeated thrice. Amount of drug present was determined from the standard calibration curve Atorvastatin calcium [14].

Surface pH of the Tablet

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 h 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 1-8 min [15-17].

Swelling Studies

Tablet was weighed individually (recorded as W1) and placed separately in Petri dish containing 5 mL of phosphate buffer (pH 6.8) solution. At regular intervals for 5 hours, the tablet was removed from the Petri dish and excess surface water was removed carefully using the filter paper [18]. The swollen BADDS was then reweighed (W2), and swelling index (SI) was calculated using formula as

$$SI = \frac{W_2 - W_1}{W_1}$$

Swelling Index =

***Ex-Vivo* Mucoadhesion Time**

The Ex-vivo Mucoadhesion time was examined after application of buccal tablet on freshly cut sheep buccal mucosa. The fresh buccal mucosa was tied on the glass slide and tablet wetted with one drop of pH 6.8 phosphate buffers and pasted to mucosa by applying a light force with finger tip. Then the slide was put in beaker containing 200 ml of phosphate buffer and keep at 37±1^{0}C after 2 minute a slow stirring was apply to stimulate buccal cavity environment and tablet adhesion was record for 12 hrs. The time require for detaching tablet from buccal mucosa was record as a mucoadhesion time [18-19].

***In-vitro* Bioadhesion Studies**

For *in-vitro* study, an apparatus designed for determination of mucoadhesive force [19]. The working of balance formed the basis of the fabricated bioadhesion test apparatus. The glass vial was fixed to one side of the balance. The Gout buccal mucosa was tied to this glass vial. The other glass vial was attached to the base of the balance within the bigger size bottle which is filled with phosphate buffer pH 6.8 to maintain the mucosa in moist condition during the study. The balance was balanced at this position by placing weight to the right side pan. The tablet was moistening in the phosphate buffer pH 6.8 and it was placed in between this two vials and press by finger slightly to stuck tablet to the buccal mucosa Then the weight was added slowly to the right side pan till the mucosal surface of the pan detached from the tablet surface. Using this bioadhesion test assembly, the bioadhesive strength expressed in weight, required for detachment of the tablet from the mucosa was determined [19-20].

***Ex-Vivo* Drug Permeation Study**

The in vitro buccal drug permeation study of Atorvastatin calcium through the sheep mucosa was performed using a modified diffusion cell at 37°C ± 0.2°C. Fresh sheep mucosa was mounted between the donor and receptor compartments of France diffusion cell. The tablet was placed with the core facing the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 mL of phosphate buffer pH 6.8. The receptor compartment was filled with phosphate buffer pH 6.8 and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at uniform slow speed. 5 ml. samples were withdrawn at predetermined time intervals and analyzed for drug content by UV spectrophotometer [21-22].

Accelerated Stability Studies

Accelerated stability testing of prepared formulation batch was carried out to determine the stability of drug and carrier and also to determine the physical stability of formulation under accelerated storage condition at various temperatures [23]. The prepared tablets were placed in borosilicate screw capped glass containers. The samples were kept at condition of 45°C+20 C /70% +5RH and were analyzed at 60th, 120th and 180 days for their changes in drug content.

RESULT AND DISCUSSION

Infrared Absorption Spectrum

The FT-IR spectra of the pure Atorvastatin Calcium and physical mixture of drug and polymers were analysed to check for any interaction between drug and polymers. The characteristic peaks of Atorvastatin Calcium were appeared in the spectra without any significant change. This indicated that there was no chemical interaction between Atorvastatin Calcium and polymers. IR spectrum showed all prominent peaks of Atorvastatin which was comparable with standard IR graph. The major IR peaks observed in Atorvastatin were 3055 (Aromatic C-H Stretching), 1572 (C=O Streching), 2970 (CH_3-O Stretching), 2937(C-H Stretching), 3363(N-H stretching vibration), 1454(CH_3-O Bending), 1622(Aromatic C=C), 1215(Aromatic C-N Stretching). Figure 1-4.

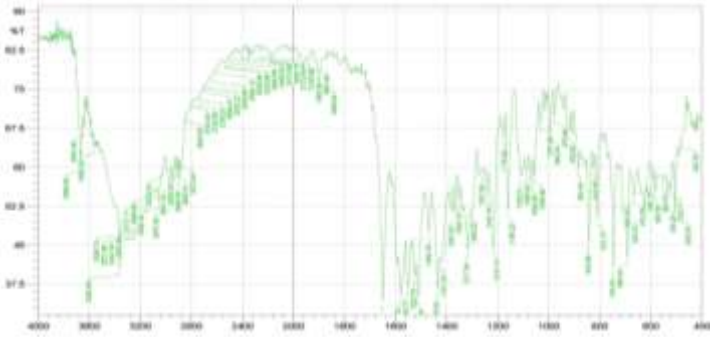


Fig. 1: IR spectrum of Atorvastatin Calcium.

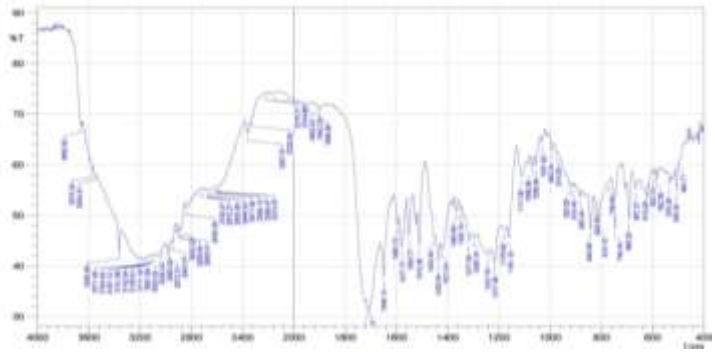


Fig. 2: IR Spectrum of Atorvastatin Calcium+ Carbopol

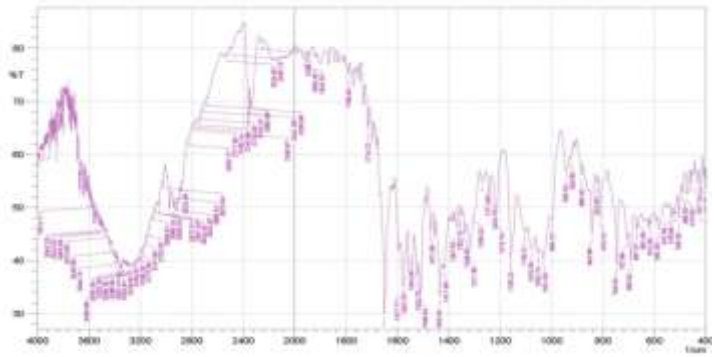


Fig. 3: IR Spectrum of Atorvastatin Calcium + β-Cyclodextrin.

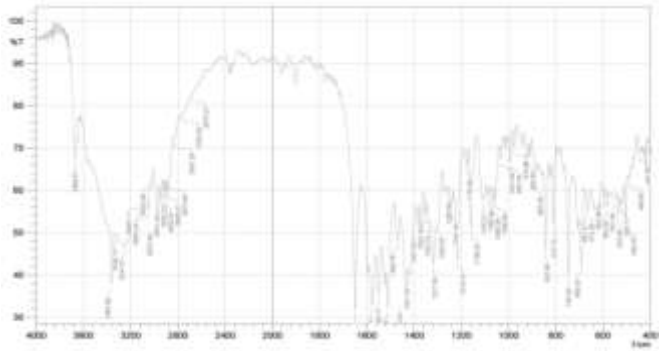


Fig. 4: IR Spectrum of Atorvastatin Calcium+ HPMC-K4M

Optimization Results

A 3^2 factorial design was constructed to study the effect of the amount of HPMCK4M (X1) and carbopol (X2) on the drug release from buccoadhesive tablet of Atorvastatin respectively. The dependent variables chosen were percentage drug release at 2 hours (Q_2) and percentage drug release at 8 hours (Q_8). A statistical model incorporating interactive and polynomial term was used to evaluate the responses.eqs.1

$Y = b0 + b1X1 + b2X2 + b12X1X2 + b11X1X1 + b22X2X2$ .....(1)

Where, Y is dependent variable, b0 is the arithmetic mean response of the 9 runs, and b1 (b1 b2, b12, b11 and b22 is the estimated coefficient for the factor X1 the main effect. (X1 and X2) represents the average results of changing one factor at a time from its low to high values. The interaction term (X1 X2) show how the response changes, when 2 factors are changed simultaneously. The polynomial term (X_1^2 and X_2^2) are included to investigate nonlinearity. The Q_2 and Q_8, for 9 batches (F1- F9) showed a wide variation (i.e.18.94-27.54, 69.52-91.54% respectively). The responses of formulation prepared by 3 factorial designs are indicated in Table 2. The data clearly indicate that the Q_2 and Q_8 were strongly dependent on the selected independent variables. The fitted equation relating the response Q_2 and Q_8 to the transformed factors are, given in eqs.2,3.

% Release at 2 hrs.$Q_2 = 26.25-1.95X_1-0.74X_2+1.43X_1X_2-02.24X_1^2-3.36X_2^2$. ($R^2$=0.8599).....(2)

% Release at 8 hrs.$Q_8 = 87.45-3.86X_1-3.99X_2+2.60X_1X_2-5.47X_1^2-6.53X_2^2$. ($R^2$=0.8826).....(3)

Table 2: Dissolution Characteristics of Formulation Batches in 3^2 Factorial Design

Batch code	Coded value		% Release at (Q_2)	% Release at(Q_8)	n	K	R^2
	X1	X2					
F1	-1	-1	27.54	91.54	0.4911	20.9450	0.9717
F2	0	-1	21.22	87.84	0.7567	14.8757	0.9895
F3	+1	-1	18.94	74.19	0.6729	19.7269	0.9872
F4	-1	0	20.07	86.29	0.7956	13.3931	0.9938
F5	0	0	26.25	87.45	0.6139	22.0669	0.9982
F6	+1	0	23.90	81.14	0.6998	19.5516	0.9933
F7	-1	+1	22.23	76.49	0.7554	14.9075	0.9937
F8	0	+1	25.05	70.82	0.7360	17.3370	0.9955
F9	+1	+1	19.33	69.52	0.6300	14.6395	0.9914

Coded value	Actual value	
	X1	X2
-1	20	20
0	30	30
+1	40	40

Where X1 –amount of HPMCK100M, X2-amount Carbopol, (Q_{2})-Percentage release at 2 hr,(Q_{8})-percentage drug release at 8 hr. n= Release exponent obtained from Koresmeyer Equation.

Table 3: Physical Parameters of Mucoadhesive Tablet.

Batches	Parameters						
	Hardness (Kg/cm^2)	Thickness (mm)	% Friability	Avg. Weight	% Wt. Variation	Surface pH	Uniformity of content
F1	5.74 ±0.18	3.62 ±0.06	0.319 ±0.05	148.79 ±0.66	148.79 ±1.86	6.24 ±0.03	97.95 ± 0.25
F2	5.66 ±0.31	3.75 ±0.15	0.587 ±0.04	147.95 ±0.57	147.95 ±2.19	6.07 ±0.03	97.54 ± 0.82
F3	5.54 ±0.26	3.59 ±0.09	0.617 ±0.05	151.86 ±0.66	151.86 ±2.02	6.62 ±0.04	101.00 ±0.94
F4	5.62 ±0.28	3.43 ±0.04	0.451 ±0.05	148.66 ±0.64	148.66 ±1.92	6.04 ±0.03	98.67 ± 0.37
F5	5.11 ±0.25	3.53 ±0.21	0.529 ±0.04	150.33 ±0.61	150.33 ±1.87	6.28 ±0.02	97.95 ± 0.55
F6	4.96 ±0.22	3.39 ±0.09	0.303 ±0.04	149.18 ±0.58	149.18 ±2.58	6.85 ±0.04	100.50 ±0.73
F7	5.15 ±0.27	3.41 ±0.16	0.463 ±0.05	151.15 ±0.59	151.15 ±1.66	6.34 ±0.03	98.36 ± 0.12
F8	4.92 ±0.16	3.39 ±0.04	0.499 ±0.06	148.92 ±0.68	148.92 ±3.11	6.79 ±0.04	99.95 ± 0.17
F9	4.76 ±0.33	3.36 ±0.07	0.558 ±0.06	148.13 ±0.65	148.13 ±2.56	6.92 ±0.05	101.50 ±0.21

Physical Characteristics of Tablet

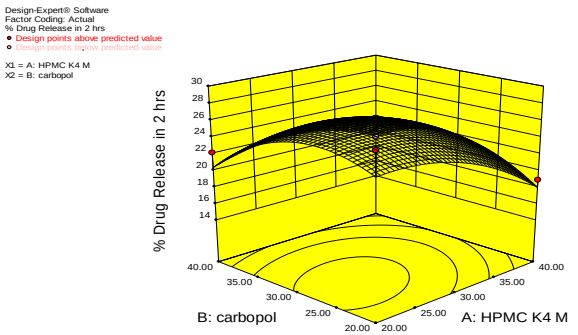
The prepared formulations were evaluated for the physical characteristics like thickness, hardness, friability weight variation, uniformity of drug content. The results obtained are shown in table 3. All the physical parameters values for the tablet were within official and some unofficial tests. The surface pH of all the tablets was within the range of 6 to 6.8 which indicated that there is no risk of mucosal damage or irritation.

The values of the correlation coefficient indicate a good fit. (Fig 5-8). The plot of the amount of HPMC K4M (X1) and amount of Carbopol (X2) versus Q_2 and Q_8 respectively. The data demonstrate that both X1 and X2 affect the drug release (Q_2 and Q_8). It was concluded that the low level of X1 and the low level of X2 favour the preparation of buccoadhesive tablets. The high value of X1X2 coefficient also suggests that the interaction between X1 and X2 has a significant effect on Q_2 An increase in the concentration of HPMC4M (X1) and

amount of Carbopol (X2), decrease rate of release of buccoadhesive tablet respectively.

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 4 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Data were analyzed using Microsoft Excel.

The fitted equations relating the responses, Q_2, Q_8 to the transformed factor are shown in the Table 4.



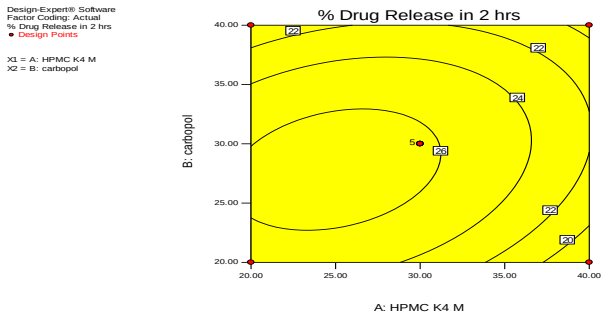


Fig. 5: Response surface plot for Q_2 Fig. 6: Counter plot for Q_2.

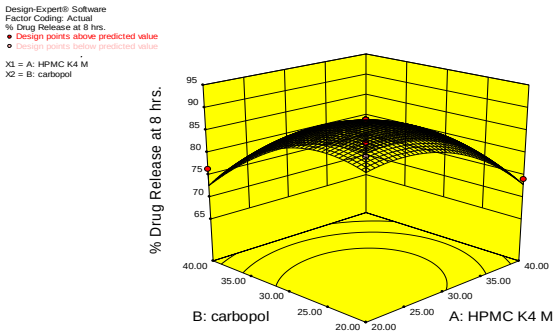


Fig. 7: Response surface plot for Q_8.

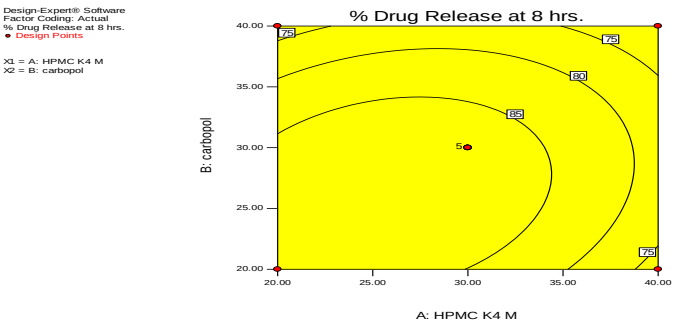


Fig. 8: Counter plot for Q_8.

Table 4: Summary of Results of Regression Analysis

Model	Q2		Qs	
	coeficent	p-value	coeficent	p-value
Intercept	26.25	0.0067	87.45	0.0037
X1	-1.95	0.0198	-3.86	0.0215
X2	-0.74	0.2894	-3.99	0.0186
X1X2	1.43	0.1637	2.60	0.2037
$X1^2$	-2.24	0.0146	-5.47	0.0059
$X2^2$	3.36	0.0019	-6.54	0.0023
R^2	0.8599		0.8826	

R2 value for Q_2, Q_8 are 0.8599 and 0.8826 respectively indicating good correlation between dependent and independent variables. The terms with P<0.05 were considered statistically significance.

The bioadhesion and drug release profile are dependent upon swelling behavior of the tablets. Swelling index was calculated with respect to time. Swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration. The formulation batch containing higher Carbopol concentration than HPMC K4M showed higher swelling index. From the results obtained, it was observed that the increased concentration of carbopol 934P and HPMC K4M in the formulation increases the swelling indices as shown in Table 5.

The result From Bioaddhesion studies revealed that the highest detachment force was observed in formulation containing carbopol-934p (F1 and F4) in higher indicating that as the concentration of Carbopol 934P in formulation increases, bioadhesion force also increases. From the dissolution study of batch F1 to F9, it was concluded that release from the tablet was largely dependent on the polymer swelling, drug diffusion and matrix erosion. The drug release study was carried out up to 12 hrsas shown in Table 6.

Table 5: Swelling studies of Buccoadhesive Tablet

Batch	% Swelling Index					
	0	1hr	3hr	5hr	7hr	10hr
F1	00	11.47±0.98	19.24±1.12	32.34±0.85	49.86±0.60	69.95±1.21
F2	00	12.78±1.01	23.56±0.98	37.12±1.61	51.67±0.48	74.78±1.02
F3	00	14.64±1.98	21.75±1.67	32.87±1.98	43.32±0.93	69.34±2.11
F4	00	13.33±1.41	26.39±1.17	36.79±1.06	61.52±2.57	81.79±1.57
F5	00	15.83±0.91	25.86±1.82	33.56±1.34	59.34±0.87	84.98±2.01
F6	00	16.78±1.01	23.56±0.98	37.12±1.61	51.67±0.48	74.78±1.02
F7	00	19.63±1.32	29.53±1.07	41.46±1.02	67.79±1.23	88.17±0.71
F8	00	20.73±1.05	26.95±1.06	38.09±0.89	52.21±1.95	86.73±1.89
F9	00	22.87±1.87	26.71±0.79	33.56±1.61	45.21±0.59	63.31±2.04

Table 6: Bioadhesion Studies and Mucoadhesive time of Mucoadhesive tablet

Batch	Bioadhesive strength (g)	Bioadhesive Force (N)	Bioadhesive time (hrs)
F1	10.76 ± 0.38	0.105 ± 0.73	14.5 ± 0.76
F2	9.8 ± 0.17	0.096 ± 0.28	13.12 ± 0.44
F3	8.7 ± 0.35	0.085 ± 0.36	12.5 ± 0.46
F4	9.5 ±0.75	0.094 ± 0.41	12.3 ± 0.43
F5	7.9 ± 0.58	0.077 ± 0.28	10.58 ± 0.21
F6	7.0 ± 0.40	0.068 ± 0.35	10.33 ± 0.33
F7	8.6 ± 0.08	0.084 ± 0.38	11.82 ± 0.32
F8	6.9 ± 0.69	0.067 ± 0.44	10.6 ± 0.35
F9	7.0 ± 0.51	0.069 ± 0.33	10.5 ± 0.22

The percentage drug release from batch F1 to F9 vary from 81.52± 0.34% to 97.79± 0.42%. Large concentration of high viscosity polymer induces the formation of strong viscous gel layer that slowed down the rate of water diffusion into the tablet matrix. Dissolution profiles for all batches were shown in (Fig. 9). The combinations of polymers significantly retard the release for more than12 hrs. As the concentration of HPMC K4 M increased the release rate decreased. An increase in the polymer This may decrease the effective diffusion coefficient of drug and therefore there is reduction in drug release rate.

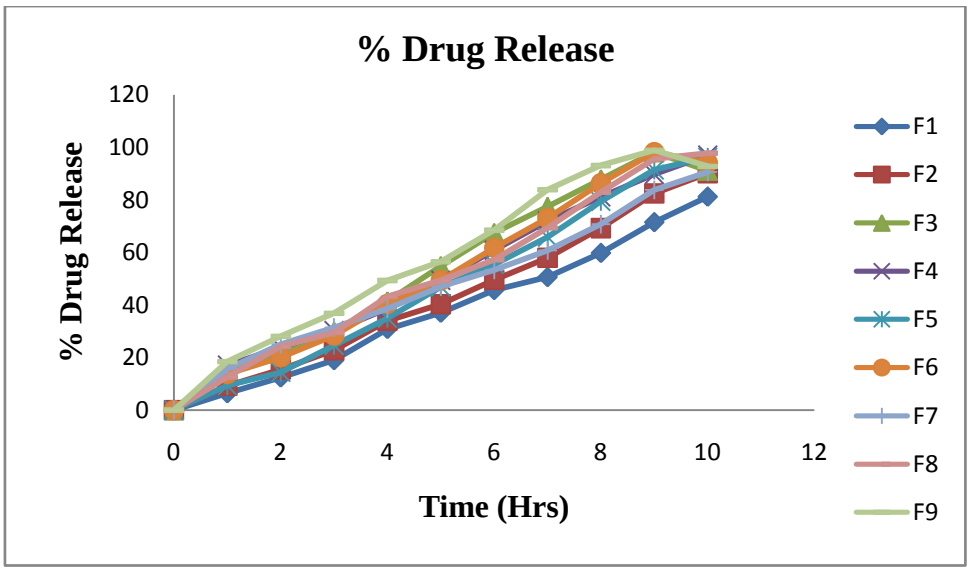


Fig. 9: % Drug Released of Formulations F1 to F9

The formulation batch F4 was studied for the in-vivo drug permeation using sheep mucosa, permeation and was found to 94.72± 0.45% after the 12 hours there was some decreased at 8 hrmay be due to matrix formation.

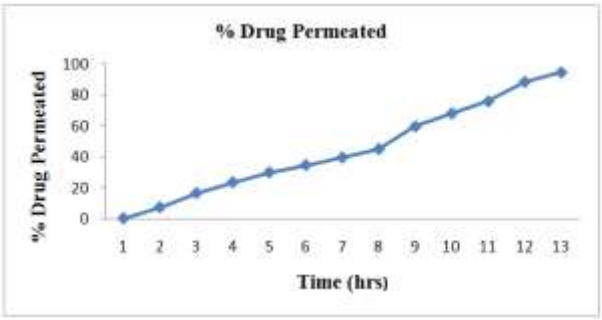


Fig. 10: Ex-vivo Diffusion Profile

Table 7: Stress stability studies optimized batch.

Parameters	Days			
	Initial	**60**	**120**	**180**
Colour	white	No Change	No Change	No Change
Hardness	5.62±0.28	5.56± 0.43	5.37 ± 0.41	5.49 ± 0.76
Drug Content (%)	98.67±0.37	98.02 ±0.15	97.18± 0.32	96.98±0.72
% Drug Release	97.10±0.71	96.45 ±0.84	96.17 ±0.83	95.98±0.78

Accelerated Stability Testing

Stress stability studies (SST) was carried for optimized batch F4 by exposing it to 40°C/75%RH for 60, 120, and 180 days. The sample was analyzed for physical parameters, colour, hardness, IR, uniformity of content, and percentage drug release.

CONCLUSION

Mucoadhesive tablets were prepared by direct compression using central composite method. Formulations batches were evaluated for physical parameter, swelling studies, bioadhesion studies, *in-vitro* drug release and *ex-vivo* drug permeation. Bioadhesion studies were carried out to determine mucoadhesive potential of prepared tablets. Tablets were evaluated for *in-vitro* drug release for 10 hrs, using USP type II method and dissolution profiles has shown non-fickian drug release mechanism, which indicated that the drug release was by diffusion and erosion mechanism. From these results it can be concluded that optimized batch F4 was most promising comprising of 1:2 ratio of HPMC K4M/Carbopol-934p.

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