TJPS-09226-Original Article

Development of Bio-adhesive Buccal Tablet of Nicorandil Using Factorial Approach
Faktöriyel Yaklaşım ile Nikorandil iceren Biyoadezif Bukkal Tabletlerin Geliştirilmesi

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ABSTRACT
Objectives: In the present investigation, bio-adhesive buccal tablets were prepared using sustained-release polymer HPMC K100M, bio-adhesive polymer neem gum and an impervious backing layer of ethyl cellulose. Nicorandil is sensitive to first-pass metabolism effect; therefore, the formulation of buccal-adhesive dosage form can avoid this effect.
Materials and methods: We used the direct compression technique to prepare tablet formulation. A 3^2 Full Factorial Design was composed in which the amount of HPMCK100M (X1) and NEEM GUM (X2) were chosen as the independent variables and the dependent variables were being the percentage drug release at 6 h (Y1) and mucoadhesive strengths in grams (Y2). Various in vitro parameters viz. thickness, friability, hardness, weight variation, surface pH, moisture absorption ration, dissolution studies, and drug release kinetics and ex vivo parameters like mucoadhesive strengths and mucoadhesion time were performed for prepared tablets. We subjected the optimized batch to comparison with the marketed formulation and stability studies.
Results: Formulation (F5) containing a 50:50 ratio of neem gum and HPMC K100M was considered to be optimum. Zero-order release kinetics model best fitted the optimized batch release profile that suggested the system would release the drug at a constant rate.
Conclusion: The optimized formulation releases the drug at a sustained rate along with bio-adhesive nature deduced that the buccal route can be an elective for the administration of Nicorandil.

ÖZ
Amaç: Bu araştırmada, biyo-yapışkan bukkal tabletler sürekli salimli polimer HPMC K100M, biyo-yapışkan polimer neem sakızı ve etil selüloz, bir geçirimsiz arka tabaka kullanılarak hazırlanmıştır. Nicorandil ilk-geçiş metabolizması etkisi karşı duyarlıdır; Bu nedenle, ağızdan yapışkan dozaj formunun formülasyonu, bu etkiyi önlemek.
Gereç ve yöntem: Tablet formülasyonu hazırlamak için doğrudan sıkıştırma tekniği kullanılabilir. 32 tam faktöriyel tasarımı olan HPMCK100M (X1) ve neem sakız (X2) miktarı, bağımsız değişken olarak seçilmiş ve bağımlı değişkenler gram olarak 6 saat (Y1) ve muko-yapışkan kuvvetlerde yüzde ilaç salım (ediliyordu oluşmaktadır Y2). Çeşitli in vitro parametreler yani. kalınlık, ufalanma, sertlik, ağırlık sapması, yüzeysel pH, nem emme oranı, çözünme çalışmaları ve ilaç salgılama kinetikleri ve muko-yapışkan güçlü gibi ex-vivo parametreleri ve muko yapışmayı zaman hazırlanmış tabletler için gerçekleştirilmiştir. Biz pazarlanan formülasyonu ve stabilite çalışmaları ile karşılaştırmak için optimize toplu tabi tutuldu.
Bulgular: Formülasyon (F5) neem zamkı ve HPMC K100M bir 50:50 oranı ihtiva eden en uygun olduğu kabul edilmiştir. Sıfır derece salım kinetiği modeli en iyi sistem sabit bir hızda ilacı tahliye edeceğini ileri sürmüştü optimize toplu salım profili takıldı.
Sonuç: Optimize edilmiş formülasyon serbest bırakır biyo-yapışkan niteliği ile birlikte sürekli bir hızda ilacın ağız yolu Nikorandilin uygulanması için seçmeli olabilir çıkarılabilir.
Keywords: Nicorandil, Neem gum, Buccal tablets, Factorial design.
Anahtar kelimeler: Nicorandil, Neem sakız, bukkal tabletler, Faktoriyel dizayn.

1 Introduction
Hypertension and angina pectoris are two most trivial cardiovascular diseases where constant monitoring is crucial. Angina pectoris is a medical condition that causes chest pain by reduced blood flow to the heart. Potassium channel openers are currently conceived as an important drug class for the treatment of such conditions. A primary medicinal agent who possesses an ability to tackle such a situation is nicorandil, a vasodilatory drug [1-3]. It appears to be active in all types of angina pectoris and has got the twin properties of nitrate and K^+ ATP channel agonist. The major problem with orally administered nicorandil is its first-pass metabolism that gives about 75% of systemic bioavailability. Moreover, it has got a short elimination half-life (1 h), which requires frequent administration of the drug (10 to 20 mg twice daily) [4-6]. Thus, higher fluctuation of drug concentration may give rise to undesirable side effects. In a nutshell, there is a strong requirement of a patient-friendly sustained-release formulation of nicorandil to reduce the frequency of administration.

Such a requirement of oral dosage form can be fulfilled by employing a buccal bio-adhesive drug delivery system. It is a captivating substitute to the oral route of drug administration that overcomes the deficiencies associated with the latter mode of administration. Precisely it prevents any chances of reductant hepatic metabolism, avoiding unneeded drug degradation in upper GIT and also it increases the contact between drug and absorbing surface [7-11]. Moreover, such type of delivery is considered to be safer since any time, drug absorption can be concluded if any toxicity occurs due to it by removing the formulation from the site of application. [12-14].

Thus, in the present research paper, buccal bio-adhesive tablet of nicorandil was prepared using a sustained-release polymer HPMC K100M [10,15], bio-adhesive polymer neem gum [16] and an impermeable backing layer of ethyl cellulose. Buccal bio-adhesive tablets were prepared by direct compression method employing 3^2 factorial design in which the amount of HPMC K100M (X_1) and NEEM GUM (X_2) were selected as independent variables and their effects on dependent variables viz. percentage drug release at 6 h (Y_1) and mucoadhesive strengths in grams (Y_2) were studied.

2 Materials and methods

2. 1 Materials

Nicorandil as a gratis sample obtained from Sun Pharm Laboratories Ltd., East Sikkim. Neem gum was purchased from the local market and remaining materials were purchased from Chem dyes Corporation, Vadodara, Gujarat, India.

2.2 Methods

2.2.1 Drug-excipients compatibility study

Accurately weighed (3 mg) nicorandil was taken and mixed thoroughly with 100 mg of potassium bromide (dried at 40° - 50° C). The mixture was compressed into pellets (under 10-ton pressure) using hydraulic press followed by scanning between 4000 – 400 cm^{-1} using FT-IR 410 PC spectrophotometer. The obtained IR spectra of pure drug (Fig. 1a) were compared with the reference standard (Fig. 1b) taken from Indian Pharmacopoeia as well as with the IR spectra (Fig. 1c) of prepared nicorandil tablet formulation to check the drug excipient compatibility.

2.2.2 Preparation of buccal tablets

Initially, the drug was accurately measured and mixed thoroughly with mannitol on butter paper using a stainless-steel spatula. Except, lubricant, all the other additives were blended for 10 min as per geometric dilution method. Post uniform blending of additives, lubricant was added and mixed for 2 min. 100 mg of such blends of each formulation was pre-compressed on a 10-station rotary tablet punching machine at a low compression force that resulted in single-layered core tablets of 8 mm diameter. Prepared core tablet was placed in the centre of 12 mm lower punch and the backing layer of 100 mg ethyl cellulose (EC) was added around and over the core tablet; the two layers were then compressed into a mucoadhesive bilayer tablet. Tablet (200 mg) was formed whose thickness was found to be 1.6 to 1.8 mm. Table 1 represents preliminary trials to evaluate bio-adhesive polymers and Table 2 depicts formulations to evaluate sustained-release characteristics of various compositions.

2.2.3 Factorial batches

Based on the preliminary studies, a 3^2 Full Factorial Design was constructed where the amount of HPMC K100M (X_1) and NEEM GUM (X_2) were selected as independent variables their level was defined. The dependent variables were % drug release at 6 h (Y_1) and mucoadhesive strengths in grams (Y_2). Table 3 represents details regarding the employed factorial design. ANOVA was calculated using the DESIGN EXPERT, 11.0 demo version software (STATE-EASE) and its responses were studied.

2.2.4 Evaluation of buccal tablets

2.2.4.1 Thickness

A Vernier calliper was used to calculate the thickness of tablets (n=10), and the mean tablet thickness was calculated.

2.2.4.2 Friability and Hardness

Friability (n=20) and hardness (n=3) were found out by a Roche friabilator and a Monsanto type hardness tester, respectively. [17]

2.2.4.3 Weight variation

Tablets (n=20) were weighed individually, and their weight variation was found out by comparing these weights to label claimed. [17]

2.2.4.4 Drug contents

Prepared tablets (n=10) were powdered and an amount corresponding to 10 mg of nicorandil was accurately weighed. The powder was extracted with a volume of buffer solution (phosphate buffer saline, pH 6.8) and analysed using spectrophotometer at 262 nm post suitable dilution.

2.2.4.5 Surface pH

To evaluate irritation possibilities of prepared tablets to the oral mucosa, the surface pH studies were performed. Tablets were soaked in 12 ml buffer solution (phosphate buffer saline, pH 6.8) and allowed to swell for 2 h at

room temperature. A pH meter containing glass electrode was utilized to find out the pH of the resultant swelled tablets by contacting the glass electrode with the surface of the tablet and allowing it to equilibrate for 1 min. [18]

2.2.4.6 Moisture absorption ratio

Hot water was taken and added the required quantity of agar (5 % w/v) into it. The resultant solution was added into Petri plates and inducted to solidify. Previously, vacuum dried nicorandil buccal tablets (n=6) were taken, weighed individually and their one was laminated with cellophane tape (impermeable backing membrane). The tablets were then placed individually to Petri plates so that their other side had contact with the agar medium followed by incubation at 37°C for 1 h. Post incubation, buccal tablets were re-weighed, and the percentage of moisture absorption was calculated using the following formula.

$$\%\ Moisture\ absorption\ =\ [(Final\ weight\ -\ Initial\ weight)\ /\ Initial\ weight]\ X\ 100$$

2.2.4.7 Ex-vivo mucoadhesive strengths

Ex-vivo mucoadhesive strengths were determined using a modified balance method. On the day of experiment, authors have visited a nearby slaughterhouse and collected surgically cut out goat buccal mucosa which can be used within 2 h of slaughter, a model substrate used for this study. To avoid being rotten, a piece of buccal mucosa was kept in Krebs buffer and stored at 4 °C for 2 h. Goat mucosa reached room temperature before further use. This model substrate then tied up with a glass slide to provide mechanical strengths to it. Upon that membrane, a tablet was gently put with manual pressure for 5 min post moistening with fluid, which led to bio-adhesion. Upon that biologically attached tablet, water was added to detach it from the model substrate, and the amount of water (in gram) needed to detach the tablet from the goat surface was determined that was known as mucoadhesive strengths. Such a procedure was repeated three times, and the average mucoadhesive strengths were reported. [19,20]

2.2.4.8 Ex vivo mucoadhesion time

Freshly cut goat buccal mucosa was used for the measurement of *ex vivo* mucoadhesion time (*n*=3) was done as per the reported method. A fresh goat buccal mucosa was collected and maintained as per procedure mentioned in section 2.2.4.7. A glass slide was taken and excised goat buccal mucosa was tied onto it. Upon this goat buccal membrane, a bio-adhesive side of the tablet, previously wetted with fluid, was pasted and force was applied with a light force with a fingertip for 30 s. The glass slide along with the pasted tablet was placed in the beaker containing 200 ml of the phosphate buffer pH 6.8 that was kept at 37°C ± 1 °C. The beaker containing the entire assembly was provided with slow stirring similar to the buccal cavity and the entire assembly was monitored for 12 h. The *ex-vivo* mucoadhesion time was calculated as the time required to detach the tablet from goat membrane that was tied to a glass slide [19,20]

2.2.4.9 Drug release studies

A previously reported method by Bhaskar, Swathi and Babu Rao[21] for Furosemide sustained release bilayered buccal tablets was simply followed in present drug release studies using the US Pharmacopeia XXIII rotating paddle apparatus. An instant adhesive (cyanoacrylate adhesive) was used for pasting the backing layer of the buccal tablet on a glass slide. The slide was then placed at the bottom of the dissolution vessel containing 250 ml of phosphate buffer saline, pH 6.8 which was maintained at 37 ± 0.5°C and rotated at 50 rpm throughout the experiment. Samples (10 ml) were withdrawn at predetermined time intervals at sink condition, followed by filter through Whatman filter (0.45 µm) paper and analyzed by using UV spectrophotometer at 262 nm.

2.2.4.10 Ex-vivo permeation of drug from buccal tablets

Ex-vivo permeation of drug from buccal tablets was performed using Franz- diffusion cell through the porcine buccal mucosa at 37°C ± 0.5°C and at 50 rpm. Fresh porcine buccal mucosa was obtained from a local slaughterhouse and used within 2 hours of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues, washed with distilled water and then with phosphate buffer pH 6.8 at 37°C. The fresh porcine buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. The membrane was collected and was stored at 4°C in Krebs buffer. This membrane was arranged between the two chambers, and phosphate buffer saline pH 6.8 was filled in the receiver chamber. The donor chamber was added with 1 ml phosphate buffer saline and to which a buccal tablet was suspended. Aliquots of 5 ml samples were collected at predefined time slots. The collected samples were filtered, suitably diluted and amount of drug permeated was determined using a double beam UV spectrophotometer using λ_{max}=262 nm. The flux (J) and permeability coefficient (P) were calculated using the given formula.

$$J = [dQ/dt] \div \Delta CA \qquad ()$$

$$P = [dQ/dt] \div A \qquad ()$$

Where 'J' flux (mg/h.cm^2), 'P' is a permeability coefficient (cm/h), 'dQ/dt' slope of the steady-state portion of the curve, 'ΔC' difference in concentration across the membrane and 'A' area of diffusion (cm^2). [22]

2.2.4.11 Drug release kinetics

To define the kinetics of drug release, the dissolution profile of optimized batch (F5) was fitted to various models such as zero order, First order, Higuchi, Hixon Crowell, Korsmeyer, and Peppas. [23]

2.2.5 Stability studies

To determine the change in bio-adhesive strengths and *in vitro* release profile on storage, a 3-months short-term stability study for the optimized batch was performed at 40°C ± 2°C in stability chamber with 75% ± 5% relative humidity (RH). Tablets were taken out at the 1-month interval and evaluated for any change in bio-adhesive strengths and *in vitro* drug release pattern. The difference factor (f_1) and similarity index (f_2) were calculated to find out the similarity between dissolution profile of batch F5 before and after storage at the level of significant ($p < 0.05$) by using the paired *t*-test.

Formulae to calculate difference factor (f_1) and similarity index (f_2) are as follows:

$$f1 = \{\sum l\, Rt - Tt\, l \div \sum Rt\} \times 100$$

$$f2 = 50 \log\{[1 + \sum_{n=1}^{n} (Rt - Tt)^2]^{0.5}\, x\, 100\}$$

Where t is 1 to n, n is the dissolution time and R_t and T_t are the reference and test dissolution value at time t. [24,25]

3 Results and Discussion

3.1 Drug excipient compatibility study

Fourier-Transform Infra-red spectroscopy was employed to study any kind of interaction between drug and additives used in the formulation. As per FTIR graph, no significant shift in the positions of the wave numbers was found for formulation (F5) when compared to that of the pure drug values which inferred no interaction between the drug and the employed additives in the formulation (Figure 1).

3.2 Preliminary study

Initially, the study was started with the preparation of preliminary tablets using various natural polymers to check their bio-adhesive properties along with tableting properties and same were compared with synthetic polymer (Carbopol 934). Table 4 shows the evaluation results for these formulations which indicated that batch B1 which contained neem gum has better bio-adhesive strengths as well as hardness. Hence, neem gum was chosen as a bio-adhesive polymer for further study. To assess the synergistic sustained-release characteristics of neem gum along with different grades of HPMC, tablet formulations (S1, S2, and S3) were prepared and checked with respect to drug release for 12 h. It was found that formulation S2 and S3 (containing HPMC K4M and HPMC K15 LV) were not able to sustain the drug release for 12 h whereas Batch S1 (containing neem gum and HPMC K4 100M) showed a sustained drug release for 12 h as depicted in Table 5. Such sustained effect would be needed for our study and hence selected for further study.

3.3 Full factorial design

3.3.1 Physico-chemical parameters

Prepared factorial formulations were evaluated for various physicochemical parameters. From the results, it was found that the weight variation within 7.5% deviation, hardness (4.33 - 5.71 kg/cm^2), thickness (1.69 - 1.86 mm), friability LT 1% and drug contents (98.97 - 101.21%) were within specified limits.

Surface pH of all the formulations was found to be between 5.5 and 7.5 (Figure 2), which seemed within the acceptable salivary pH range (5.5-7.0). It was inferred that the tablets would not produce local irritation to the mucosal surface.

3.3.2 Moisture absorption ratio

The moisture absorption ratio was calculated to assess the relative moisture absorption potential of polymers as well as their strengths to maintain the integrity of the formulation post that absorption. Prepared tablets were subjected to such studies and the results are shown in Figure 3. Formulation F4 was found to have minimum value (28 %) whereas formulation F8 of the maximum value (51 %) which may be attributed to the high concentration of hydrophilic neem gum.

3.3.3 *Ex vivo* Mucoadhesive strengths and time

The *ex vivo* Mucoadhesive strengths and time of the tablets was determined for all formulations using goat buccal mucosa. The Mucoadhesive strengths and time were found to be increased with increased concentrations of polymers. The best bio-adhesive strength was found for F9 batch (21.28 g) and the lowest for F1 batch (17.25 g). The mucoadhesion was attributed to the formation of a hydrogen bond between polymers due to swelling and mucin of the mucus membrane. F9 batch was prepared with higher concentration of neem gum and HPMC which might have resulted in high swelling and ultimately higher value of mucoadhesion. Figure 4 shows the results appeared from the test. This test indicated the mucoadhesive potential of polymers used in formulations.

3.3.4 *In vitro* drug release studies

Prepared factorial tablets were subjected to *in vitro* dissolution studies for 12 h to check the effect of the various concentration of neem gum with HPMC K100M and results are given in Figure 5. The dissolution pattern was found to be F1<F7<F2<F4<F8<F3<F6<F5<F9. Based on the criteria selected as per theoretical drug release profile of nicorandil at 1h (12%), 5h (50%) and 8h (80%), F5 formulation is considered to be promising as it has drug release of 11.25% at 1h, 51.81% at 5h and 79.20% at 8h. Additionally, it sustained the drug release for 12 h which was attributed to synergistic effect occurred due to the presence of HPMC K100M as well as neem gum.

To ensure the drug release kinetics from the optimized buccal tablet, dissolution profile was fitted to different

release kinetic models: zero-order, first-order, Hixson-Crowell, Higuchi, and Weibull's equations. The regression analysis was done for batch F5 and residual values were used to analyze the best fit of the experimental data to the predicted models ($r^2 > 0.99$ and minimum residual mean square, RMS and model parameters). The results are shown in Figure 6. As it can be seen, the zero-order model was suited best to the dissolution data for F5, which suggested that the rate of drug release was perpetual over a course of time independent of the drug concentration.

3.3.5 *Ex-vivo* permeation studies

Ex-vivo permeation studies (n=3) were performed for the optimized buccal tablet (F5). The slope, flux, and permeability coefficient for various formulations were found to be 0.623, 0.889±0.12, 0.241±0.07, respectively. Cumulative percentage of drug permeated from the prepared formulation is shown in Figure 7. Results of permeation study affirmed that the drug was liberated controllably from the tablet and impregnated steadily through the porcine buccal membrane and could possibly be infiltrated through the human buccal membrane as well.

3.4 ANOVA statistics for the factorial formulations

Total nine formulations were advised by the 3^2 factorial design for two independent variables: the amount of Neem gum (X_1, mg) and HPMC K100M (X_2, mg). The effect of these factors on Y_{60} (release in 60 min), Y_{240} (release in min), $T_{50\%}$ (Time in min required for 50% release) and Mucoadhesive strengths in gram force (MS) was examined as response parameters in the study. Summaries of the variables and observed responses are conferred in Table 6 & 7. The Design Expert 7.0 software calculated suitable model equations after fitting these data. As per ANOVA results, all the models were found to be significant ($p < 0.05$). Model simplification was carried out by eliminating non-significant terms ($p > 0.05$) in equations, giving: The model equation relating

$Y_{60} = 20.60 - 8.95X_1 + 0.6050X_2$----------Eq. no. (1)

$Y_{240} = 56.61 - 18.74X_1 - 5.88X_2$----------Eq. no. (2)

$T_{50\%} = 221.22 + 88.67X_1 + 14.50X_2$----------Eq. no. (3)

$MS = 18.99 + 0.8183X_1 + 1.07X_2$----------Eq. no. (4)

The data obviously demostrated that the response values are strongly dependent on the chosen independent variables. From the equations (1-4), it was established that independent variables (X_1 and X_2) have significant effects on chosen responses. The effects of factors (X_1 and X_2) on responses were demonstrated by plotting 3D surface plots and contour plots as shown in figure 8. It was found that responses may be changed by a convenient choice of the levels of X_1 and X_2. Results of dependent variables were selected to check the suitability of prepared tablets as mucoadhesive sustained-release formulation. Based on the theoretical requirement to prepare sustained-release tablet formulation of Nicorandil, Y_{60} should be 11.25%, Y_{240} should be 35% and $T_{50\%}$ should be 300 min. F5 formulation was found to have similar results to the theoretically calculated requirements. Hence, it is considered to be optimized formulation and can be explored further for the future study.

3.5 Stability studies

To assess the physicochemical nature of optimized formulation (F5) with respect to dissolution characteristics and Mucoadhesive strengths, it was wrapped in aluminum foil and kept in the stability chamber with well-controlled conditions of temperature (40°±2°C) and humidity (75%±5% RH). Post-storage, dissolution parameters and Mucoadhesive strengths were determined and their results are depicted in Table 8. The precise way to find similarities between dissolution curves is to find out the similarity factor f_2 than the difference factor f_1. According to the FDA, f_1 values less than 15 and f_2 values greater than 50 should establish an agreement between the dissolution curves, demonstrating an average disparity of no more than 10 % at the sample time points. According to this guideline, the dissolution curves corresponding to batch F5 before storage were similar to that obtained with the same formulation after storage. No significant changes were found as per the results which concluded that the prepared tablet formulation is stable.

Conclusion

To avert the first-pass metabolism and provide sustained drug release, buccal drug delivery of nicorandil is considered to be one of the best surrogate routes of administration. Additionally, it will lead to patient compliance as well by reducing the frequency of administration. To attain this, a factorial approach was used with a combination of HPMC K100M and neem gum to prepare sustained-release buccal tablets of nicorandil that have resulted in a sustained formulation, which can be used in once a day tablet.

Acknowledgments

The authors are thankful to Sun Pharma Laboratories Ltd., East Sikkim, for providing nicorandil as a gratis sample to carry out this research work.

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Table 1 Preliminary trial for selection of bioadhesive polymer (B1-B5)

Ingredients	B1	B2	B3	B4	B5
Core tablet					
Nicorandil	10	10	10	10	10
Neem Gum	30	-	-	-	-
Guar Gum	-	30	-	-	-
Na Alginate	-	-	30	-	-
Carbopol 934	-	-	-	30	-
Xanthan Gum	-	-	-	-	30
PVP K30	10	10	10	10	10
Mannitol	68	68	68	68	68
Magnesium stearate	1	1	1	1	1
Aspartame	1	1	1	1	1
Backing layer					
Ethyl Cellulose	80	80	80	80	80
Total (mg)	200	200	200	200	200

Table 2 Compositions of formulation for optimization of sustained release polymer (S1-S3)

Ingredients	S1	S2	S3
Core tablet			
Nicorandil	10	10	10
Neem Gum	30	30	30
HPMC K4 100M	30	-	-
HPMC K4 M	-	30	-
HPMC K15 LV	-	-	30
PVP K30	10	10	10
Mannitol	38	38	38
Magnesium stearate	1	1	1
Aspartame	1	1	1
Backing layer			
Ethyl Cellulose	80	80	80
Total (mg)	200	200	200

Table 3 3^2 Experimental design for buccal tablet formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Core tablet									
Nicorandil	10	10	10	10	10	10	10	10	10
Neem Gum	20	20	20	30	30	30	40	40	40

HPMC K4100M	20	30	40	20	30	40	20	30	40
Mannitol	58	48	38	48	38	28	38	28	18
PVP K30	10	10	10	10	10	10	10	10	10
Magnesium stearate	1	1	1	1	1	1	1	1	1
Aspartame	1	1	1	1	1	1	1	1	1
Backing layer									
Ethyl Cellulose	80	80	80	80	80	80	80	80	80
Total Weight in mg	200	200	200	200	200	200	200	200	200

Table 4 Evaluation of preliminary batches for selection of bioadhesive polymer

Batches	Hardness (kg/cm^2) (*n*=3)	Mucoadhesive strength (gram force) (*n*=3)
B1	5.74±0.75	19.07±1.12
B2	5.86±0.67	17.45±1.14
B3	5.34±0.47	17.01±1.11
B4	6.47±0.42	21.24±0.99
B5	5.14±0.33	16.67±1.10

Table 5 Evaluation of preliminary batches for optimization of sustained release polymer

Time (h)	Cumulative percentage drug release		
	S1	S2	S3
0	0	0	0
1	18.23±0.56	22.14±0.64	30.23±0.54
2	26.60±0.64	39.89±0.84	36.02±0.64
3	35.11±0.68	47.02±0.24	41.05±0.66
4	46.12±0.67	57.64±0.26	56.31±0.52
5	57.46±0.62	63.74±0.34	71.26±0.34
6	64.34±0.54	73.23±0.28	83.27±0.25
7	73.23±0.45	83.37±0.94	98.63±0.47
8	79.26±1.20	90.54±0.34	-
9	86.23±0.87	91.23±0.67	-
10	90.14±0.67	101.2±0.84	-
11	95.46±0.75	-	-
12	100.47±0.84	-	-

Table 6 Response values for buccal tablet formulations as per experimental design

Batch code	Y_{60} (%)	Y_{240} (%)	T_{50} (Min)	Mucoadhesive strength (gram force)
F1	33.42	87.52	120	17.25
F2	22.56	68.24	145	18.12
F3	11.32	47.56	275	18.23
F4	22.31	63.26	162	18.49
F5	12.83	32.3	350	18.42
F6	12.01	42.56	312	20.36
F7	32.38	81.81	110	19.22
F8	27.45	56.24	180	19.52
F9	11.10	30.01	337	21.28

Table 7 ANOVA for linear model

Y_{60}						
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	482.45	2	241.23	7.83	0.0213	Significant
A-HPMC K100M	480.26	1	480.26	15.59	0.0076	
B-Neem gum	2.20	1	2.20	0.0713	0.7984	
Residual	184.89	6	30.81			
Cor Total	667.34	8				
Y_{240}						
Source	Sum of Squares	Df	Mean Square	F-value	p-value	
Model	2315.09	2	1157.54	6.72	0.0294	Significant
A-HPMC K100M	2107.88	1	2107.88	12.25	0.0128	
B-Neem gum	207.21	1	207.21	1.20	0.3146	
Residual	1032.84	6	172.14			
Cor Total	3347.93	8				
$T_{50\%}$						
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	48432.17	2	24216.08	5.52	0.0437	significant
A-HPMC K100M	47170.67	1	47170.67	10.75	0.0168	
B-Neem gum	1261.50	1	1261.50	0.2876	0.6111	
Residual	26321.39	6	4386.90			
Cor Total	74753.56	8				
Mucoadhesive strength						
Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	10.89	2	5.44	21.71	0.0018	significant
A-HPMC K100M	4.02	1	4.02	16.03	0.0071	
B-Neem gum	6.87	1	6.87	27.40	0.0019	
Residual	1.50	6	0.2507			

Cor Total	12.39	8				

Table 8 Evaluation of stability studies of formulation (F5) for 3 months (Mean ± SD, *n*=3)

Batch F5	*In-vitro* drug release at 12h (%)	Mucoadhesive strength (grams)
Before storage	96.35 ± 1.54	18.42 ± 0.54
After storage at 40°±2°C temperature and 75%±5% Relative humidity	98.25 ± 2.03	20.56 ± 1.20
Similarity and dissimilarity (f_1 & f_2) factor	f_1 = 4 f_2 = 77	Not applicable

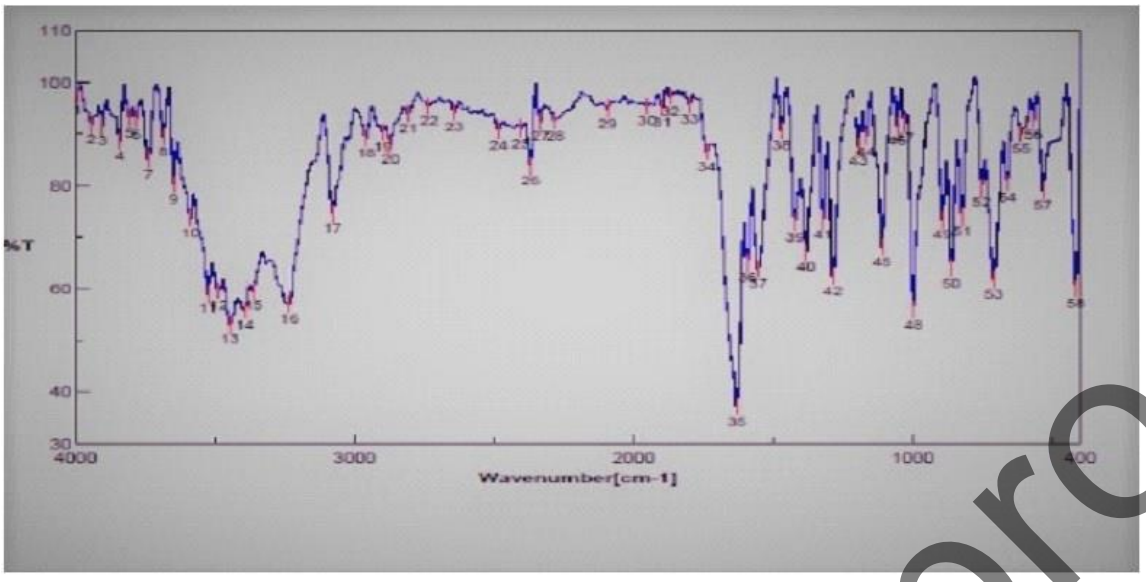


Fig. 1(a)

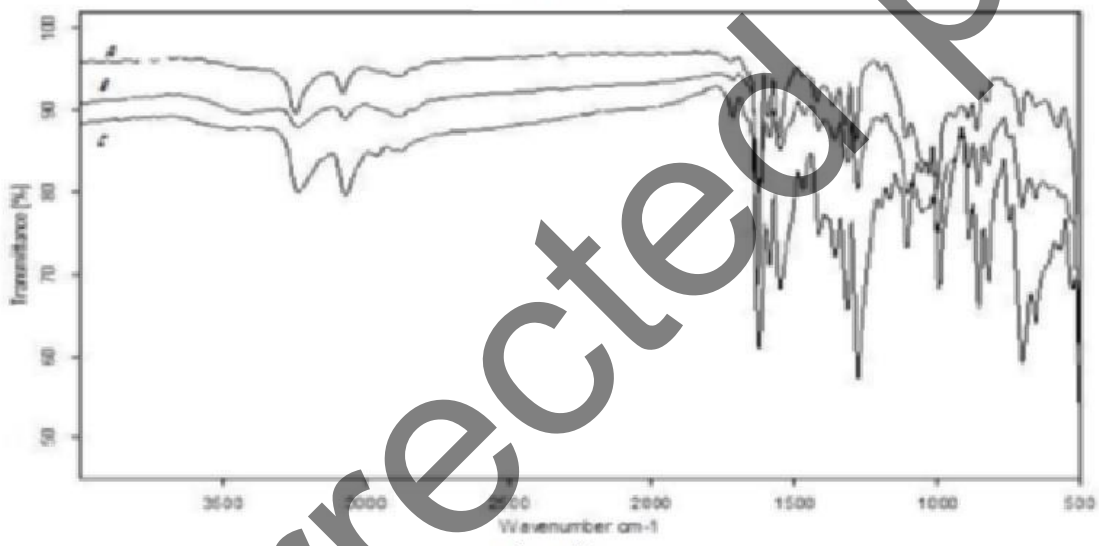


Fig. 1(b)

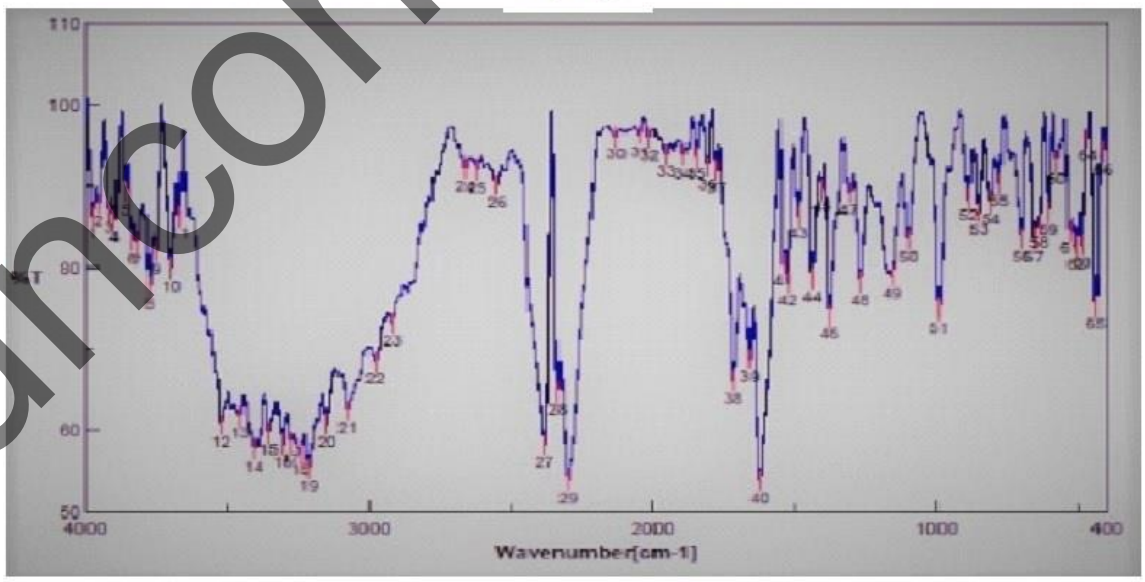


Fig. 1(c)

Figure 1 FTIR spectra a) b) c)

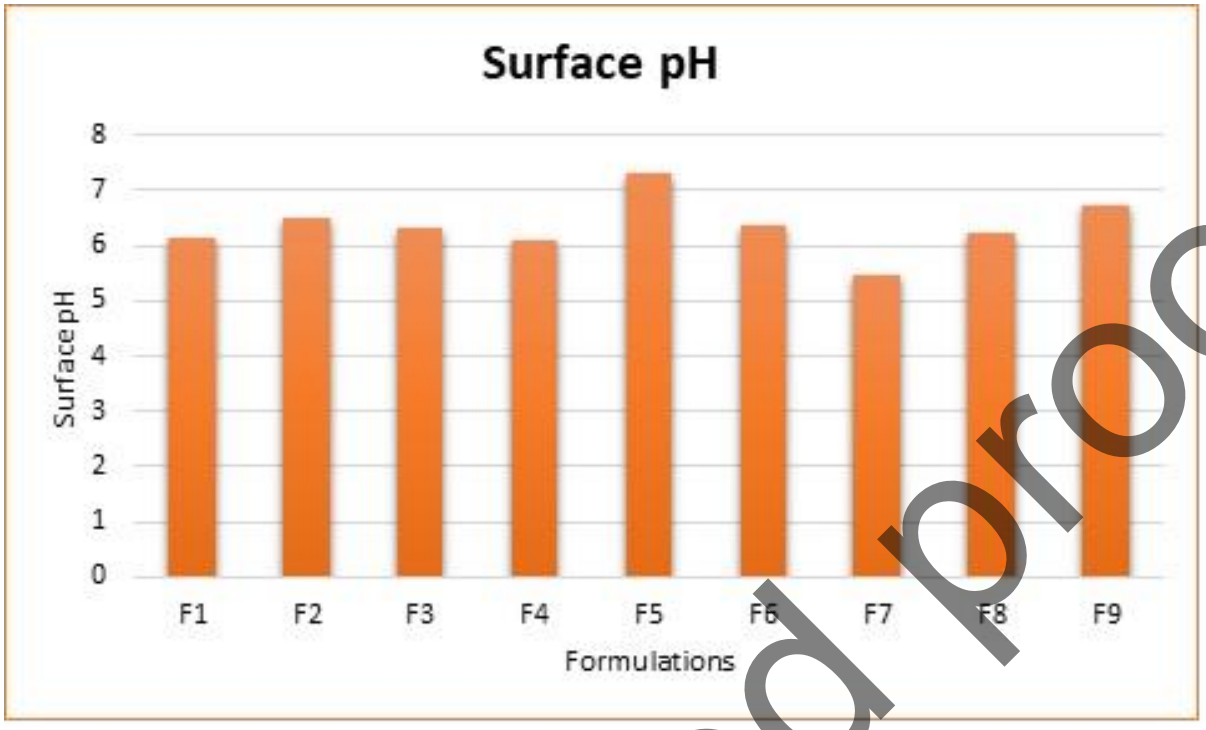


Figure 2 Surface pH of factorial batches

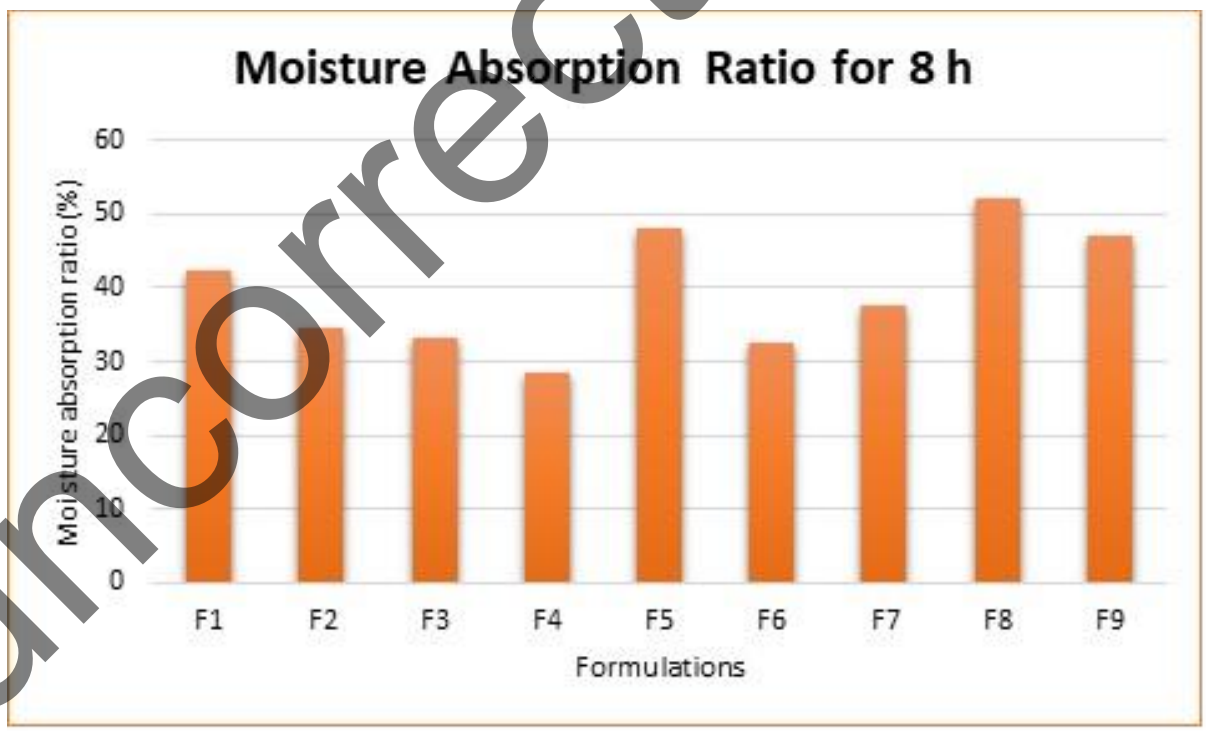


Figure 3 Moisture absorption ratio for 8 h of factorial batches

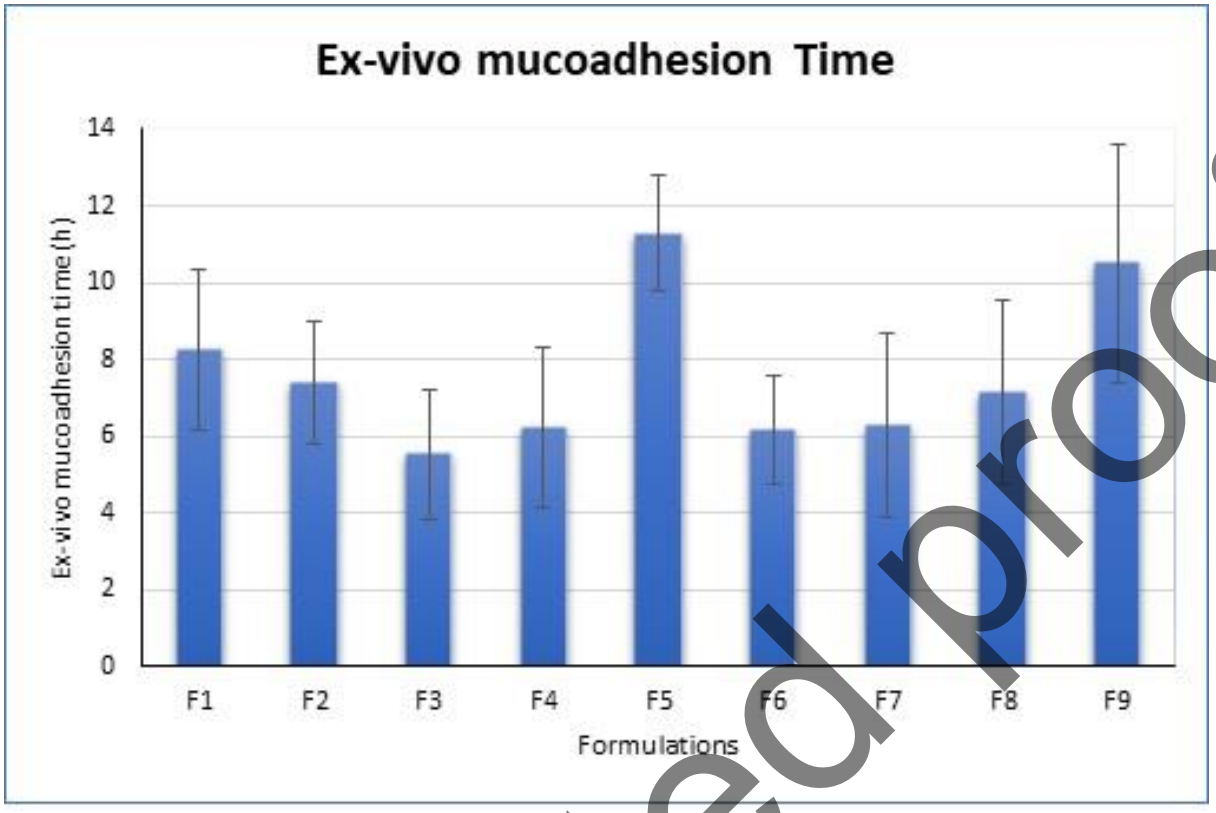


Figure 4 Ex-vivo Mucoadhesion time of factorial batches

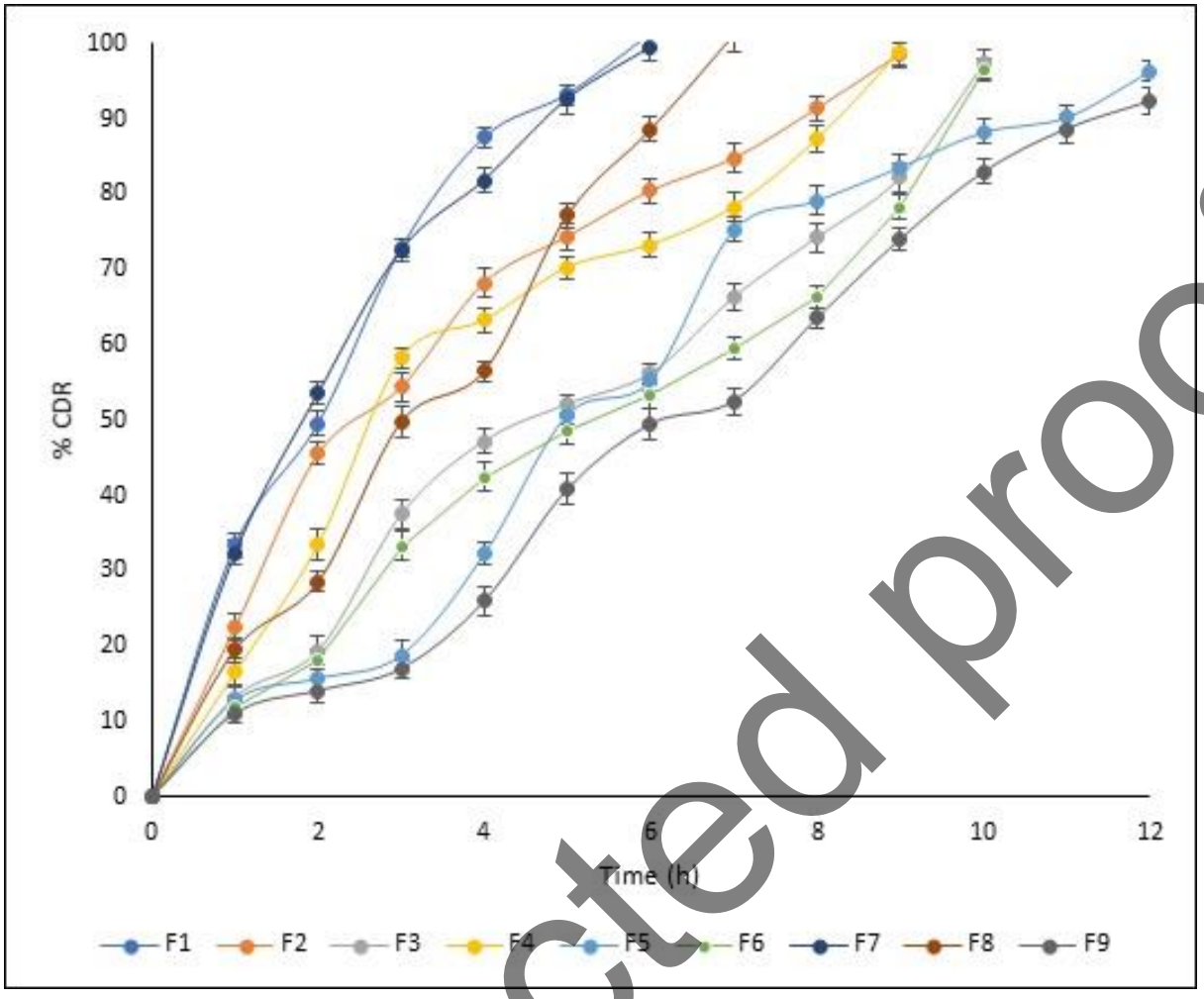


Figure 5 Cumulative percentage drug release profiles

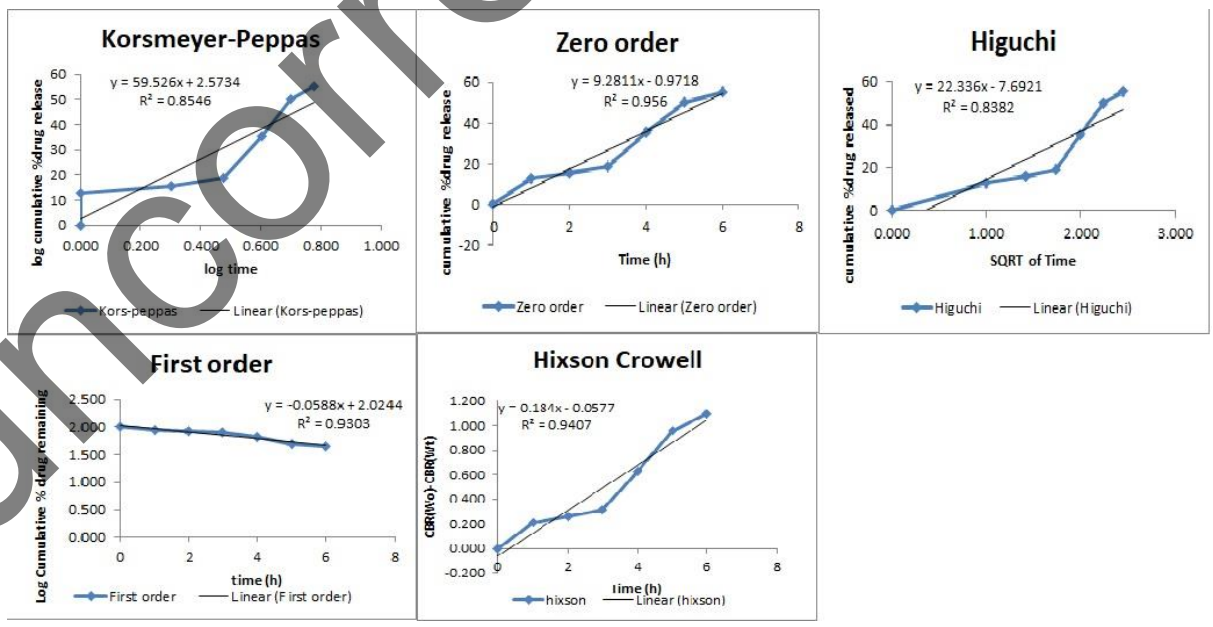


Figure 6 Release kinetics results of optimized formulation (F5)

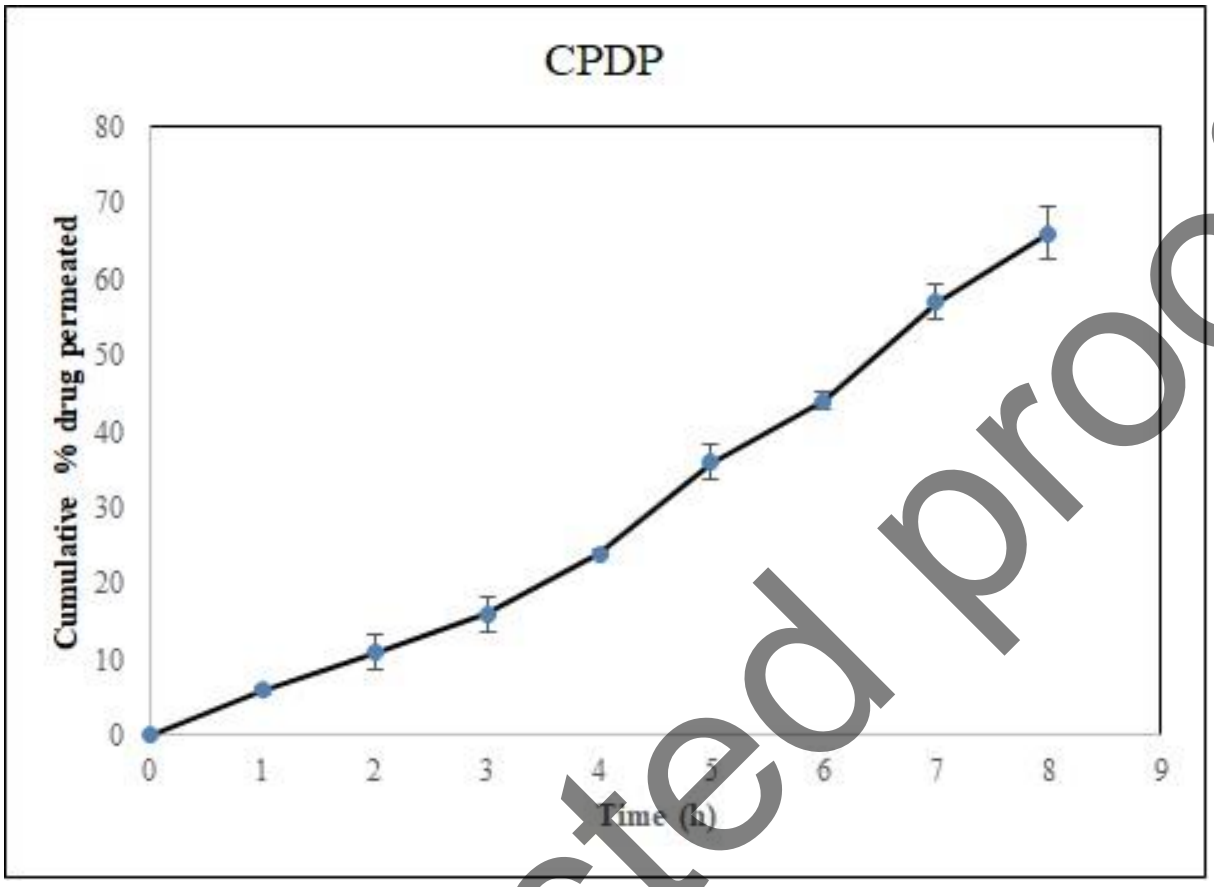
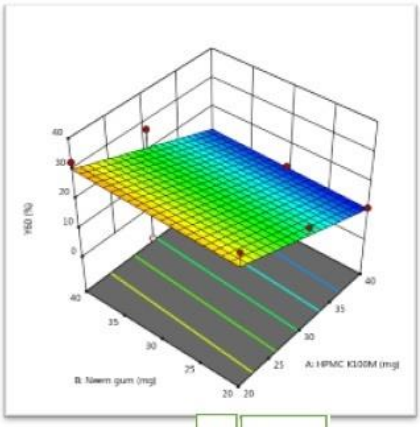
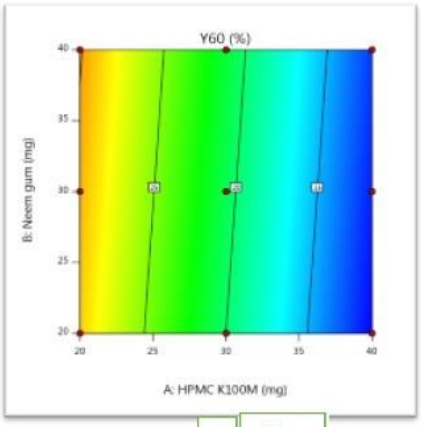


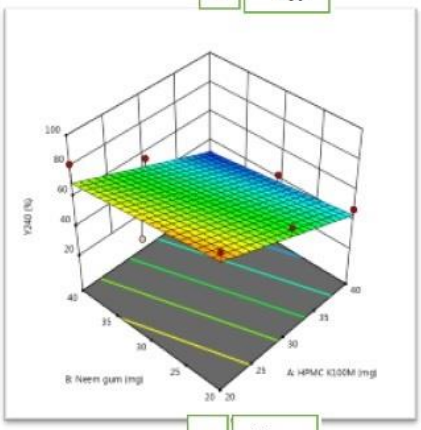
Figure 7 Cumulative percentage drug permeation of (F5)



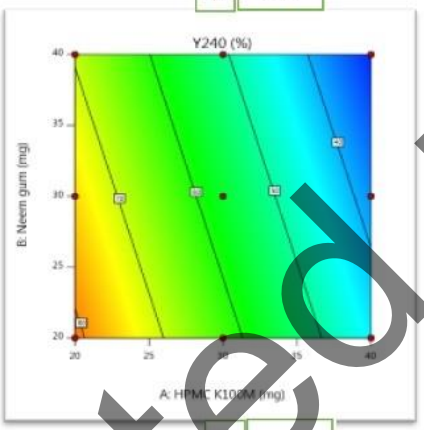
a Y_{60}



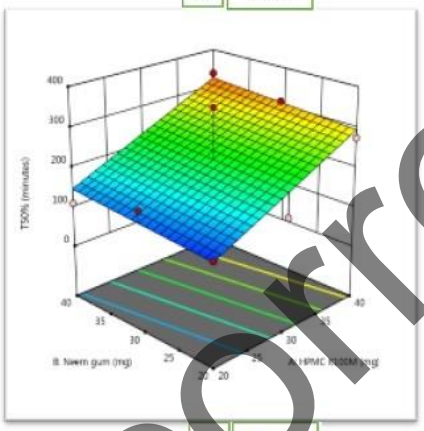
b Y_{60}



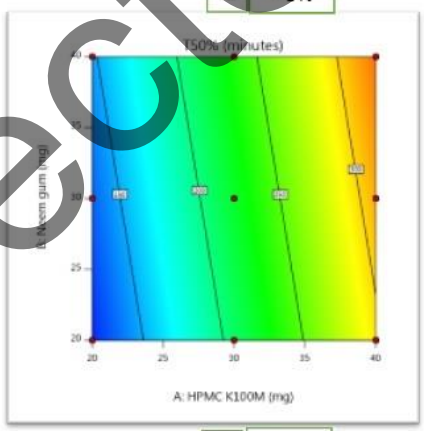
c Y_{240}



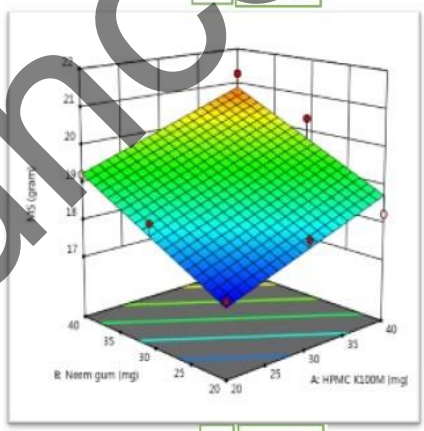
d Y_{240}



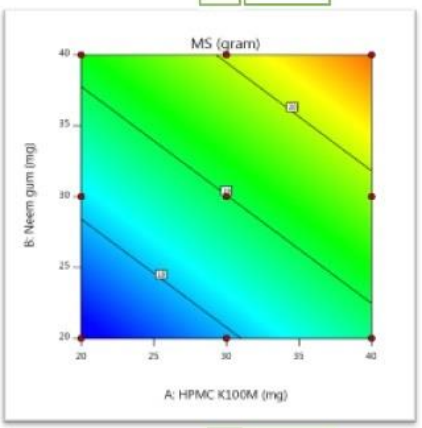
e $T_{50\%}$



f $T_{50\%}$



g MS



h MS

Figure 8 Surface plots (a, c, e, g) and contour plots (b, d, f, h)