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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL TABLET OF IVABRADINE HYDROCHLORIDE

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Abstract

The study aimed to develop buccal tablets of Ivabradine HCl, focusing on mucoadhesive properties. Various polymers, including Natrosol 250 M, Natrosol 250 HHX, Natrosol 250 G, and Carbopol 934 P, were employed via direct compression. Infrared spectrum analysis confirmed no drug-polymer interactions. Tablets met pharmacopoeial standards for weight, hardness, thickness, friability, and drug content. Their surface pH indicated safe mucosal use. Swelling up to 8 hours in distilled water ensured bioadhesion integrity. In-vitro release extended to 8 hours, with formulation F6 exhibiting 99% drug release, hence chosen for optimization using factorial design. Factorial batches (I1-I9) with Carbopol 934 P and Natrosol as variables showed significant outcomes. Batch I8 achieved desired drug release. Batch O1 was fine-tuned for drug release and mucoadhesive strength, releasing 99% over 8 hours, with good permeability. Zero order was determined to be the best-fitting model (R^2 = 0.99832), suggesting non-Fickian diffusion. Stability assessment over a month confirmed formulation stability. Batch O1 outperformed a commercial product, becoming the optimized formulation.

Key Words: Ivabradine HCl, Natrosol 250 M, Natrosol 250 HHX, Natrosol 250 G, and Carbopol 934 P.

Introduction

Buccal drug delivery stands out for systemic administration due to its advantages, such by delivering the drug directly to the body's systemic circulation, eliminating pre-systemic removal, and avoiding the first-pass impact. Compared to routes like rectal, vaginal, sublingual, and nasal, buccal mucosa offers rich blood supply and relative permeability, making it an attractive option.While other routes like nasal drug delivery have been explored, concerns about potential irritation and damage to the nasal cavity's ciliary action have relegated them to secondary choices. Despite advantages offered by rectal, vaginal, and ocular mucosa, low patient acceptability limits their use primarily to local applications.The buccal mucosa's ability to sustain drug delivery and its efficient absorption due to rich blood supply make it appealing for both local and systemic drug delivery. Its accessibility for self-medication and the ease of promptly removing the dosage form in case of toxicity add to its appeal.

Ivabradine hydrochloride is used to treat instable angina pectoris, which produces chest pain, as well as mild to severe chronic heart failure. Another name for ivabradine is an agent that lowers heart rate.5-7 The illness known as angina pectoris is characterised by a low oxygen supply. To lessen chest pain during an angina episode, the oxygen supply must be balanced right away. Reduced oxygen demand can increase oxygen supply. The medication that lowers oxygen demand and balances oxygen supply demand is ivabradine.

the goal of the current study was to accelerate the rate of absorption by incorporating potential superdisintegrants such as crospovidone, sodium starch glycolate, and croscarmellose sodium at varying quantities. This would increase the ivabradine hydrochloride's start of action.

Materials and methods

Ivabradine HCL was obtained from Torrent Pharmaceuticals LTD.Natrosol from Labdhi Chemicals, Ahmedabad.Carbopol 934 P, from Chemdyes Corporation, Rajkot-360001. Ethyl Cellulose, Magnesium Stearate, Talc, Lactose, Sucralose All other ingredients from Chemdyes Corporation, Rajkot-360001.(Gujarat).

Method of Preparation of Buccal Tablets

The **Direct Compression** Method was used to make the buccal tablets. All the ingredients dispense as per formula sheet. Pass the dry mixing part ingredients through 40 # sieve. Except Magnesium Stearate and Talc 60 #.Mix the adhesive layer material in poly bag properly (5 min). Add Magnesium stearate and lubricate the blend for 5 min. Compress the adhesive layer in compression machine. On the adhesive layer put ethyl cellulose as backing layer and again compress to get second layer on tablet.

Table 1 Formulation Table of Trial Batches of Buccal tablets

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ivabradine HCl	5.0	5.0	5.0	5.0	5.0	**5.0**	5.0	5.0	5.0
Natrosol 250 G	10.0	20.0	30.0	-	-	**-**	-	-	-
Natrosol 250 HHX	-	-	-	10.0	20.0	**30.0**	-	-	-
Natrosol 250 M	-	-	-	-	-	**-**	10.0	20.0	30.0
Carbopol 934 P	10.0	10.0	10.0	10.0	10.0	**10.0**	10.0	10.0	10.0
Lactose	60.0	50.0	40.0	60.0	50.0	**40.0**	60.0	50.0	40.0
PVPK 30	5.0	5.0	5.0	5.0	5.0	**5.0**	5.0	5.0	5.0
Sucralose	4.0	4.0	4.0	4.0	4.0	**4.0**	4.0	4.0	4.0
Talc	4.0	4.0	4.0	4.0	4.0	**4.0**	4.0	4.0	4.0
Magnesium Stearate	2.0	2.0	2.0	2.0	2.0	**2.0**	2.0	2.0	2.0
Ethyl Cellulose	50.0	50.0	50.0	50.0	50.0	**50.0**	50.0	50.0	50.0
Total (mg)	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**

Table 2 Layout of Factorial Design

3^2 Full Factorial Designs		
Batch No.	**X1 Amount of Natrosol 250 HHX**	**X2 Amount of Carbopol 934 P**
I1	-1	-1
I2	-1	0
I3	-1	+1
I4	0	-1
I5	0	0
I6	0	+1
I7	+1	-1
I8	+1	0
I9	+1	+1

Translation of coded level in actual limit			
Independent variables	**Real Value**		
	Low (-1)	**Medium (0)**	**High (+1)**
Amount of Natrosol 250 HHX (mg) X1	25.0	30.0	35.0
Amount of Carbopol 934 P (mg) X2	5.0	10.0	15.0

Independent variables
X_1-Amount of Natrosol 250 HHX (mg)
X_2-Amount of Carbopol 934 P (mg)

Dependent variables
Y1- % Drug release at 1 hour
Y2- Mucoadhesive Strength

Table 3 Formulation Table of Factorial Batches of Buccal tablets

Ingredients (mg)	I1	I2	I3	I4	I5	I6	I7	I8	I9
Ivabradine HCl	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Natrosol 250 HHX	25.0	25.0	25.0	30.0	30.0	30.0	35.0	35.0	35.0
Carbopol 934 P	5.0	10.0	15.0	5.0	10.0	15.0	5.0	10.0	15.0
Lactose	50.0	45.0	40.0	45.0	40.0	35.0	40.0	35.0	30.0
PVPK 30	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0	5.0
Sucralose	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Talc	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Magnesium Stearate	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.0
Baking layer Ethyl	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0	50.0
Total (mg)	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**	**150.0**

Methodology

Preformulation

Characterization of API: -

Organoleptic property:
This involves documenting the drug's hue and scent using precise language. and record the same in results and discussion chapter.

Flow Property:
The study examined the flow characteristics of API/powder blends. To determine bulk density, 10 grams of powder were carefully poured into a 50-milliliter measuring cylinder without compaction, and the volume of the powder was recorded. After tapping the powder 100 times, the volume was measured to obtain the desired tapped density. The powder mixtures' Carr's index (CI) & Hausner ratio (HR) were calculated using the measurements of powder densities.

Melting point:
The Melting Point Testing Apparatus: technique was incorporated into the device to determine the drug's (API) melting point.

Using a modern melting point apparatus, the following steps are needed to measure melting point:

- make sure the sample is completely dry and powdered
- put the sample in a capillary tube
- insert the capillary tube to the melting point apparatus
- quickly heat the sample to a predetermined temperature
- slow down the rate of temperature increase to see when the sample melts
- view the melting point through a viewing eyepiece
- digitally record the melting point.

Determination of λ Max

The standard solution of Ivabradine was scanned across various concentrations within the wavelength range of 200 to 400 nanometers to determine its maximum absorption wavelength (λ max).

Calibration curve for Ivabradine HCl[45]

A calibration curve for Ivabradine HCl was established in a phosphate buffer with a pH of 6.8 using a UV-visible spectrophotometer (UV 1700, Shimadzu).

Procedure: Approximately 10 milligrams of Ivabradine HCl were precisely weighed and dissolved in a sufficient amount of 6.8 pH phosphate buffer in a 100 milliliter volumetric flask. The solution was then sonicated for 15 minutes and diluted to a final volume of 100 milliliters with the same solvent, resulting in a concentration of 100 micrograms per milliliter. Various concentrations of the drug solution were prepared

by pipetting appropriate aliquots from In order to get concentration ranging from 10 to 50 micrograms per millilitre of Ivabradine HCl, the standard stock solution was placed into a series of 10 millilitre volumetric flasks. The volume was then diluted to the appropriate mark using 6.8 pH phosphate buffer.

Drug Excipients Compatibility studies

FTIR Spectroscopy

The drug's physical and chemical interactions with the used excipients were examined using the Fourier transform infrared (FTIR) technology. The KBr mixing procedure was used to acquire the FTIR spectra of the Physical Mixture and the pure medication.

Evaluation Parameters of Buccal Tablets

(A) Pre compression Parameters: -

Bulk Density:

Computed using the formula that follows.

Bulk density = Weight of powder / Bulk volume

Tapped Density

Computed using the formula that follows

Tapped density = Weight of powder / Tapped volume

Compressibility Index (CI):

Computed using the formula that follows

Carr's Compressibility index (%) = {(TD- BD) / TD} X 100.

Table 4 Scale of flow ability by Compressibility index

C.I.	Category	Hausner's Ratio
<10	Excellent	1.00–1.110
11 – 15	Good	1.12–1.180
16 – 20	Fair	1.19–1.250
21 – 25	Passable	1.26–1.340
26 – 31	Poor	1.35–1.450
32 – 37	Very poor	1.46–1.590
>38	Very very poor	>1.600

Hausner's Ratio:

The formula below can be used to compute this.

Hausner's ratio = Tapped density / Bulk density

(B) Post Compression Parameters

Weight Variation

An electric digital balance was used to weigh twenty tablets of each formulation, and the average weight was determined.

Table 5 IP/BP/USP limit of weight variation test.

IP/BP Average weight of tablet (mg)	% Deviation	USP Average weight of tablet (mg)
130 or less	10.0	80 or less
From 130 to 324	7.5	From 80 to 250
More than 324	5.0	More than 250

Hardness

Hardness was assessed by diametrically compressing six tablets from each batch using a Monsanto hardness tester, and average values were subsequently computed.

Friability

Friability, which indicates tablet strength, was assessed using a Roche-type friabilator following this procedure: After twenty tablets were weighed precisely, they were put into the tumbling device, which turned at a speed of twenty-five revolutions per minute, lowering the tablets every six inches. The tablets were tumbling for four minutes, and a percentage of weight loss was computed by reweighing the tablets.

% loss = initial wt.-final wt. / initial wt. × 100

Thickness

Using vernier callipers, the thickness of the buccal tablets was measured. A random selection of ten tablets was made from each batch. and their thickness was individually assessed. The average thickness was then calculated from the recorded measurements.

Drug content

Weighing ten tablets, we used a glass mortar and pestle to grind them into a fine powder. From each batch, a quantity of powder equal to one tablet's mass was placed into individual 100 millilitre volumetric flasks holding 100 millilitres of 6.8 phosphate buffer each. The flasks were stirred constantly for 15 minutes. The resulting solutionswere filtered, diluted, and subsequently analyzed at a wavelength of 286 nanometers using a UV spectrophotometer.

Swelling study

After each tablet was weighed separately (W1), it was put onto a different Petri dish with five millilitres of pH 6.8 artificial saliva in it. Each tablet was withdrawn from the Petri dish at intervals of 1, 2, 4, 6, and 8 hours, the excess water carefully wiped away with filter paper, and the swelled tablet was weighed again (W2). The given formula was used to get the percentage of hydration.

% Swelling Index (S.I) = $[(W_2-W_1)/ W_1] \times 100$

W_1 = initial weight

W_2= final weight

Surface pH

The buccal tablets' surface pH was examined to determine whether there would be any unfavourable in vivo consequences.. Maintaining a neutral surface pH was prioritized to minimize irritation to the buccal mucosa, which could result from acidic or alkaline conditions. An amalgamated glass electrode was employed in this evaluation. For two hours at room temperature, the tablets were submerged in five millilitres of distilled water with a pH of 7.0 ± 0.05 to allow them to swell. The electrode was placed in contact with the tablet surface and left to stabilise for one minute in order to test the pH.

Mucoadhesion studies

In the laboratory, a custom apparatus was constructed to evaluate the bioadhesive properties of the tablets. Using the buccal mucosa of sheep as a model mucosal membrane, the mucoadhesion strength was determined using a modified physical balance. Using a double-beam physical balance, the left pan was taken out.. A thick thread of appropriate length was suspended from the left arm of the balance. A glass vial with a capacity of 30 milliliters and a uniform surface was attached to the bottom side of the thread. A clean 500 milliliter glass beaker was positioned beneath the hanging glass vial, within which another glass beaker with a capacity of 100 milliliters was placed in an inverted position. Temperature control was achieved by placing a thermometer in the 500 milliliter beaker and periodically adding hot simulated saliva (pH 6.8) to maintain the temperature at 37.0±0.5 degrees Celsius.

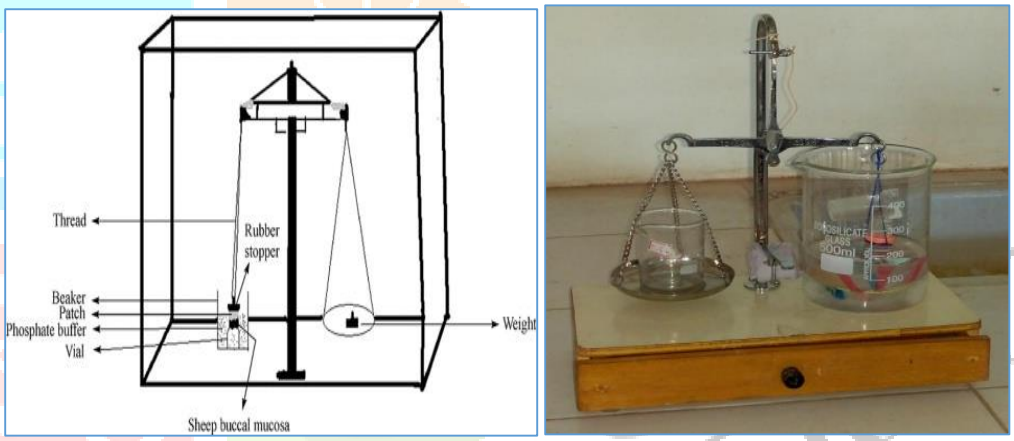


Figure 1 Modified physical balance used to measure mucoadhesive strength

Mucoadhesive time

The ex vivo the adhesion of (residence) time for the tablets was ascertained using a locally modified USP disintegration device. To produce fresh sheep buccal mucosa, loose tissues and underlying fat were removed. Following a 37°C wash with distilled water, the mucosal membrane was exposed to 6.8 phosphate buffer. One side of each tablet was moistened using a drop of 6.8 phosphate buffer and gently placed onto the sheep buccal mucosa for 20 seconds after a 4-centimeter-long slice of mucosa was attached to a glass slide. After that, the glass slide was attached to the device vertically so that the tablet could move vertically and be fully immersed in the buffer solution at both its lowest and highest points. The medium was an 800 millilitre beaker with 6.8 phosphate buffer at 37 ± 1 degrees Celsius. The mucoadhesion time was measured as the amount of time it took for the tablet to separate from the buccal mucosa.

In-vitro release study

A USP type II dissolution device was used to study the drug release from buccal tablets. Sixteen hundred millilitres of pH 6.8 phosphate buffer made up the dissolving media. The device was revolving at 50 revolutions per minute (rpm) and the dissolution procedure was carried out at 37 ± 0.5 degrees Celsius. Using instant glue, the tablet's impermeable layer was attached to a glass slide. The tablet was able to stay on the top side of the slide because it was placed at the bottom of the dissolving vessel. Five millilitre

samples were removed during the dissolution process at prearranged periods and replaced with new media. After passing these samples through Whatman filter paper, they were subjected to spectrophotometric analysis at 286 nanometers. The blank used for this analysis was phosphate buffer at pH 6.8.

kinetic analysis

Numerous mathematical models, such as the zero order, first order, Higuchi, Hixon Crowell, and Korsmeyer-Peppas release models, were used to analyse the data gathered from all formulations. When there may be more than one release mechanism at work or when the release mechanism is not completely understood, the Korsmeyer-Peppas model is especially helpful. When there is non-Fickian release, the parameter "n" usually has a value between 0.5 and 1.0. In the case of Fickian diffusion, "n" is either 0.5 or less. "n" equals 1 in cases of zero-order release (also called case II transport). Super case II transport is indicated by "n" values larger than 1..

In vitro buccal permeability studies

A 20 millilitre Franz diffusion device and sheep buccal mucosa were used in an in-vitro study on buccal permeation. After being purchased from a nearby butcher shop and kept in phosphate buffer at a pH of 6.8, sheep buccal mucosa was utilised two hours after the animals were killed. With extreme caution, the mucosa was severed from the underlying connective tissues and pinched between the diffusion cell's donor and receptor compartments. The buccal pill was placed so that the mucosa was facing its centre. One millilitre of pH 6.8 phosphate buffer was placed in the donor compartment, while a receptor compartment also held pH 6.8 phosphate buffer. The compartment's hydrodynamics were preserved by slowly and steadily stirring using a magnetic bead. One millilitre samples were taken out at regular intervals and subjected to UV spectrophotometry analysis.

Stability Studies

Stability studies were conducted on the optimized formulation, with the chosen formulation subjected to storage conditions of 40 ± 2°C and 75 ± 5% relative humidity. After one month, samples were withdrawn and analyzed for critical parameters such as physical appearance, dissolution, and drug content.

Results & discussion

Preformulation Study

Table 6 API properties

API Properties	Results Observed
State of Powder	Solid State
Description of Powder	It is white to off white Crystalline powder
Colour of Powder	It is White to off white in colour
Bulk Density (g/ml) of Powder	0.225±0.001 g/ml
Tapped Density (g/ml) of Powder	0.486±0.001 g/ml
Compressibility Index (CI): of Powder	2.12±0.02 (Poor Flow)
Hausner Ratio of Powder	52.88±0.02 (Poor Flow)
Solubility of API	It was observed that Ivabradine HCl was freely soluble in water and 6.8 Phosphate buffer at room temperature.
Melting Point of API	196.0 °C

Determination of λ Max and Calibration curve of Ivabradine HCl

The λ_{max} found 286.0 nm in 6.8 pH phosphate buffer Solution.

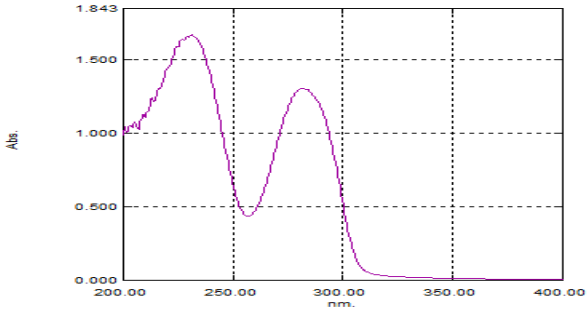


Figure 1 λmax of 100 ppm Ivabradine HCl in 6.8 pH phosphate buffer

Standard calibration curve of Ivabradine HCl in 6.8 pH phosphate buffer

Concentration (µg/ml)	Mean Absorbance at (286 nm) ± SD
0	0
10	0.196± 0.003
20	0.381± 0.003
30	0.548± 0.004
40	0.721± 0.005
50	0.912 ± 0.003

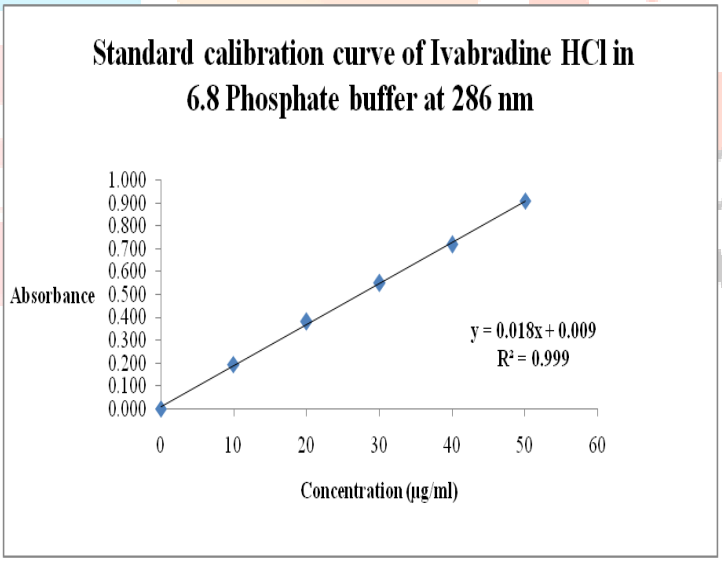


Figure 2 Calibration curve of Ivabradine in 6.8 pH phosphate buffer at 286 nm

Drug- excipient compatibility studies

The medication and some excipients were compatible, according to an FTIR investigation. There were no interactions of any type between the medication and the excipients. Please refer to figures.

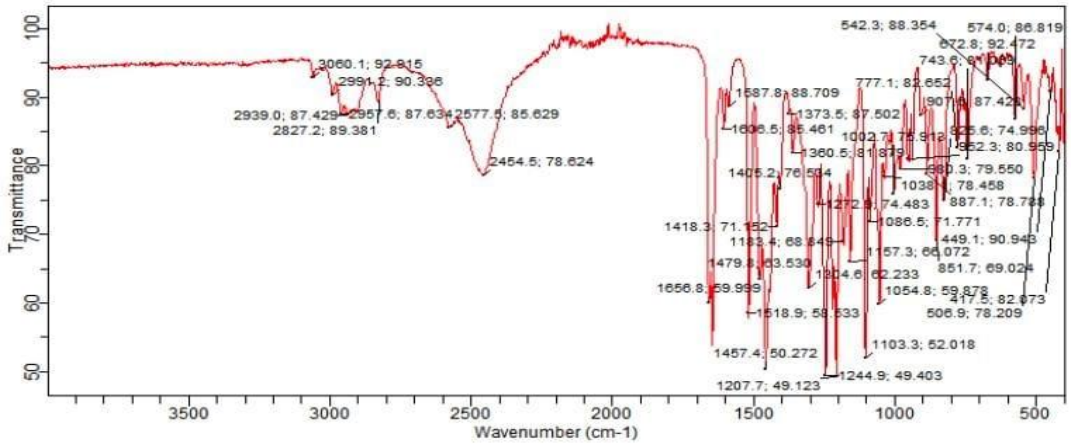


Figure 3 FTIR spectra of Ivabradine HCl

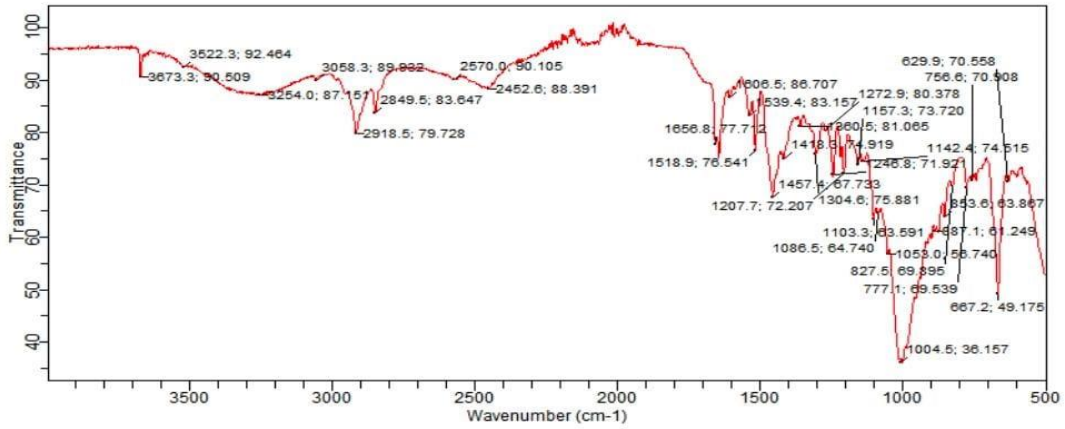


Figure 4 FTIR of Physical Mixture of Optimized Formulation

Table 7 Interaction studies through IR spectroscopy

FUNCTIONAL GROUP	Pure Drug peak (cm^{-1})	Final Formulation peak (cm^{-1})
C=C	1103.30	1103.30
C-C	1457.40	1457.40
C-N	2454.50	2452.60
C-H	1457.40	1457.40

Conclusion: Based on the FTIR study findings presented above, it was concluded that there were no notable interactions observed between the drug and excipients. Therefore, the drug and other excipients are deemed compatible with each other.

Pre compression Parameters of Trial Batches

Table 8 Result of Pre compression parameters of Trial Batches

Formulation Code	Bulk density (g/ml) (n=3)	Tapped density (g/ml) (n=3)	% Compressibility (n=3)	Hausner's ratio (n=3)	Angle of repose (Ɵ) (n=3)
F1	0.50 ± 0.07	0.58 ± 0.02	13.79 ± 0.02	1.16 ±0.06	29.92º ±1.2
F2	0.51 ± 0.11	0.59 ± 0.05	13.27 ± 0.04	1.15 ±0.07	27.90º ±2.3
F3	0.49 ± 0.08	0.57 ± 0.05	13.88 ± 0.05	1.16 ±0.08	28.22º ±2.5
F4	0.46 ± 0.07	0.53 ± 0.02	12.55 ± 0.08	1.14 ±0.03	21.12º ±3.1
F5	0.52 ± 0.06	0.59 ± 0.03	11.41 ± 0.09	1.13 ±0.04	28.20 º±1.9
F6	0.52 ± 0.09	0.60 ± 0.07	13.04 ± 0.07	1.15 ±0.05	27.14º ±2.4
F7	0.51 ± 0.08	0.57 ± 0.08	11.15 ± 0.04	1.13 ±0.06	29.08º ±2.3
F8	0.46 ± 0.05	0.52 ± 0.07	12.21 ± 0.06	1.14 ±0.04	26.21º ±1.3
F9	0.47 ± 0.07	0.54 ± 0.05	13.60 ± 0.03	1.16 ±0.06	28.32º ±2.3

It can be concluded from the flow property data above that the blended flow is of a good nature and handles compression smoothly.

Evaluation of post compression parameters Trial Batches

The weight variation test was conducted on each batch of formulations F1 to F9 in accordance with the IP standards, and the results are detailed in Table 6.5. All formulations met the IP limit of ± 7.5% for weight variation. Uniform thickness was observed across all tablets in formulations F1 to F9. Tablet hardness, crucial for consumer acceptance and handling, ranged from 4.7 to 5.5 kg/cm2 across all formulations (F1 to F9), as outlined in Table 6.5. Friability testing, performed according to IP guidelines, revealed results below 1% for all formulations, indicating strong mechanical integrity of the tablets. Evaluation of drug content for each batch of formulations F1 to F9 followed standard IP protocols, with results presented in Table 6.5. The observed drug content percentages ranged from 96 to 99%, confirming compliance within acceptable limits for all formulations.

Table 9 Results of post compression parameters of Trial Batches

Formulation Code	Weight variation (mg) (n=20)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability %	Drug content % (n=3)
F1	150.1 ± 0.5	2.62±0.02	5.5±0.1	0.96 ±0.05	98.7 ±0.9
F2	150.2 ± 0.4	2.93±0.03	5.4 ±0.1	0.85 ±0.06	96.9 ±0.7
F3	150.8 ± 0.6	2.55±0.02	5.4 ±0.1	0.76 ±0.02	97.4 ±0.5
F4	148.2±0.5	2.12±0.01	5.4 ±0.1	0.95 ±0.06	95.6 ±0.4
F5	150.2±0.5	2.43±0.02	4.7 ±0.1	0.69 ±0.05	97.6 ±0.3
F6	**151.8±0.4**	**3.35±0.03**	**5.8 ±0.1**	**0.66 ±0.02**	**98.8 ±0.2**
F7	149.9±0.3	3.23±0.02	4.9 ±0.1	0.6 ±0.03	96.9 ±0.4
F8	151.6±0.6	3.14±0.01	5.3 ±0.1	0.56 ±0.01	93.7 ±0.3
F9	150.2±0.6	2.56±0.02	5.4 ±0.1	0.54 ±0.04	95.1 ±0.1

Surface pH and Mucoadhesive Strength Determination of Trial Batches

Surface pH

The surface pH measurements of formulations F1 to F9 ranged from 7.01±0.25 to 7.20±0.21. These results suggest that there is unlikely to be any local irritation to the mucosal surface, indicating the safe usability of all formulations.

Bioadhesive strength

A modified physical balance was used in the in-vitro biological adhesion study to determine the strength (in grammes) needed to separate the tablet. The amount of bioadhesive polymers used has an impact on the bioadhesive qualities. As indicated in Table 14, increasing the polymer concentration resulted in higher bioadhesive strength for the formulation, ranging between 23.97 ± 0.22 to 33.52 ± 0.03 grams.

Table 10 Result of surface pH and Mucoadhesive Strength measurement of Trial Batches

Formulation Code	Surface pH	Mucoadhesive strength (g)	Mucoadhesive Time (hours)
F1	7.1 ±0.3	29.66±0.04	4.9 ± 0.5
F2	7.2±0.2	25.49±0.03	5.4 ± 0.9
F3	7.2±0.1	23.97±0.02	5.9 ± 0.6
F4	7.1±0.2	32.19±0.24	8.0 ± 0.5
F5	7.0±0.3	27.89±0.22	8.0 ± 1.0
F6	**7.0±0.2**	**33.52±0.23**	**8.0 ± 1.0**
F7	7.1±0.6	30.03±0.26	8.0 ± 0.3
F8	7.1±0.3	31.21±0.04	8.0 ± 0.6
F9	7.1±0.3	30.52±0.03	8.0 ± 0.2

In-vitro release study of Trial Batches

A study on in vitro drug release was conducted to ascertain the rate at which the adhesive buccal tablet containing ivabradine HCl released. Table 6.7 displays the results.

Table 11 Drug release of the Ivabradine HCl of Trial Batches

Time (hour)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0 ± 0.0	0 ± 0.0	0 ± 0.0	0 ± 0.0	0 ± 0.0	**0 ± 0.0**	0 ± 0.0	0 ± 0.0	0 ± 0.0
1.0	35.9 ± 4.5	30.4 ± 3.1	26.8 ± 4.2	33.2 ± 3.0	30.4 ± 2.8	**30.5 ± 3.6**	12.6 ± 2.8	10.9 ± 1.9	8.6 ± 3.6
2.0	52.6 ± 2.9	48.3 ± 2.8	45.9 ± 3.3	43.9 ± 2.8	40.3 ± 2.4	**39.8 ± 2.8**	30.6 ± 2.4	25.3 ± 1.6	19.6 ± 2.8
3.0	70.6 ± 3.4	65.8 ± 2.6	61.5 ± 2.5	58.8 ± 2.1	55.9 ± 2.2	**54.9 ± 2.4**	40.1 ± 2.3	35.2 ± 1.3	30.4 ± 2.4
4.0	86.8 ± 2.7	83.2 ± 2.4	82.6 ± 2.3	69.4 ± 1.9	66.7 ± 1.9	**63.8 ± 2.1**	49.4 ± 2.1	45.3 ± 1.4	41.3 ± 2.3
5.0	99.5 ± 2.3	96.9 ± 2.3	92.8 ± 2.0	82.4 ± 1.4	78.3 ± 1.5	**75.6 ± 2.0**	59.4 ± 2.6	55.6 ± 1.1	49.5 ± 1.8
6.0	--	--	98.7 ± 1.6	91.6 ± 1.2	86.9 ± 1.2	**86.4 ± 1.5**	70.1 ± 1.5	66.2 ± 1.0	62.3 ± 1.4
7.0	--	--	99.8 ± 0.9	98.7 ± 0.8	96.9 ± 0.9	**94.1 ± 1.1**	79.4 ± 1.2	76.2 ± 0.9	73.9 ± 1.0
8.0	--	--	--	--	97.8 ± 0.8	**98.5 ± 0.9**	89.4 ± 0.9	85.9 ± 0.7	82.8 ± 0.7

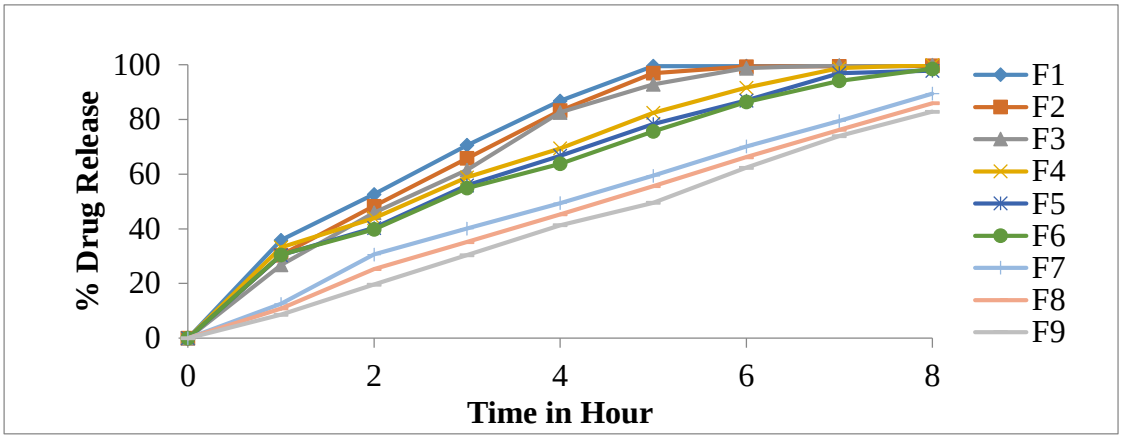


Figure 5 Drug release of Batch F1-F9 of Trial Batches

The comparison of drug release data from batches F1 to F9 led to the conclusion that the amount of polymer plays a crucial role in the formulation. Increasing the amount of polymer prolongs the drug release time. All three polymers exhibited satisfactory drug release profiles, but batch F7, containing Natrosol 250 G, demonstrated extended drug release for up to 8 hours. Conversely, Natrosol 250 M facilitated earlier release within 5-6 hours, while Natrosol 250 HHX retarded the release, achieving only 80-90% release at the end of 8 hours. Based on the results of trial batches, batch F6, which closely matched was chosen for additional factorial screening because it met the theoretical release profile and showed good adhesive strength as well as residence time.

Swelling Index of Mucoadhesive Buccal Tablets of Trial Batches

Swelling studies were performed on all formulations, namely F1 to F9, with results summarized in Table 16. Tablets were typically hydrated by immersing them in water for durations ranging from 1 to 8 hours. The formulation that exhibited the highest hydration, reaching 62, was F6. This increased swelling may be attributed to the rapid hydration of the polymer utilized in this formulation.

Table 12 Swelling Index of Mucoadhesive Buccal Tablets F1-F9 of Trial Batches

Formulation code	0.5 hrs.	1 hrs.	2 hrs.	4 hrs.	6 hrs.	8 hrs.
F1	24±2.9	28±2.8	30±4.6	31±1.9	33±3.7	37±2.8
F2	22±3.5	27±3.6	32±3.1	35±1.3	38±2.5	40±2.1
F3	17±2.6	23±5.2	35±4.5	37±2.1	42±2.9	44±2.3
F4	27 ± 2.4	31 ± 3.7	35 ± 4.8	39 ± 3.5	41 ± 3.4	44 ± 2.9
F5	29 ± 1.9	31 ± 3.4	34 ± 1.8	37 ± 4.6	41 ± 4.6	48 ± 3.1
F6	**23 ± 2.3**	**29 ± 3.6**	**33 ± 4.6**	**48 ± 5.6**	**54 ± 4.9**	**62 ± 2.8**
F7	25 ± 2.1	27 ± 3.1	30 ± 4.3	32 ± 4.1	35 ± 2.5	39 ± 1.8
F8	29 ± 1.9	31 ± 2.6	37 ± 4.1	40 ± 2.3	44 ± 1.9	47 ± 3.1
F9	29 ± 1.5	33 ± 2.0	44 ± 1.2	49 ± 3.9	53 ± 3.4	55 ± 2.9

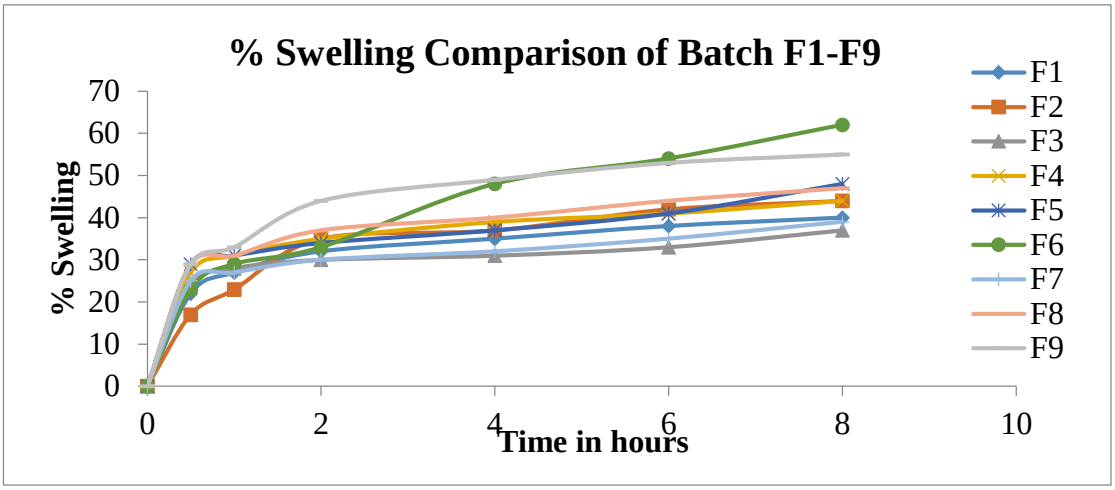


Figure 6 % Swelling Comparison of Batch F1-F9 of Trial Batches

The most promising batch F6, which was chosen for additional factorial screening based on trial batch findings, was close to the theoretical release profile and had good adhesive strength as well as residence time.

Evaluation of factorial batches

All evaluation parameters were tested for factororial batches I1–I9, and the results are shown in table below.;

Table 13 Results of Pre compression parameters of factorial batches

Formulation Code	Bulk density (g/ml) (n=3)	Tapped density (g/ml) (n=3)	% Compressibility (n=3)	Hausner's ratio (n=3)
I1	0.42 ± 0.03	0.49 ± 0.01	14.29 ± 0.03	1.17 ± 0.03
I2	0.45 ± 0.05	0.51 ± 0.06	11.76 ± 0.05	1.13 ± 0.08
I3	0.43 ±0.06	0.53 ± 0.04	18.87 ± 0.03	1.23 ± 0.07
I4	0.48 ± 0.03	0.56 ± 0.04	14.29 ± 0.05	1.17 ± 0.06
I5	0.48 ± 0.04	0.55 ± 0.06	12.73 ± 0.06	1.15 ± 0.05
I6	0.48 ± 0.06	0.54 ± 0.05	11.11 ± 0.09	1.13 ± 0.05
I7	0.46 ± 0.05	0.50 ± 0.07	08.00 ± 0.08	1.09 ± 0.07
I8	0.43 ± 0.07	0.49 ± 0.05	12.24 ± 0.06	1.14 ± 0.03
I9	0.46 ± 0.06	0.52 ± 0.05	11.54 ± 0.05	1.13 ± 0.05

Table 14 Results of post compression parameters of factorial batches

Formulation Code	Weight variation (mg) (n=20)	Thickness (mm) (n=3)	Hardness (kg/cm^2) (n=3)	Friability %	Drug content %(n=3)
I1	149.21 ± 0.19	2.72 ± 0.07	5.60 ± 0.12	0.63 ± 0.03	99.25 ± 0.07
I2	151.13 ± 0.26	2.36 ± 0.07	5.29 ± 0.13	0.59 ± 0.04	99.10 ± 0.06
I3	152.15 ± 0.34	2.45 ± 0.08	5.30 ± 0.09	0.55 ± 0.06	98.45 ± 0.05
I4	149.36 ± 0.37	2.32 ± 0.05	5.25 ± 0.11	0.60 ± 0.04	98.14 ± 0.05
I5	150.54 ± 0.43	2.49 ± 0.07	5.10 ± 0.17	0.45 ± 0.08	97.65 ± 0.05
I6	151.12 ± 0.27	3.30 ± 0.08	5.35 ± 0.14	0.39 ± 0.05	99.42 ± 0.04
I7	149.99 ± 0.34	3.15 ± 0.05	5.15 ± 0.13	0.53 ± 0.03	98.41 ± 0.06
I8	150.46 ± 0.41	3.00 ± 0.05	5.48 ± 0.13	0.49 ± 0.05	98.16 ± 0.03
I9	151.42 ± 0.28	2.89 ± 0.06	5.50 ± 0.12	0.44 ± 0.07	96.25 ± 0.04

Table 15 Evaluation of mucoadhesive properties of factorial batches

Formulation Code	Surface pH (n=3)	Mucoadhesive strength (g) (n=3)	Mucoadhesion Time (hours)
I1	6.90 ± 0.35	25.61 ± 0.42	8.2 ± 0.9
I2	7.10 ± 0.31	27.40 ± 0.15	8.4 ± 1.2
I3	7.05 ± 0.20	30.83 ± 0.19	8.5 ± 1.1
I4	7.10 ± 0.10	31.24 ± 0.26	8.3 ± 0.8
I5	7.00 ± 0.05	32.51 ± 0.28	8.5 ± 0.5
I6	7.10 ± 0.15	34.22 ± 0.38	8.5 ± 0.4
I7	6.95 ± 0.20	35.82 ± 0.65	8.3 ± 0.4
I8	6.90 ± 0.10	37.93 ± 0.28	8.6 ± 0.6
I9	7.10 ± 0.15	38.41 ± 0.51	8.6 ± 1.1

Table 16 Swelling Index of Mucoadhesive Buccal Tablets of I1-I9

Formulation code	2 hrs.	4 hrs.	6 hrs.	8 hrs.
I1	9.8 ± 2.5	18.5 ± 3.4	23.8 ± 2.5	32.2 ± 1.5
I2	11.3 ± 3.1	19.5 ± 3.1	24.6 ± 2.1	35.4 ± 2.6
I3	13.2 ± 2.5	21.6 ± 1.6	26.9 ± 2.6	39.9 ± 2.8
I4	15.6 ± 1.9	24.3 ± 1.4	33.6 ± 2.4	42.5 ± 1.9
I5	16.2 ± 2.6	26.5 ± 2.3	40.1 ± 3.1	48.3 ± 2.8
I6	17.8 ± 2.9	28.6 ± 2.5	39.5 ± 1.9	51.7 ± 3.5
I7	20.3 ± 2.1	29.7 ± 2.7	45.2 ± 1.4	56.4 ± 3.9
I8	23.5 ± 2.3	30.1 ± 1.9	45.9 ± 2.6	59.2 ± 4.1
I9	24.1 ± 1.9	32.8 ± 1.1	50.3 ± 2.1	66.3 ± 2.8

All findings indicated satisfaction across the board. Weight variation limits were met by all batches, with satisfactory hardness and friability levels below 1%. Swelling indices for all batches were deemed good. Additionally, precompression parameters were favorable, ensuring good blend flow. The required neutral pH of the surface was maintained by all batches, and their residence times might reach up to eight hours. Moreover, mucoadhesive strength was found to be enough.

Table 17 Drug release study of factorial batches

Time (hour)	0	1	2	4	6	8
I1	0 ± 0.00	39.0 ± 5.4	50.1 ± 3.1	74.5 ± 2.7	98.5 ± 0.9	99.9 ± 1.6
I2	0 ± 0.00	39. 0± 3.8	49.2 ± 3.5	72.3 ± 1.8	96.5 ± 1.5	98.9 ± 1.4
I3	0 ± 0.00	38.0 ± 2.5	48.3 ± 2.4	70.2 ± 1.7	95.9 ± 1.3	99.9 ± 0.9
I4	0 ± 0.00	36.0 ± 1.9	46.8 ± 2.6	69.4 ± 1.3	92.5 ± 1.2	99.9 ± 0.4
I5	0 ± 0.00	35.0 ± 2.6	45.2 ± 1.4	67.9 ± 2.2	89.1 ± 0.8	99.8 ± 0.9
I6	0 ± 0.00	33.0 ± 3.8	42.9 ± 2.5	65.9 ± 3.4	87.5 ± .9	99.7 ± 0.7
I7	0 ± 0.00	31.0 ± 4.6	42.5 ± 2.3	63.9 ± 2.9	85.3 ± 1.7	99.8 ± 0.3
I8	0 ± 0.00	27.0 ± 3.9	39.5 ± 1.9	59.5 ± 2.1	83.5 ± 1.1	99.8 ± 0.4
I9	0 ± 0.00	22.0 ± 4.9	30.6 ± 1.8	55.4 ± 1.6	80.6 ± 1.2	93.1± 0.8

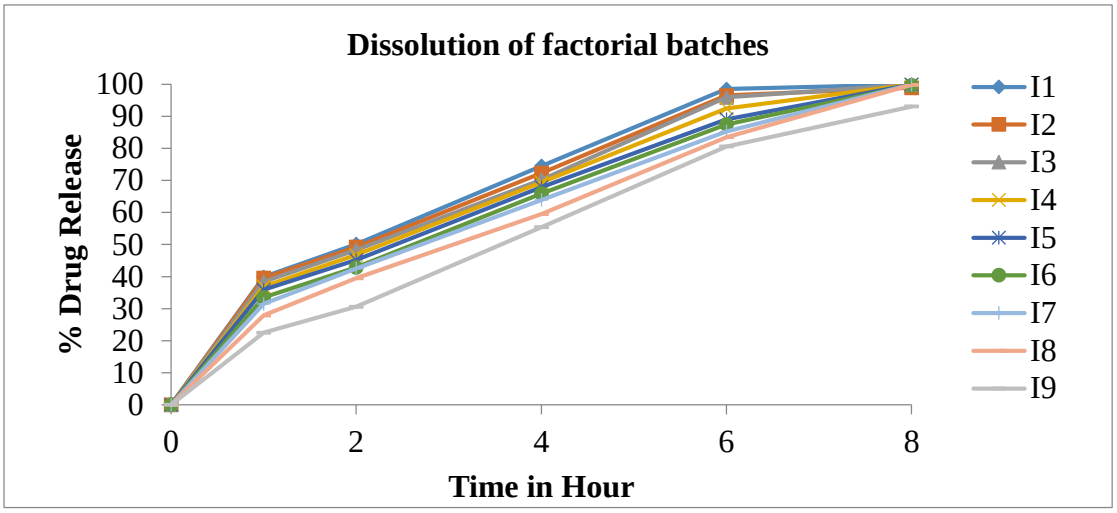


Figure 7 % Drug release of factorial batch I1-I9

The factorial batches results will be used to initially model the factorial design. Following this, a validation batch will be prepared. Once the model is validated, the final optimized batch will be formulated, and a comprehensive analysis will be conducted on this optimized batch.

Table 18 Drug Permeability study of factorial batches

% Drug Permeability (n=3)					
Time (hour)	**0**	**1**	**2**	**4**	**8**
I1	0 ± 0.0	25.5 ± 2.6	39.7 ± 3.2	59.4 ± 1.8	77.3 ± 2.2
I2	0 ± 0.0	23.6 ± 3.2	37.1 ± 4.4	61.1 ± 1.5	75.8 ± 2.2
I3	0 ± 0.0	21.6 ± 2.8	35.6 ± 1.3	67.2 ± 1.7	73.4 ± 1.5
I4	0 ± 0.0	20.9 ± 1.5	34.2 ± 2.5	54.6 ± 1.3	71.3 ± 1.5
I5	0 ± 0.0	18.6 ± 2.7	31.5 ± 2.4	51.3 ± 1.4	62.3 ± 1.4
I6	0 ± 0.0	15.9 ± 1.8	28.4 ± 1.7	45.6 ± 1.3	55.6 ± 1.6
I7	0 ± 0.0	16.7 ± 2.4	29.4 ± 2.1	50.3 ± 2.4	59.4 ± 1.7
I8	0 ± 0.0	17.7 ± 2.3	42.9 ± 3.2	65.9 ± 2.2	81.2 ± 1.4
I9	0 ± 0.0	14.9± 2.4	25.6 ± 1.3	41.6 ± 1.2	53.4 ± 1.8

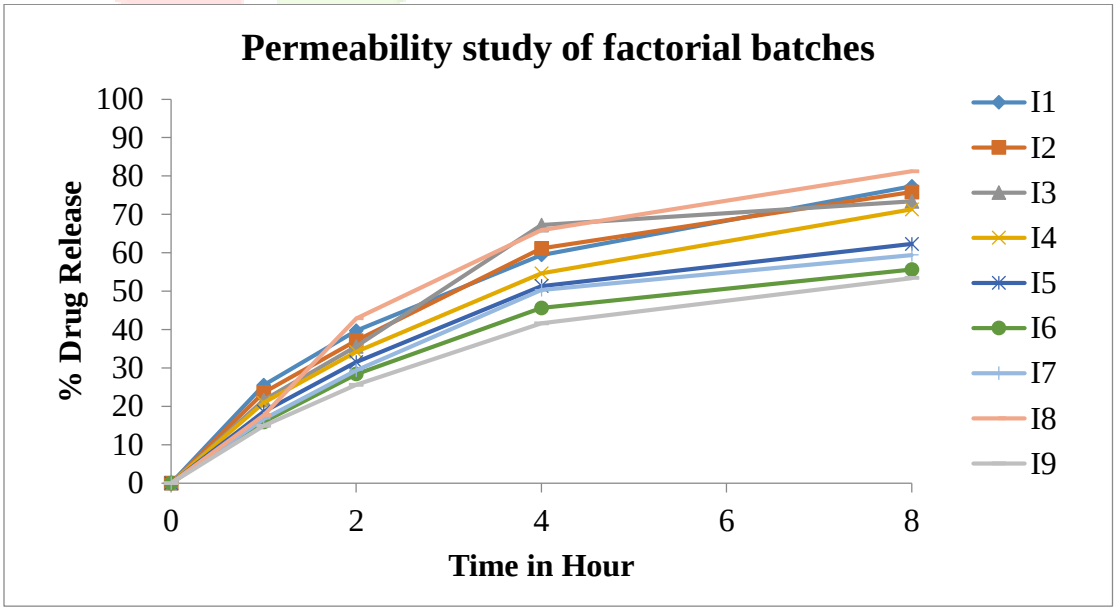


Figure 8 Drug Permeability study of factorial batch I1-I9

Drug Release Kinetic Study

In vitro drug release study data was fitted in kinetic models and results obtained were shown in below table.

Table 19 Drug Release Kinetic Study of factorial batches I1-I9

FORMULATIONS	ZERO ORDER	FIRST ORDER	HIGUCHI MODEL	KORS PEPAS	
	R^2	R^2	R^2	R^2	N
I1	0.9698	0.9547	0.9849	0.9906	0.489
I2	0.9743	0.9606	0.9863	0.9902	0.483
I3	0.9798	0.9665	0.9879	0.9906	0.497
I4	0.9867	0.9690	0.9936	0.9944	0.516
I5	0.9914	0.9730	0.9957	0.9949	0.522
I6	0.9944	0.9763	0.9958	0.9947	0.552
I7	0.9971	0.9770	0.9967	0.9975	0.572
I8	0.9981	0.9773	0.9977	0.9978	0.633
I9	0.9938	0.9728	0.9922	0.9934	0.729

Analysis of factorial design

Following data fitted in design Expert software to analyze the design.

Table 20 Factorial design analysis table

Batch	Natrosol 250 HHX (mg)	Carbopol 934 P (mg)	% Drug release at 1 hour	Mucoadhesive Strength (g)
I1	25.0	5.0	39.0	25.61
I2	25.0	10.0	39.0	27.40
I3	25.0	15.0	38.0	30.83
I4	30.0	5.0	36.0	31.24
I5	30.0	10.0	35.0	32.51
I6	30.0	15.0	33.0	34.22
I7	35.0	5.0	31.0	35.82
I8	35.0	10.0	27.0	37.93
I9	35.0	15.0	22.0	38.41

ANOVA for Quadratic model

Response 1: (% Drug release at 1 hour)

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	268.67	5	53.73	120.90	0.0012	significant
A-Natrosol 250 HHX	216.00	1	216.00	486.00	0.0002	
B-Carbopol 934 P	28.17	1	28.17	63.37	0.0041	
AB	16.00	1	16.00	36.00	0.0093	
A^2	8.00	1	8.00	18.00	0.0240	
B^2	0.5000	1	0.5000	1.12	0.3667	
Residual	1.33	3	0.4444			
Cor Total	270.00	8				

Factor coding is **Coded**.
Sum of squares is **Type III - Partial**

The **Model F-value** of 120.90 implies the model is significant. There is only a 0.12% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B, AB, A^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation in Terms of Actual Factors

(% Drug release at 1 hour	=
-22.66667	
+4.40000	Natrosol 250 HHX
+2.36667	Carbopol 934 P
-0.080000	Natrosol 250 HHX * Carbopol 934 P
-0.080000	Natrosol 250 HHX ²
-0.020000	Carbopol 934 P²

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

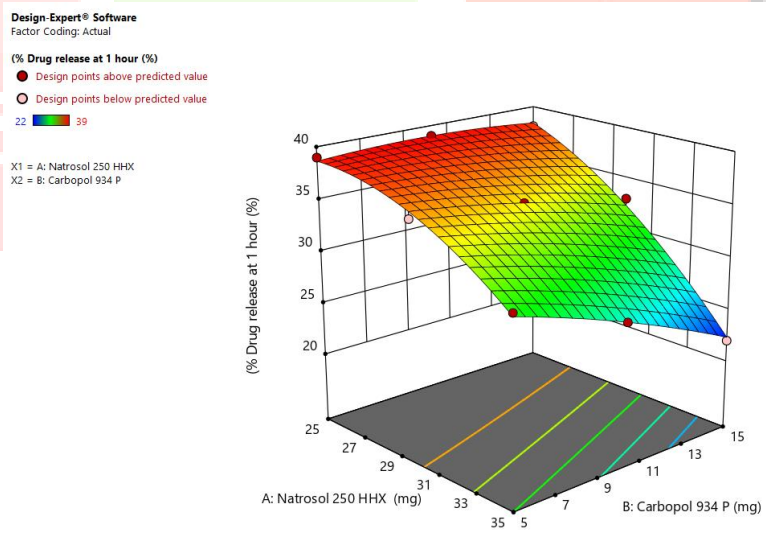


Figure 9 Drug Permeability study of factorial batch I1-I9

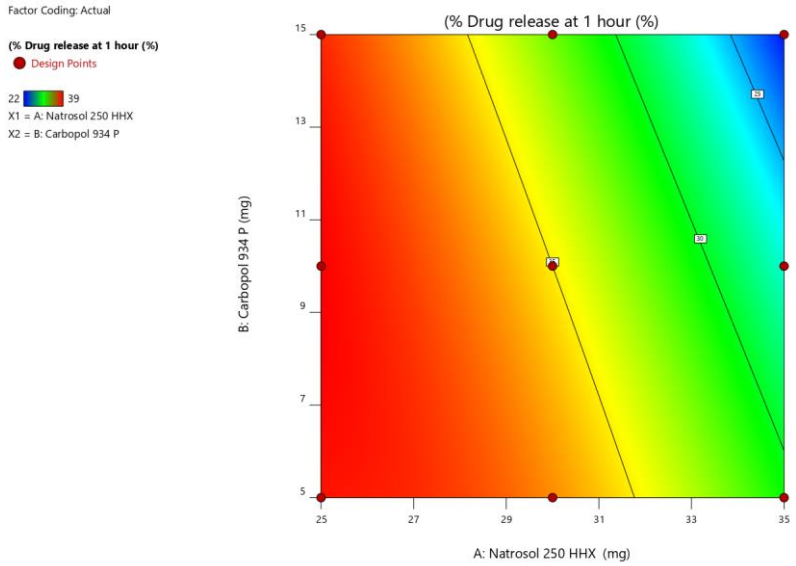


Figure 10 Surface Plot for drug release at 1 hour

ANOVA for Quadratic model

Response 2: Mucoadhesive Strength

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	152.03	5	30.41	105.93	0.0014	significant
A-Natrosol 250 HHX	121.50	1	121.50	423.29	0.0003	
B-Carbopol 934 P	28.17	1	28.17	98.13	0.0022	
AB	2.25	1	2.25	7.84	0.0679	
A^2	0.0556	1	0.0556	0.1935	0.6897	
B^2	0.0556	1	0.0556	0.1935	0.6897	
Residual	0.8611	3	0.2870			
Cor Total	152.89	8				

Factor coding is **Coded**.

Sum of squares is **Type III - Partial**

The **Model F-value** of 105.93 implies the model is significant. There is only a 0.14% chance that an F-value this large could occur due to noise.

P-values less than 0.0500 indicate model terms are significant. In this case A, B are significant model terms. Values greater than 0.1000 indicate the model terms are not significant. If there are many insignificant model terms (not counting those required to support hierarchy), model reduction may improve your model.

Final Equation in Terms of Actual Factors

Mucoadhesive Strength	=
-1.77778	
+0.800000	Natrosol 250 HHX
+1.20000	Carbopol 934 P
-0.030000	Natrosol 250 HHX * Carbopol 934 P
+0.006667	Natrosol 250 HHX ^{2}
+0.006667	Carbopol 934 P^2

The equation in terms of actual factors can be used to make predictions about the response for given levels of each factor. Here, the levels should be specified in the original units for each factor. This equation should not be used to determine the relative impact of each factor because the coefficients are scaled to accommodate the units of each factor and the intercept is not at the center of the design space.

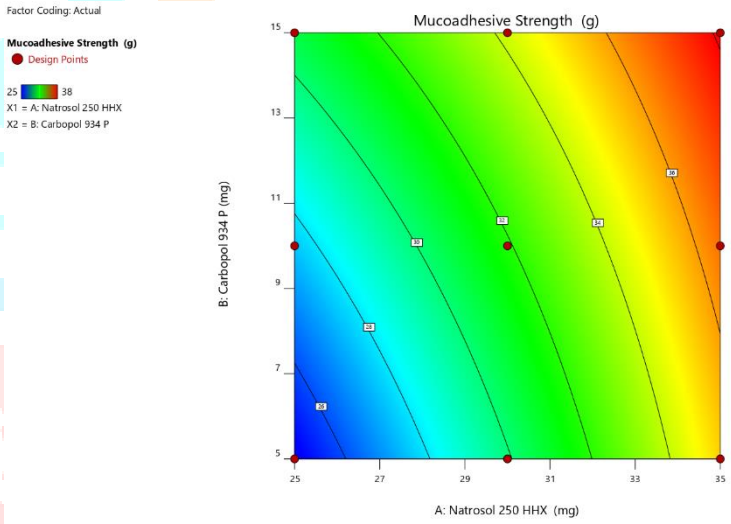


Figure 11 Contour Plot for mucoadhesive strength

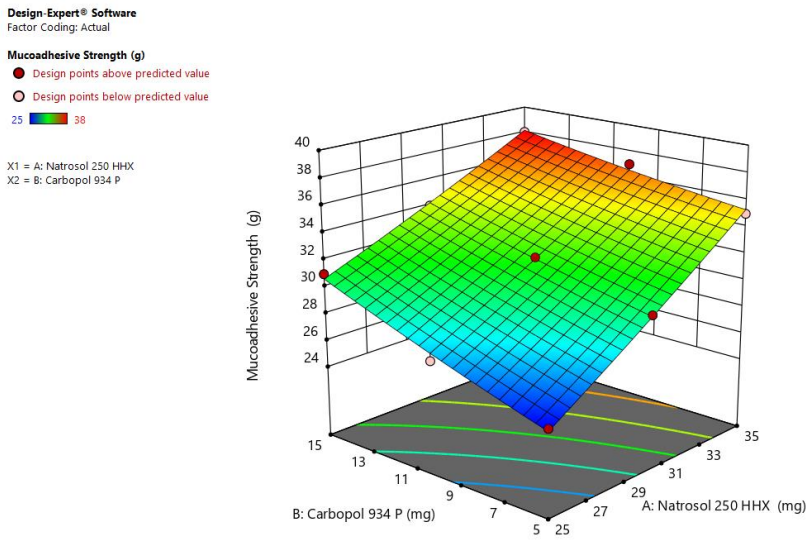


Figure 12 Surface Plot for mucoadhesive strength

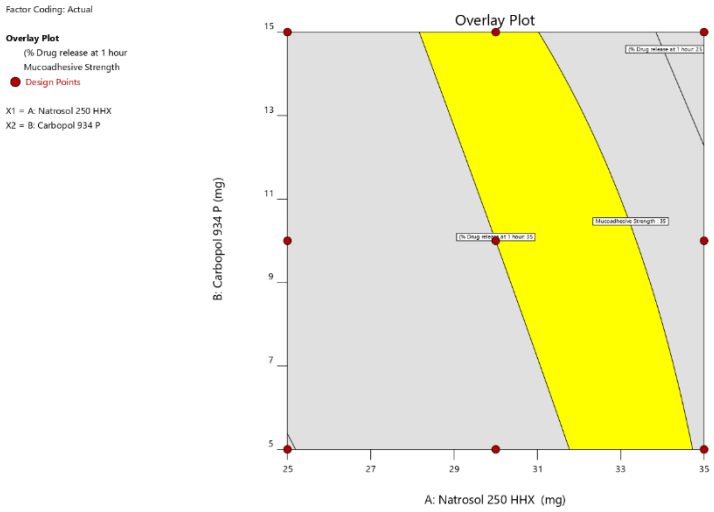


Figure 13 Overlay Plot

Validation of Factorial design

Check point batch CP1 was taken based on Overlay contour plot and the predicted responses check against the actual one. The % Bias calculated and validated the design. Following was the summary of check point batch. The model was validated successfully.

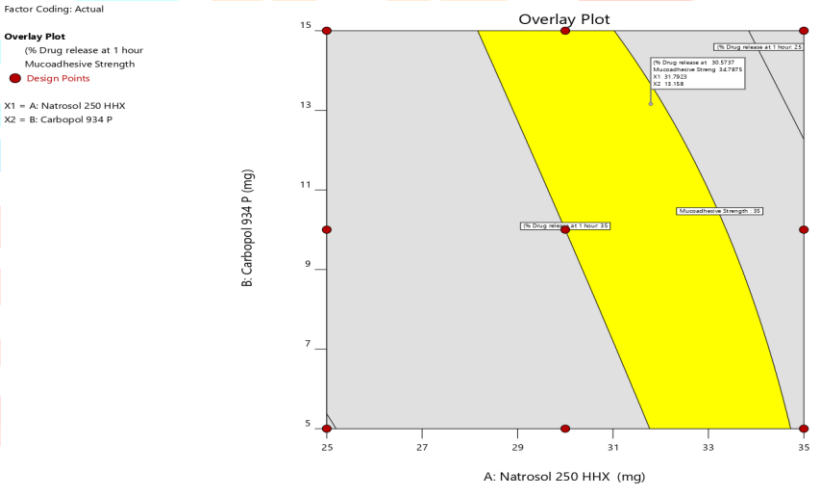


Figure 14 Overlay Contour plot Check point batch

Table 21 Check point batch

X1	31.80	
X2	13.10	
Drug release at 1 hour %	Predicated	30.50
	Observed	30.90
	% Bias	0.9870
Mucoadhesive strength %	Predicated	34.70
	Observed	34.50
	% Bias	1.000
Remarks	Acceptable	

Optimized Batch

Finally, optimized batch (O1) was prepared from the overlay plot and completed analysis was done for the same.

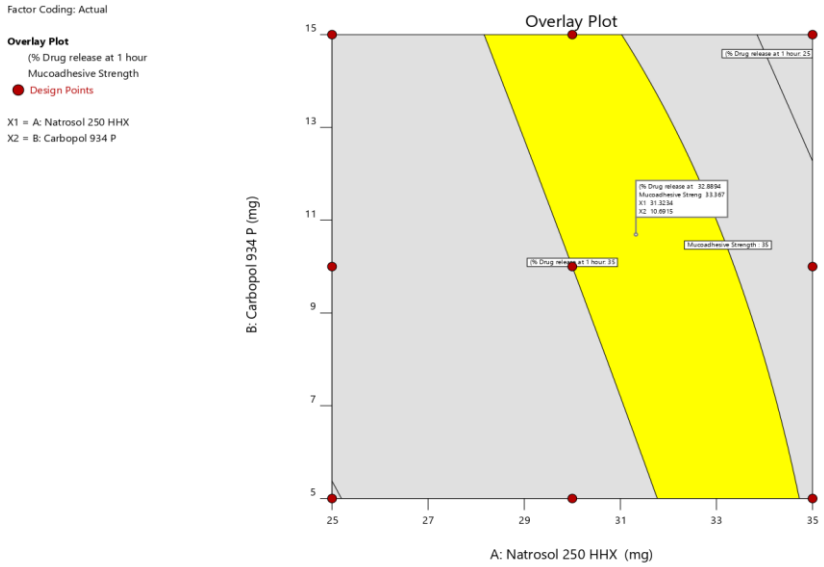


Figure 15 Overlay Contour plot for optimized batch

Table 20 Formulation table for Optimized batch O1

Ingredients (mg/Tablet)	O1
Ivabradine HCl	5.0
Natrosol 250 HHX	31.3
Carbopol 934 P	10.6
Lactose	38.1
PVPK 30	5.0
Sucralose	4.0
Talc	4.0
Magnesium Stearate	2.0
Baking layer Ethyl Cellulose	50.0
Total (mg)	**150.0**

Table 21 Evaluation table for Optimized batch O1

Parameters	Results for O1 Batch
Appearance	White colored round shape tablet
Weight Variation (mg) (±SD) (n=20)	151±3
Thickness (mm) (±SD) (n=3)	3.25±0.02
Hardness (kg/cm^2) (±SD) (n=3)	5.1±0.1
Friability (%) (±SD) (n=3)	0.48±0.03
Drug Content (%) (±SD) (n=3)	99.8±1.5
% Swelling at 8 hours (±SD) (n=3)	53.9±4.3
Mucoadhesive Strength (g) (±SD) (n=3)	33.4±0.8
Mucoadhesive Time (hours) (±SD) (n=3)	8±1.0
Surface pH (±SD) (n=3)	6.9±0.2

% Drug Release of Final Batch O1						
Time (hour)	**0**	**1**	**2**	**4**	**6**	**8**
O1	0±0.00	32.9±1.4	39.7±1.6	59.4±2.4	82.6±1.2	99.8±1.2

Release Kinetic Study of Final Batch O1					
Batch	**Zero order**	**First order (R^2)**	**Higuchi plot (R^2)**	**Koresmeyer-peppas Plot**	
	(R^2)	**(R^2)**	**(R^2)**	**(R^2)**	**n**
O1	0.9983	0.9814	0.9864	0.9833	**0.547**

Zero order was determined to be the best-fitting model (R^2 = 0.99832), while Peppas's model's n and R2 values suggested that the release of ivabradine hydrochloride was not caused by Fickian diffusion.

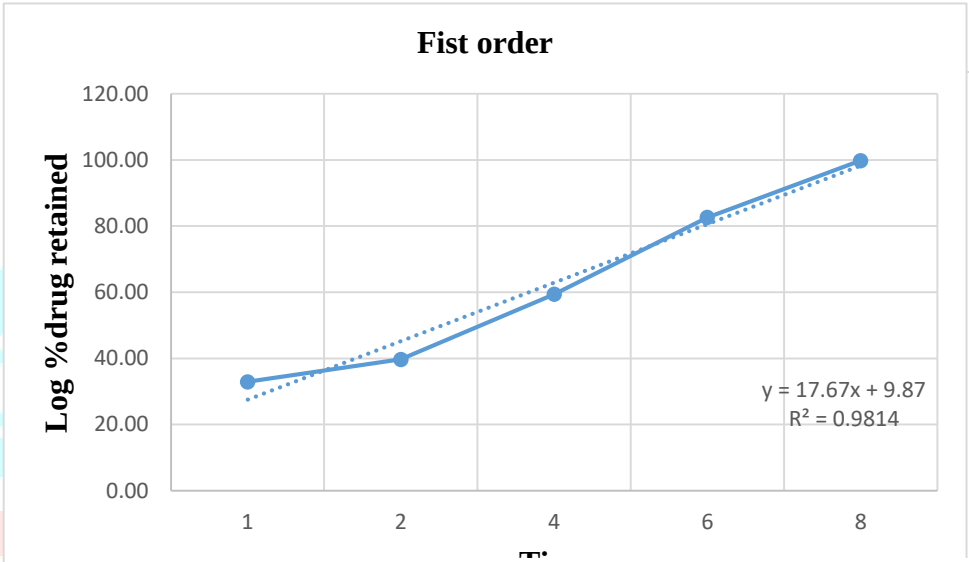
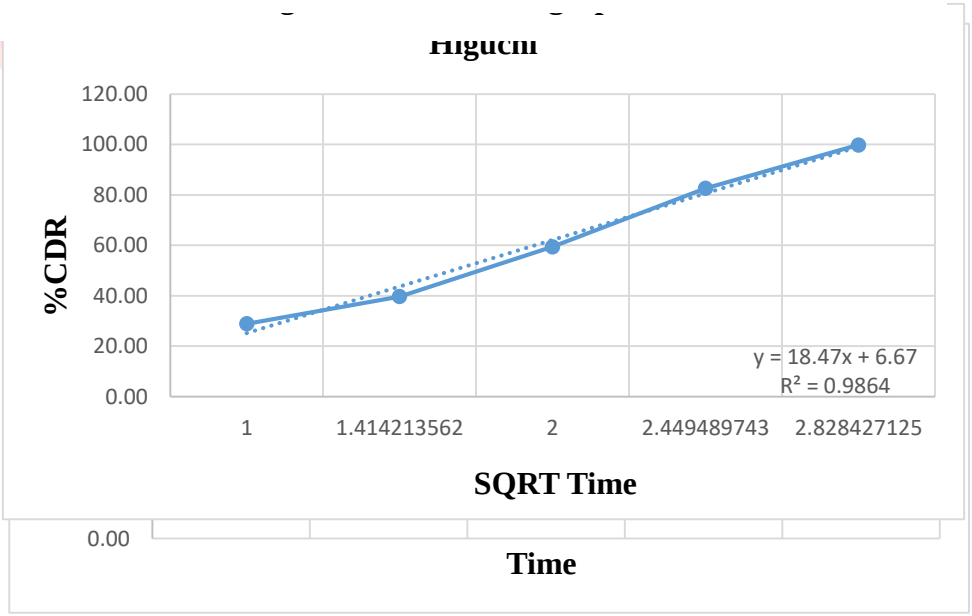


Figure 19 Higuchi graph

Figure 18 Korse graph



A formulation was chosen for an ex vivo permeation investigation based on ex vivo the adhesion of, ex vivo residential duration, and in-vitro release experiments. For investigations on Ivabradine Hydrochloride Permeation, porcine buccal mucosa was selected., as it closely resembles human buccal tissue in structure and composition. The results indicated that Ivabradine Hydrochloride was released from the buccal tablet and permeated through the porcine buccal membrane, suggesting potential permeation through the human buccal membrane. The drug permeation occurred at a slow and steady rate, with 81.6% of Ivabradine Hydrochloride permeating through the buccal membrane over an 8-hour period. Detailed results are provided in Table

.

Table 22 Ex vivo Permeability study of Optimized batch IO1

% Drug Permeability						
Time (hour)	**0**	**1**	**2**	**4**	**6**	**8**
O1	0±0.00	14.9±4.3	25.8±3.2	45.5±1.8	64.3±1.7	81.5±1.9

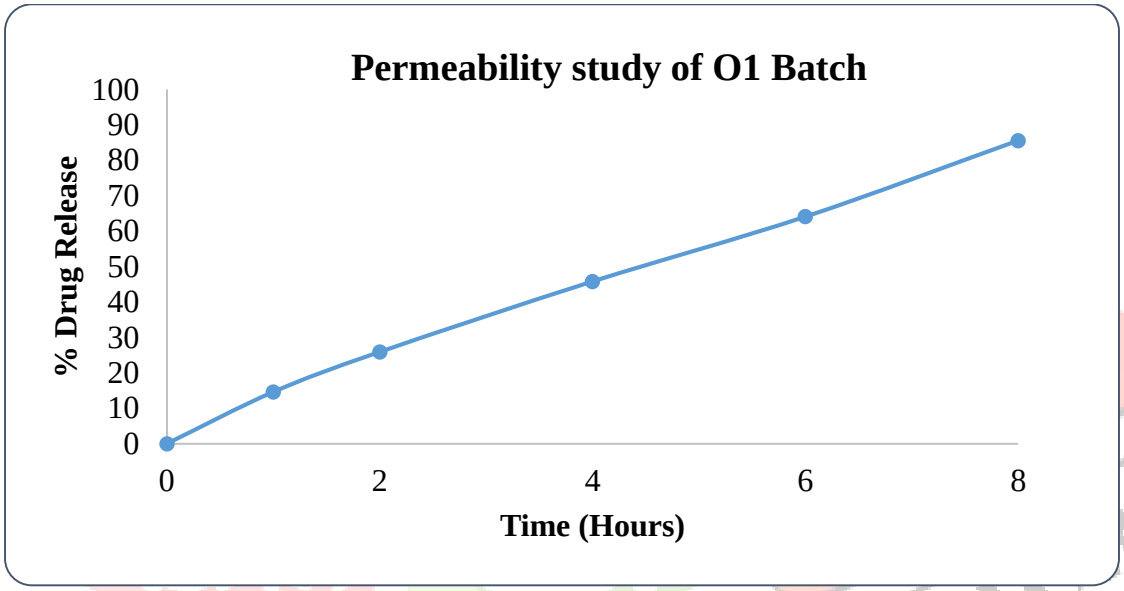


Figure 16 Ex vivo permeability study of O1 Batch

Stability study

A 30-day stability investigation of the optimised batch O1 was conducted. Samples were gathered and examined for a number of criteria after 30 days. The results are shown in the table below.During stability, Formulation O1 was confirmed to be stable, and no critical observations were noted.

Table 0-22 Results of stability study of optimized formulation O1

Parameter	**Initial**	**After 30 days**
Appearance	White colored round shape tablet	White colored round shape tablet
Drug Content (%) (±SD) (n=3)	99.8±1.5	99.2±1.8
% Drug release in 8 hours (±SD) (n=3)	99.8±0.3	99.1±0.4

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