FORMULATION AND EVALUATION OF IVABRADINE BUCCAL TABLETS

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ABSTRACT: ***The purpose of this research was to develop and characterize bioadhesive buccal tablets of Ivabradine using HPMC k5M, ethyl cellulose. The tablets were evaluated for weight variation, thickness, hardness, friability, surface pH, mucoadhesive strength, swelling index, in vitro drug release. The swelling index, friability and in vitro drug release. The surface pH of all tablets was found to be satisfactory close to neutral pH; hence buccal cavity irritation should not occur with these tablets. F5 formulation was considered optimum based on good bioadhesive strength and maximum similarity factor. The drug release from optimum batch followed zero order kinetics with non-Fickian diffusion. Drug and excipients compatibility study showed no interaction between drug and excipients. Stability study of optimized formulation showed that tablets were stable at accelerated environment condition. Thus, buccal adhesive tablet of Ivabradine could be an alternative route to bypass hepatic first pass metabolism and to improve bioavailability of Ivabradine.***

Key words: Bioadhesion, buccal drug delivery, Ivabradine, polymers, FTIR studies, direct compression technique, in vitro drug release studies, Zero order kinetics.

I. INTRODUCTION

Buccal drug delivery system is an alternative method of systemic drug delivery that offers several advantages over both injectable and enterable methods.[1] Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration[2] and hence can \ be used for targeting a drug to particular region of the body for extended period of time[3]. Bioadhesive tablets are usually prepared by direct compression and they are placed between the cheek and gum providing local or systemic effects.[4] Ivabradine is a novel medication used for the symptomatic management of stable angina pectoris. Ivabradine acts by reducing the heart rate in a mechanism different from beta blockers and calcium channel blockers, two commonly prescribed anti-anginal drugs. It is classified as a cardiotonic agent. The plasma half-life is about 2 hrs, and bioavailability. [5]

II. MATERIALS

Ivabradine was obtained from Hetero lab, HYD. HPMC and Ethyl cellulose were procured from Synpharma Research Labs, Hyderabad, and other chemicals, and the reagents used were of analytical grade.

Methodology

Drug excipient compatibility studies[6]

Drug excipients compatibility studies were performed to know the compatibility of excipient with drug at accelerated conditions. The study was conducted by preparing homogenous mixture of excipients with drug and filled in HDPE bags and LDPE bags. Glass vials were exposed to 600 C and 400C/75 %RH for 4 weeks and LDPE bags were exposed to 400C±75 %RH for 4 weeks. Samples were observed periodically for any physical change.

Formulations Table:

Table-1: Formulation of buccal tablets of Ivabradine

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Ivabradine	10	10	10	10	10	10	10	10
HPMC K_5M	100	-	50	25	75	50	25	75
Ethylcellulose	-	100	50	75	25	50	75	25
Lactose	80	80	80	80	80	80	80	80

Talc	2	2	2	2	2	2	2	2
Magnesium Stearate	3	3	3	3	3	3	3	3
Sodium starch glycolate	5	5	5	5	5	5	5	5
Total wt	200	200	200	200	200	200	200	200

Preparation method:[7]

Different tablet formulations were prepared by direct compression method. The formulations are composed of polymers. All powders were passed through 100-mesh sieve.The microcrystalline and the polymer were mixed uniformly. Drug was added to the polymers and blended for 20 min. The resulting powder were mixed with magnesium Stearate and talc in polyethylene bag for 10 min. The lubricated powder were compressed using 8 mm punch (single punch tablet machine) in to tablets. The total weight of tablet was kept at 200 mg.

Evaluation parameters[8,9,10]

Post compression parameters:

Weight variation:

Twenty tablets were randomly selected form each batch and individually weighed. The average weight and standard deviation of 20 tablets was calculated. The batch passes the test for weight variation test if not more then two of the individual tablet weight deviate from the average weight by more than the percentage.

Thickness

Twenty tablets were randomly selected form each batch and there thickness was measured by using vernier caliper. Thickness of three tablets from each batch was measured and mean was calculated.

Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm. Three tablets were randomly picked and hardness of the tablets were determined.

Friability:

Friability test is performed to assess the effect of friction and shocks, which may often cause tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects a number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Twenty tablets were weighed and placed in the Roche friabilator, which was then operated for 25 rpm for 4 min. After revolution Tablets were dedusted and reweighed. Compressed tablets should not loose more than 1% of their weight.

The percentage friability was measured using the formula,

$$\% F = \{1-(Wo/W)\} \times 100$$

Where,

% F = friability in percentage

Wo = Initial weight of tablet

W = weight of tablets after revolution

Content Uniformity:

Twenty tablets from each batch were powdered and weighed accurately equivalent to 100 mg Ivabradine. Dissolve the weighed quantity of powder into 100 ml of 0.1 N NaOH solution by stirring it for 15 min. 1 ml of solution was pipette out into 10 ml volumetric flask and make up the volume with distilled water. Immediately analyze the drug by taking absorbance at nm using reagent blank.

Swelling index

Swelling index study The extent of swelling was measured in terms of percentage weight gain by the tablet. The swelling index of all formulation was studied. One tablet from each batch was kept in a Petridis containing 2% agar gel plates with the core facing the gel surface and incubated at 37±1 °C. The tablet was removed every two hour interval up to 12 hour and excess water blotted carefully using filter paper. The swollen tablets were re-weighed (Wt). The swelling index (SI) of each tablet was calculated according to the following equation.

$$SI = (W_t - W_0)$$

Where

W0 = initial weight,

Wt = weight after time t.

***In- Vitro* Release study:**[11]

In-Vitro drug release studies were carried out using Tablet dissolution test apparatus USP II at 100 rpm. The dissolution medium consisted of 900 ml of Standard buffer 0.1 N HCL for 2 hr and followed by pH 6.8 period of time. Temperature maintained at 37±5.The sample of 1ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. From that 1 ml sample, 1 ml sample was withdrawn and placed in a 10 ml volumetric flask, and make the volume with buffer. The diluted samples were assayed at 280nm against reagent blank.

Drug release kinetics:[12]

The obtained dissolution data was fitted into various kinetic models to understand the pattern of the drug release from floating tablets. The models used were zero order (equation 1) First order (equation 2) and Higuchi model (equation 3) and KoresmeyerPeppas model (equation 4).

i) zero order release kinetics:

$R = K_o t$ -- (1)

R=cumulative percent drug release

Ko=zero order rate constant

ii) First order release kinetics

$\log C = \log Co - K_1 t / 2.303$ -- (2)

where C = cumulative percent drug release

K_1 = first order rate constant

iii) Higuchi model

$R = K_H t^{0.5}$ -- (3)

Where R = cumulative percent drug release

K_H =higuchi model rate constant

iv) korsmeyerpeppas model:

$M t / M \alpha = K_k t^n$

$\log M t / M \alpha = \log K_k + n \log t$ -- (4)

where K_k = korsrmeyerpeppas rate constant

'M t / M α' is the fractional drug release, n = diffusional exponent, which characterizes the mechanism of drug release (Simon Benita, 2007).

Diffusional exponent (n)		Drug release mechanism
0.43	--	Fickian diffusion
0.43- 0.85	--	Anamolous (non- fickian) transport
0.85- 1	--	Case II transport
> 1	--	Supercase II transport

The obtained regression co-efficient (which neared 0.999) was used to understand the release pattern of the drug from the floating tablets.

Stability studies:[13]

The success of an effective formulation can be evaluated only through stability studies. The purpose of stability testing is to obtain a stable product which assures its safety and efficacy up to the end of shelf life at defined storage conditions and peak profile

The preparedIvabradinebuccal tablets were placed on plastic tubes containing desiccant and stored at ambient conditions, such as at room temperature, 40±2^{o}c and refrigerator 2-8^{o}c for a period of 90 days.

III.RESULTS AND DISCUSSION

Compatibility Study:

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied.

The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug was compatible with the formulation components.

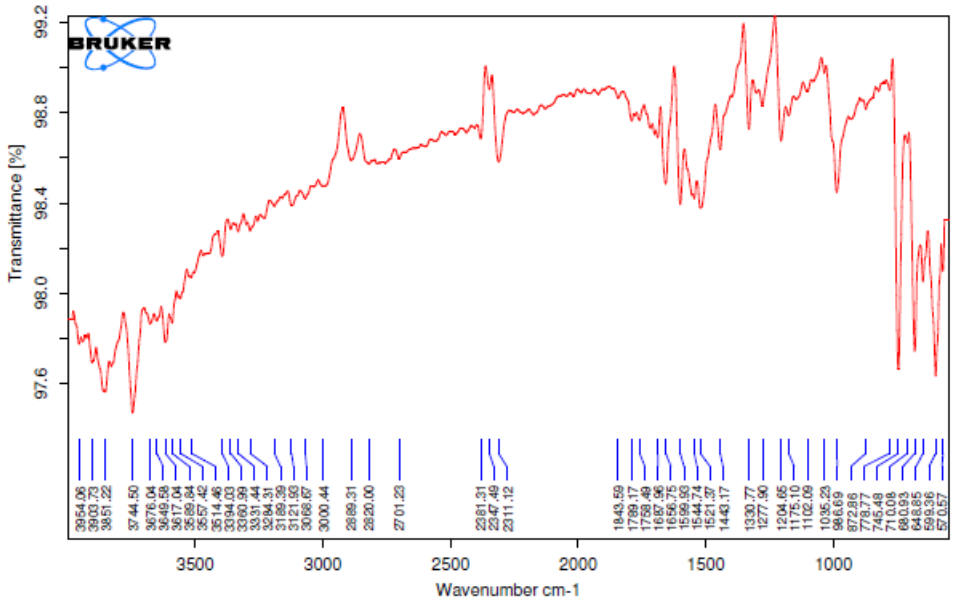

Fig.1. FTIR Spectra of Ivabradine

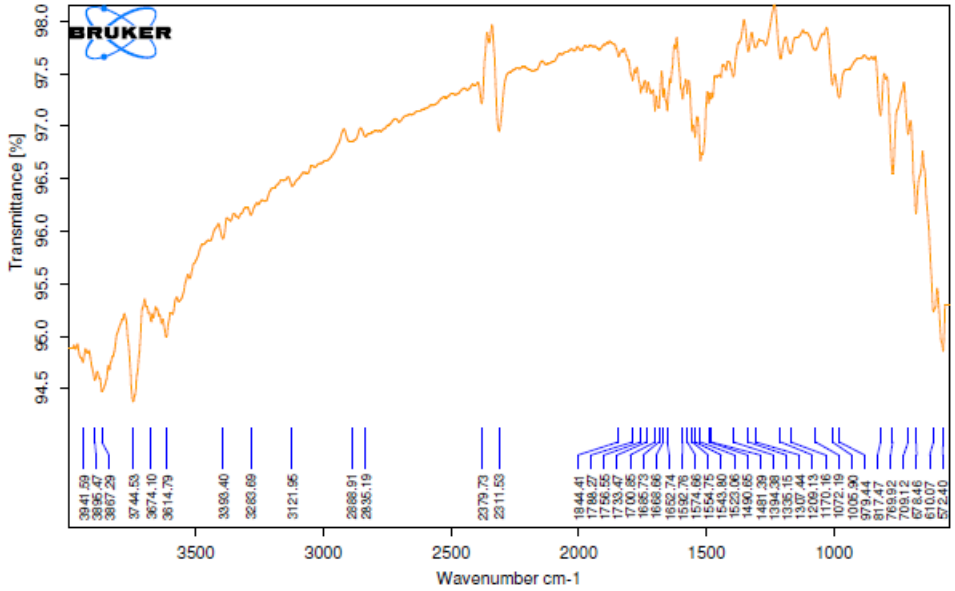

Fig.2. FTIR Spectra of Optimized formulation

Compatibility studies were performed using IR spectrophotometer. The IR spectrum of Pure drug and physical mixture of drug and excipients were studied. The characteristic absorption of peaks were obtained as above and as they were in official limits (±100 cm-1) the drug is compatible with excipients.

Post compression parameters

Weight variation:

All the formulated (F1 to F8) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values.

Thickness:

Tablets mean thickness were uniform in F1 to F8 formulations and were found to be in the range of 3.18mm to 3.23 mm.

Hardness:

The measured hardness of tablets of each batch ranged between 6.5 to 7 kg/cm^2. This ensures good handling characteristics of all batches.

Friability:

The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Content Uniformity:

The percentage of drug content for F1 to F8 was found to be between 89.25% and 98.98% of Ivabradineit complies with official specifications.

Surface pH

The Surface pH for F1 to F8 was found to be between 5- 7.43.

Swelling Index

The Swelling index forF1 to F8 was found to be between 27.11- and 78.04.

Table-2: Results of Evaluation parameters of tablets

F. No.	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)	Surface PH	Swelling Index
F1	200	3.20	6.16	0.42	93.69	6.56	42.55
F2	199	3.18	6.20	0.43	94.58	5.23	57.83
F3	201	3.21	6.23	0.39	95.89	5.77	78.04
F4	200	3.19	6.15	0.40	91.15	7.08	27.11
F5	200	3.23	6.17	0.42	97.58	6.94	38.02
F6	199	3.20	6.18	0.43	90.27	5.00	45.90
F7	200	3.19	6.18	0.39	92.98	7.43	40.90
F8	199	3.18	6.19	0.40	89.25	5.12	60.43

Table-3: In-vitro Dissolution StudyTable-3: *In vitro* release data of tablet F_1 to F_8

Time (hrs.)	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8
0	0	0	0	0	0	0	0	0
1	23.35	25.50	20.41	22.30	28.50	23.65	20.40	26.41
2	34.62	31.15	32.81	32.42	33.72	35.20	29.72	30.85
3	40.92	38.65	39.90	41.18	42.70	41.28	32.70	40.28
4	52.65	48.23	53.41	50.90	56.65	52.62	49.65	51.27
5	61.25	59.95	65.50	63.82	65.38	60.74	52.38	62.32
6	73.12	72.82	74.84	73.86	73.72	78.56	68.72	71.63
7	80.19	81.84	83.90	84.82	85.09	81.68	75.09	82.75
8	91.16	92.32	93.25	94.12	95.25	91.62	88.25	89.90

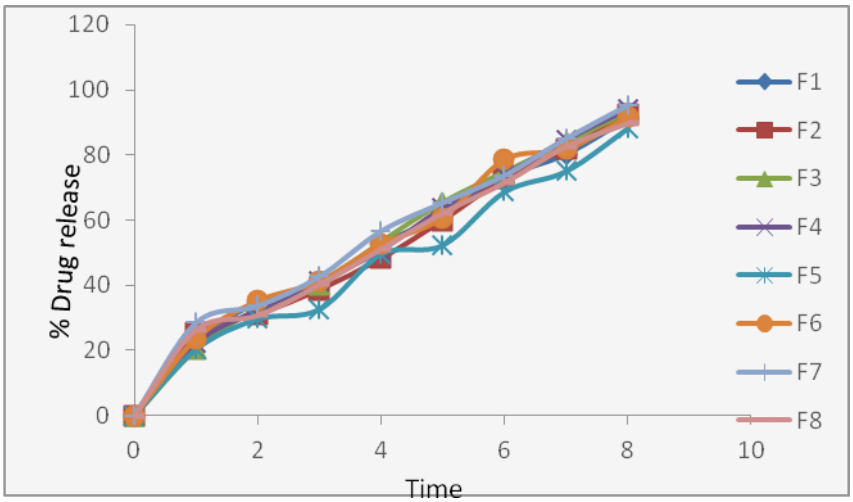

Fig.3. In vitro drug release studies

Kinetic modeling of drug release

All the 8 formulation of prepared matrix tablets of Ivabradine were subjected to in vitro release studies these studies were carried out using dissolution apparatus.

The dissolution medium consisted of 900 ml of Standard buffer pH 1.2 for the first 2 hrs, followed by pH 6.8 for remaining period of time.

The results obtaining in vitro release studies were plotted in different model of data treatment as follows:

1. Cumulative percent drug released vs. time (zero order rate kinetics)
2. Log cumulative percent drug retained vs. time (First Order rate Kinetics)
3. Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)
4. Log of cumulative % release Vs log time (Peppas Exponential Equation.

Zero order kinetics

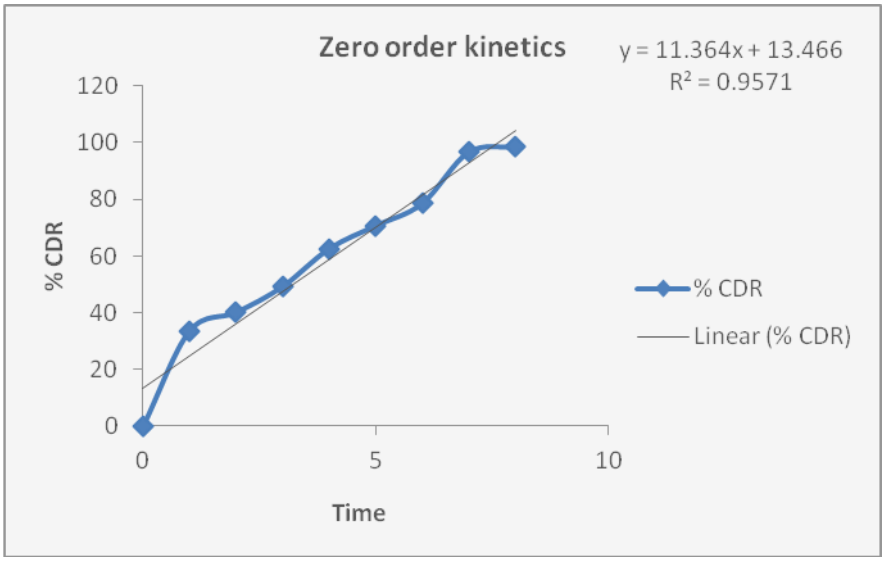

Fig.4. Zero order kinetics of Optimized formulation

First order kinetics

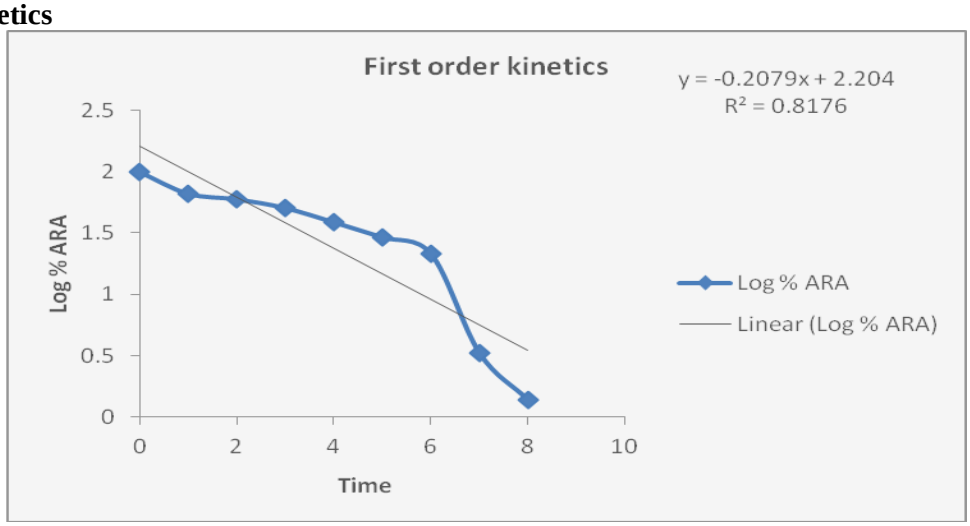

Fig.5. First order kinetics of Optimized formulation

Higuchi model

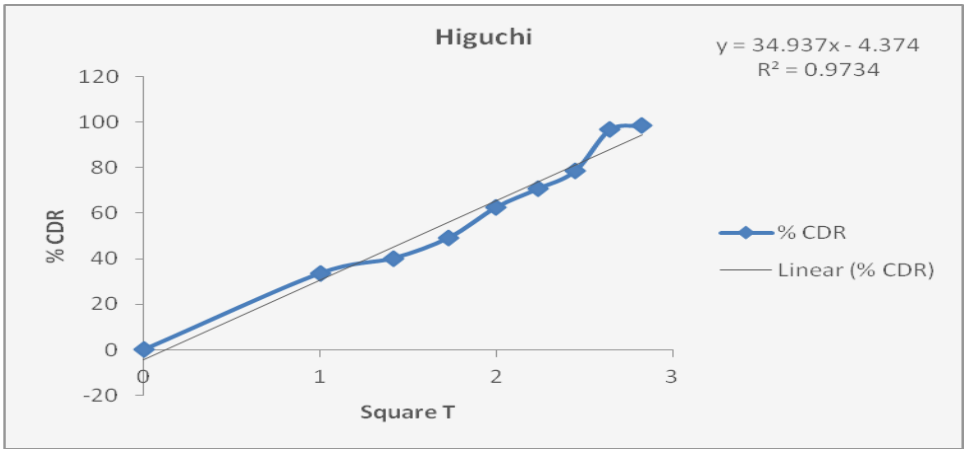

Fig.6. Higuchi model of Optimized formulation

Korsmeyer peppas

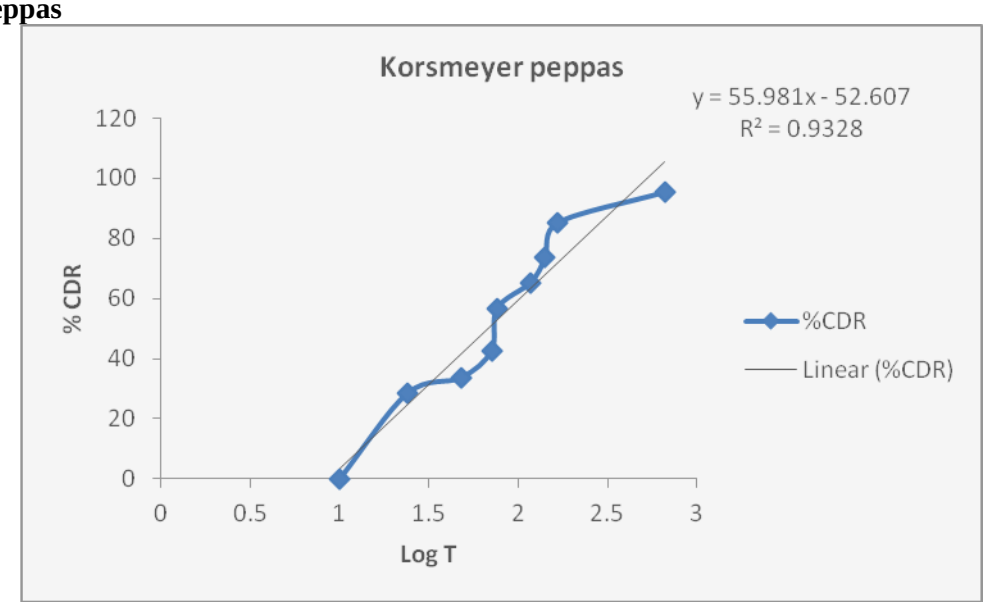

Fig.7. Korsmeyer peppas of Optimized formulation

The kinetic values obtained for formulation F5 were shown. The values of in vitro release were attempted to fit into various mathematical models.

Regression values are higher with Zero order release kinetics. Therefore all the Ivabradine tablets Zero order

release kinetics. Therefore all the Ivabradine tablets follow first order release kinetics.

Stability studies

There was no significant change in physical and chemical properties of the tablets of formulation F-5 after 3 months. Parameters quantified at various time intervals were shown;

Table-4: Results of stability studies of optimized formulation F5

Formulation Code	Parameters	Initial	1st Month	2nd Month	3rd Month	Limits as per Specifications
F-5	25^0C/60%RH % Release	95.25	94.24	93.17	92.12	Not less than 85 %
F-5	30^0C/75% RH % Release	95.25	94.21	93.15	92.10	Not less than 85 %
F-5	40^0C/75% RH % Release	95.25	94.19	93.12	92.09	Not less than 85 %

IV. CONCLUSION

The results of the present study indicate that buccoadhesive tablets of Ivabradine with sustained drug release can be successfully prepared by direct compression method using HPMC K5M, along with ethyl cellulose as mucoadhesive polymers and ethyl cellulose as backing layer.

The formulation F5 containing hydroxypropyl methylcellulose K5M, and ethyl cellulose was found to be promising, which shows an in vitro drug release of 95.25% in 8 h along with satisfactory results.

From the above experimental results it can be concluded that mucoadhesive buccal tablets of Ivabradine can be prepared by using different proportion & combination of Excipients and we selected F5 as best formulation based on dissolution profile and physical characteristics. Formulation (F5) showed total drug release in 8 hr and showed fair flow properties when compared to other formulations. The formulations F5, followed Zero order kinetics.

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