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FORMULATION AND *IN VITRO* EVALUATION OF IVABRADINE MUCOADHESIVE BUCCAL TABLETS

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Abstract

The main objective of the present study was to formulate and evaluate Ivabradine mucoadhesive buccal tablets by direct compression technique. Ivabradine is a novel medication used for the symptomatic management of stable angina pectoris and it has short half -life (2 hrs) with a bioavailability of 40% orally.The drug identity was confirmed by UV spectroscopy. The polymers used to sustain the drug release are Guar gum, Xanthan gum, HPMC K4M and Carbopol 934 . The compatibility studies between the drug and the polymer were studied using the FTIR spectroscopy and were found to be compatible. Preformulation parameters like tapped density, bulk density, carr's index, Hausner's ratio, compressibility index, angle of repose are studied and the results were found to be within the limits. Using the above polymers formulations f1 to f12 were manufactured by direct compression technique and the tablets were evaluated for their thickness, hardness, friability, weight variation and content uniformity test. The in vitro drug release studies were performed in Phosphate buffer of pH6.8 using USP type-II dissolution apparatus. From the dissolution studies it was found that f2 formulation containing HPMC K4M was best since it release minimum amount of drug (9.8%) initially and maximum drug (99.6%) at the end of 8hrs.The f2 formulation was subjected to stability studies for about 3months as per ICH guidelines and found to be stable.

Key words: Buccal; mucoadhesive; angina pectoris; Ivabradine

Introduction

In recent years, the interest in novel routes of drug administration occurs from their ability to enhance the bioavailability of drugs. Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration. Extensive first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via buccal route. Buccal delivery involves administration of desired drug through the buccal mucosal membrane lining of oral cavity.

The oral cavity is an attractive site [1] for the administration of drugs because of ease of administration [2], avoidance of possible drug degradation in gastro intestinal tract and first-pass hepatic metabolism

[3].Various dosage forms like tablets, capsules, liquid preparations are administered by oral route. Among these buccal route of drug delivery offers several advantages like accessibility, patient compliance, rapid cellular recovery following local stress and ability to withstand environmental extremes like change in pH, temperature etc [4].

Mucoadhesive drug delivery systems are delivery systems, which utilized the property of bioadhesion of certain polymers, which become adhesive on hydration [5] and hence can \ be used for targeting a drug to particular region of the body for extended period of time [6]. Bioadhesive tablets are usually prepared by direct compression [7] and they are placed between the cheek and gum providing local or systemic effects [8]. It is an alternative route to administer drugs to patients who are unable to take orally. Therefore, adhesive mucosal dosage forms are suggested for buccal delivery including adhesive tablets, adhesive gels, and adhesive patches [9].

Ivabradine is indicated for the symptomatic treatment of chronic stable angina pectoris in patients with normal sinus rhythm who cannot take beta blockers. It is rapidly absorbed from oral route but undergoes first pass metabolism which results in only 40% oral bioavailability. The half life of Ivabradine is approximately 2 hrs. Ivabradine was selected as model drug to avoid first pass hepatic metabolism and to improve the oral bioavailability and to control the release of the drug from the tablets by matrix forming polymers, as the half- life of drug is low.

Materials and Methods

Ivabradine HCL was obtained from Chandra labs, HYD. Hydroxypropyl methyl cellulose K4M, Carbopol, Xanthan gum were obtained from Merck specialties private limited, India. Guar gum, Mannitol, Aspartame and Magnesium stearate was obtained from SD Fine chemicals. All other chemicals, reagents and solvents were used are of analytical grade.

Method of Preparation of Buccal Tablets

Direct compression method has been employed to prepare buccal tablets of Ivabradine using HPMC K4M and Xanthan gum and Guar gum as polymers. All the ingredients including drug, polymer and excipients were weighed accurately. The drug is thoroughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricant were mixed in the order of ascending weights and blended for 10 min. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend (150 mg) of each formulation was then compressed using an 8mm diameter die on a multi station tablet punching machine.

Results and discussion

Preformulation studies:

Calibration curve of Ivabradine in water:

From the primary stock solution (100 µg/ml), appropriate aliquot i,e., 0.1, 0.2, 0.3, 0.4, 0.5 were transferred to series of 10 ml volumetric flasks and made upto 10 ml with pH 6.8 phosphate buffer so as to get concentration of 1,2,3,4 and 5 µg/ml. The absorbance of the solution was measured at 286 nm. A calibration curve was plotted.

Table: 1 calibration curve data

S.No	Concentration (µg/ml)	Absorbance(nm)
1	0	0
2	1	0.165
3	2	0.325
4	3	0.471
5	4	0.627
6	5	0.789

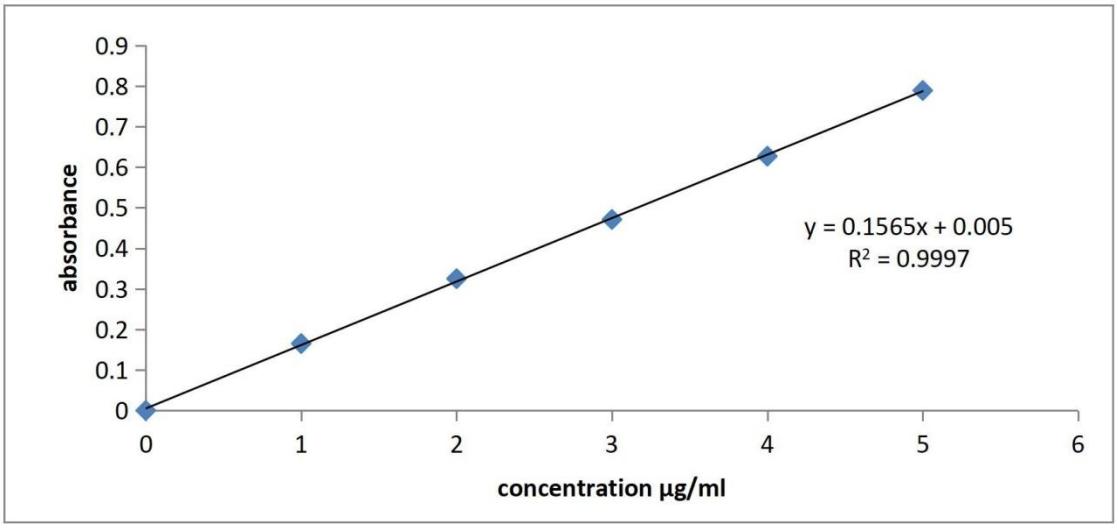


Fig: 1 Calibration curve plot of Ivabradine in 6.8 phosphate buffer

Compatibility studies

The FTIR spectroscopy is a useful tool for identifying chemical interaction between drug and the used polymers. The FT-IR spectrum did not show presence of any additional peaks for new functional groups indicating no chemical interaction between drugand the used polymers.

FTIR studies: Drug polymer interactions were studied by FT-IR spectroscopy. The FT-IRspectra of pure Ivabradine and formulation were given in fig 2 and 3.

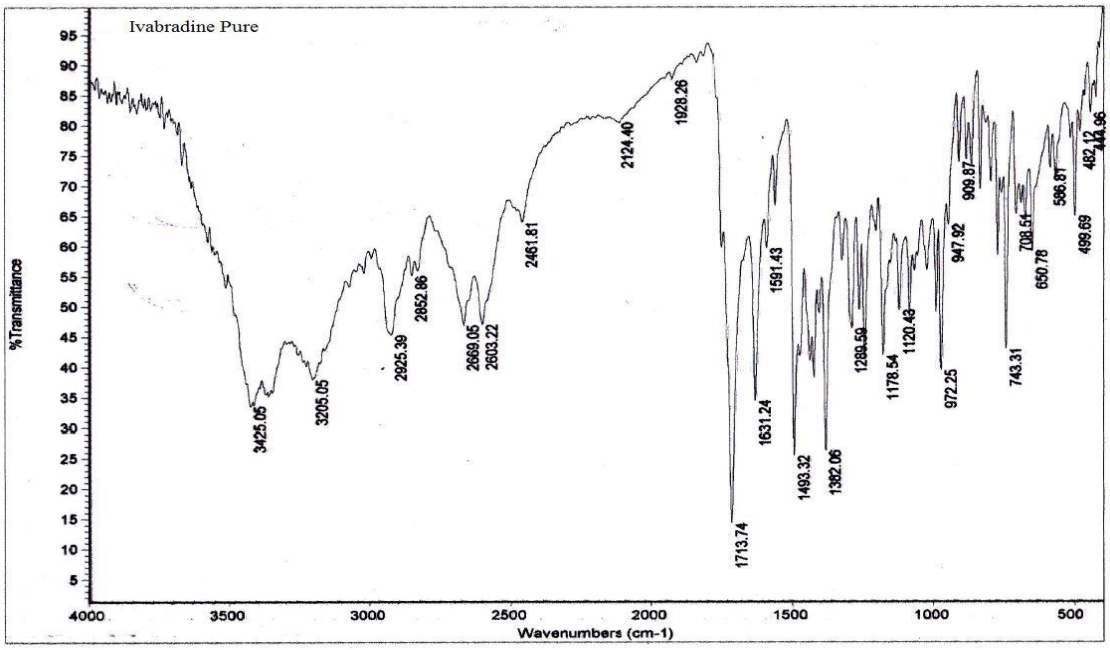


Fig: 2 FT-IR Spectra of Ivabradine Pure drug

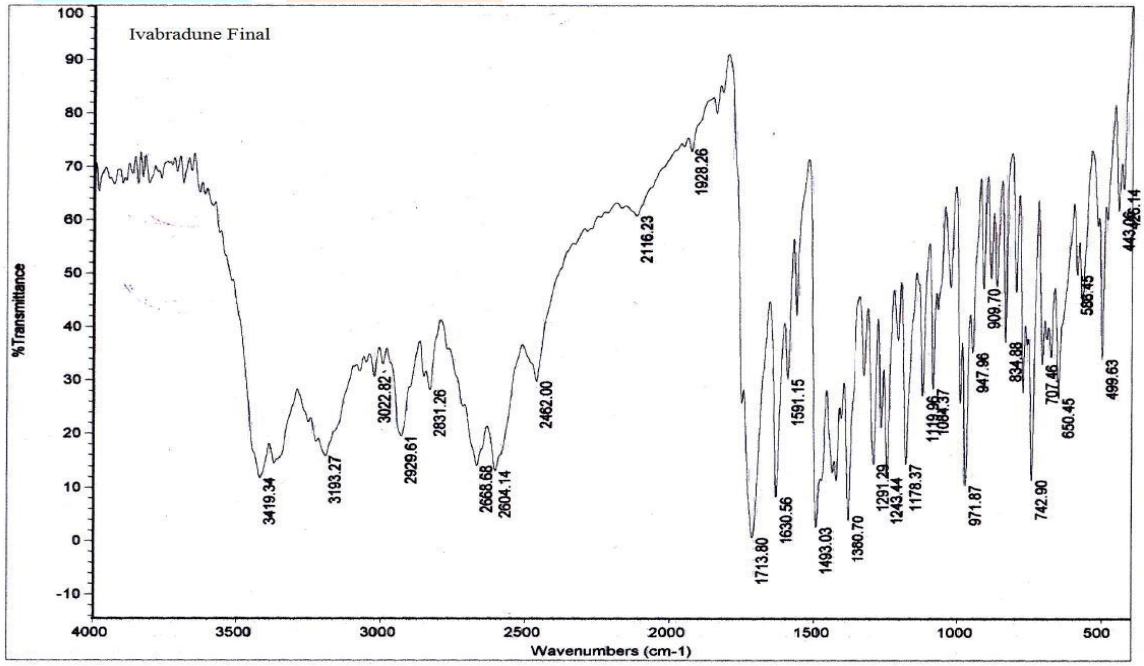


Fig: 3 FT-IR Spectra of Ivabradine optimized

Discussion: Drug-excipient compatibility study indicates that the all used excipients in the optimized formulation are compatible with the drug based on FT-IR spectra.

Characterization of Blend:

The blends for Buccoadhesive tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. Angle of repose was less than 30° and Carr's index values were less than 15 for the blend of all the batches indicating excellent to good flowability and compressibility. Hausner's ratio was less than 1.11 for all the batches indicating excellent flow properties and given in table 2.

Table 2: Physical Properties of Pre-compression Blend

Formulations	Angle of repose (°)	Bulk Density (g/mL)	Tapped Density (g/mL)	Carr's Index (%)	usner'sratio	Flow property
F1	30.25^0	0.342	0.386	11.39896	1.128655	Good
F2	30.43^0	0.358	0.412	13.1068	1.150838	Good
F3	22.87^0	0.326	0.334	2.39521	1.02454	Excellent
F4	22.45^0	0.334	0.348	4.022989	1.041916	Excellent
F5	24.37^0	0.442	0.499	11.42285	1.128959	Excellent
F6	29.41^0	0.321	0.334	3.892216	1.040498	Good
F7	22.88^0	0.326	0.333	2.39531	1.02464	Excellent
F8	30.13^0	0.360	0.414	13.1071	1.1509	Good
F9	24.30^0	0.447	0.500	11.42687	1.1311	Excellent
F10	22.87^0	0.326	0.334	2.39521	1.02454	Excellent
F11	22.45^0	0.334	0.348	4.022989	1.041916	Excellent
F12	30.43^0	0.358	0.412	13.1068	1.150838	Good

Physical evaluation of buccoadhesive tablets

The results of the uniformity of weight, hardness, thickness, friability, and drug content of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight as their weights varied between 148.6±0.41and 151.6±1.14mg. The hardness of the tablets ranged from 6.34±0.57to 6.86±0.55kg/cm^2 and the friability values were less than 0.5% indicating that the Buccoadhesive tablets were compact and hard. The thickness of the tablets ranged from 2.52±0.17 to 2.65±0.66 mm. All the formulations satisfied the content of the drug as they contained 98 to 101 % of Ivabradine and good uniformity in drug content was observed. Thus all the physical attributes of the preparedtablets were found be practically within control.

Table:3 Physical Evaluation of Buccoadhesive Tablets

F.Code	Hardness (kg/cm^2)	Thickness (mm)	Weight (mg)	Friability (%)	Drug content (%)
F1	6.50 ±0.44	2.52±0.17	150.8±1.48	0.36	98.25±1.37
F2	6.60±0.31	2.57±0.25	149.4±0.54	0.39	99.48±0.80
F3	6.72±0.40	2.54±0.80	148.6±0.41	0.43	99.12±2.47
F4	6.86±0.55	2.50±0.20	148.8±1.64	0.12	100.22±0.88
F5	6.34±0.57	2.65±0.66	150.6±1.14	0.54	100.24±1.25
F6	6.49±0.30	2.63±0.25	148.2±0.83	0.58	99.53±1.87
F7	6.51±0.32	2.57±0.81	148.7±0.46	0.36	99.50±0.60
F8	6.53±0.35	2.58±0.80	148.9±0.64	0.39	99.32±0.87
F9	6.52±0.31	2.57±0.82	148.9±0.44	0.43	99.58±0.60
F10	6.76±0.55	2.30±0.20	149.8±1.64	0.12	99.22±0.88
F11	6.44±0.57	2.45±0.66	151.6±1.14	0.18	100.24±1.0
F12	6.59±0.30	2.33±0.25	149.2±0.83	0.26	100.53±1.0

***In-vitro* drug release study:**Table 4: Cumulative drug release of formulation F1-F12

	%CDR											
Time (hrs)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0	0	0	0	0	0	0
1	17.6	9.87.2		21.3	20.6	19.8	21.3	20.6	19.8	29.6	30.1	25.4
2	39.8	17.2	15.0	34.9	30.4	25.1	34.9	30.4	25.1	35.9	39.6	35.1
3	52.31	23.80	20.9	48.6	42.6	33.6	48.6	42.6	33.6	59.6	45.8	49.5
4	70.61	45.6	33.8	52.1	54.1	48.2	52.1	54.1	48.2	72.4	61.5	64.5
5	86.3	60.1	58.0	74.8	68.7	56.1	74.8	68.7	56.1	92.1	72.8	79.2
6	98.2	70.8	65.1	98.5	85.9	68.5	97.3	77.4	68.5	100.5	90.5	88.1
7	--	89.0	79.3	--	99.6	74.2	--	85.9	74.2	--	99.9	100.2
8	--	99.6	86.7	--	--	90.6	--	98.6	80.6	--	--	--

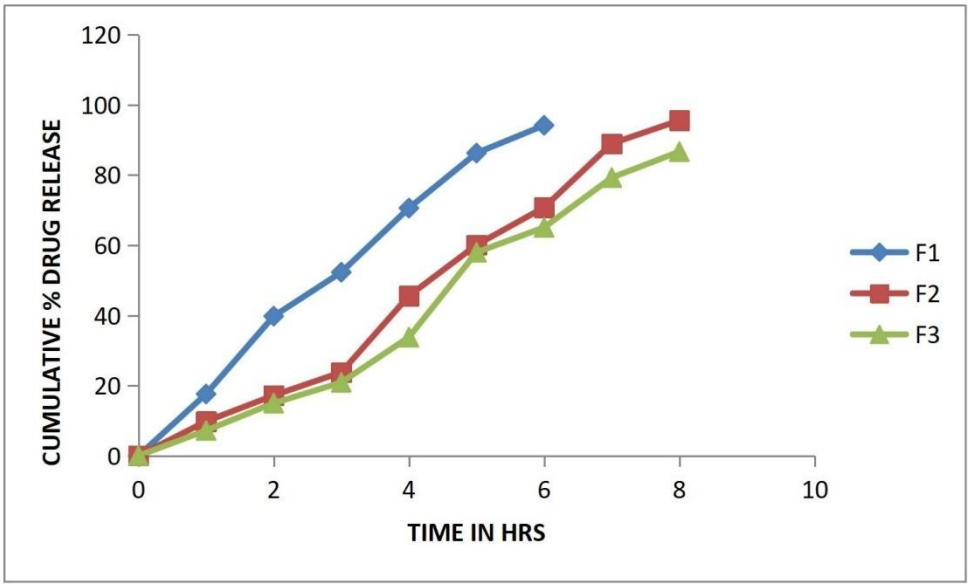


Fig 4: *In-Vitro* Drug Release for Formulation F1, F2, F3

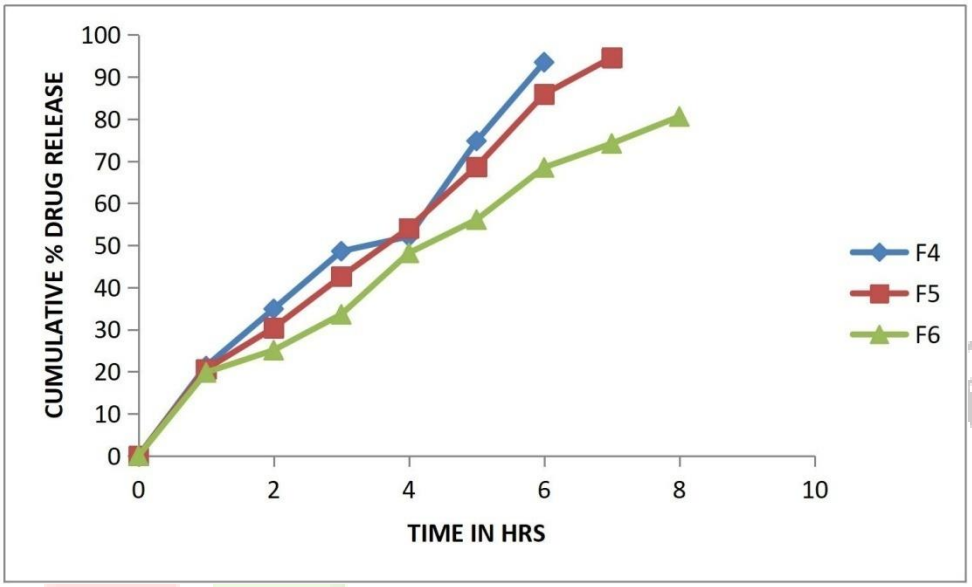
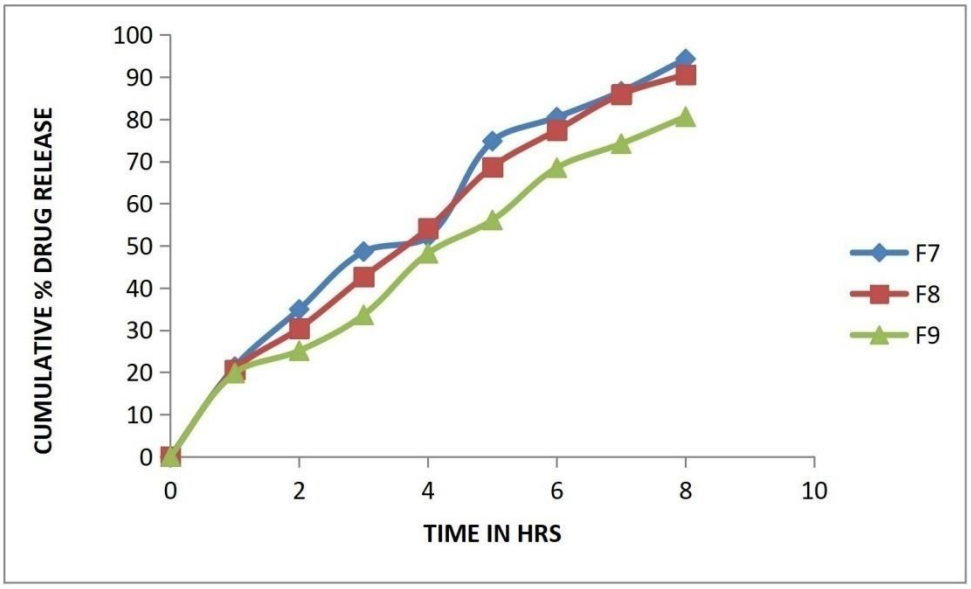


Fig 5: *In-Vitro* Drug Release for Formulation F4, F5, F6



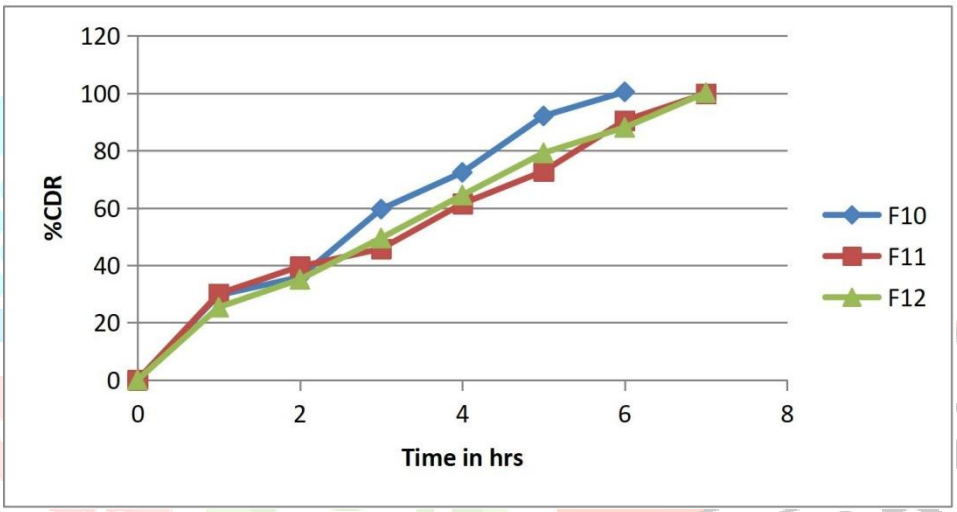


Fig 6: *In-Vitro* Drug Release for Formulation F7, F8, F9

Fig 7: *In-Vitro* Drug Release for Formulation F10, F11, F12

***In-vitro* drug release study**

The *In-vitro* drug release study has been done for various formulations (F1-F12). The different ratios of polymers were used. The results shown that as the proportion of polymers in the formulation increases, cumulative percent drug release was found to be reduced. Among the twelve batches, formulation F1, F4 and F7 have released 98.2%, 98.5% and 97.3% drug release in 6th hr respectively, F2 and F8 formulations shows drug release of 99.6% and 98.6% respectively. Among all F2 and F8 were optimized based on sustained drug release and highest drug release at 98.6% and 99.6 respectively at 8^{th} hr. But mucoadhesion time for F8 formulation was less than 8 hours so F2 was considered as best formulation.

Drug Release Kinetics for Optimized Formula F2

R2 Value of various kinetic models

Kinetic model		Result
Zero order	R2	0.984
First order	R2	0.844
Higuchi	R2	0.858
Korsmeyer-Peppas	R2	0.828

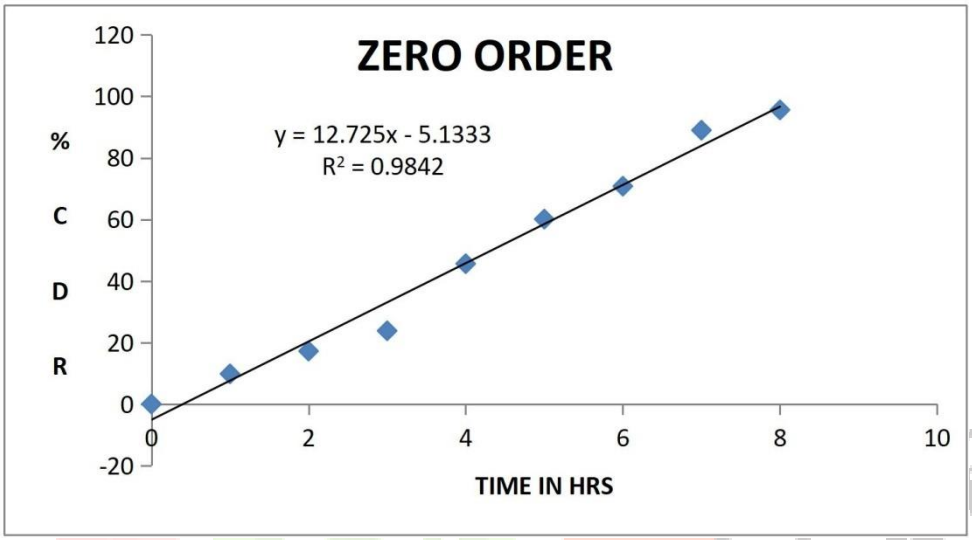


Fig 8: Zero order graph for formulation F2.

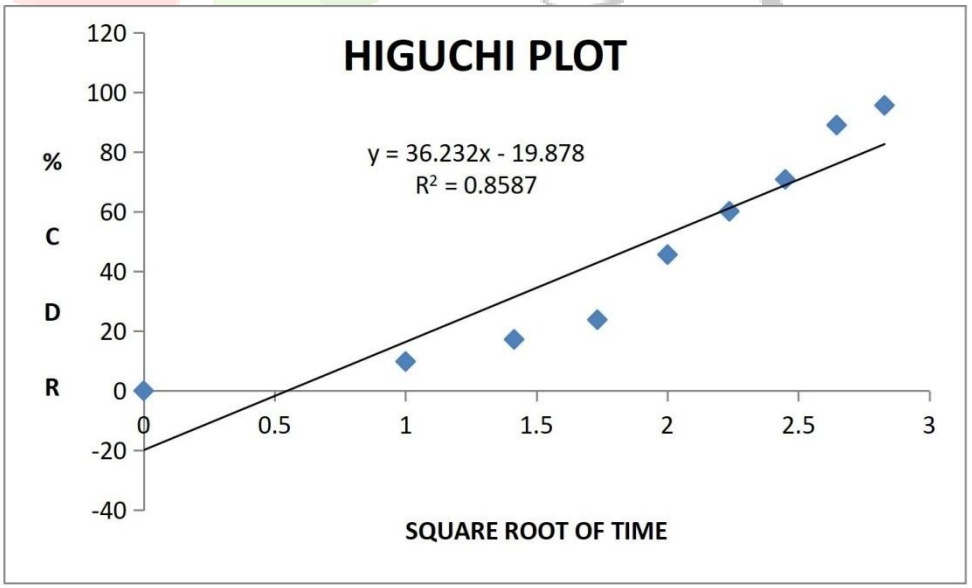


Fig 9: Higuchi plot for formulation F2.

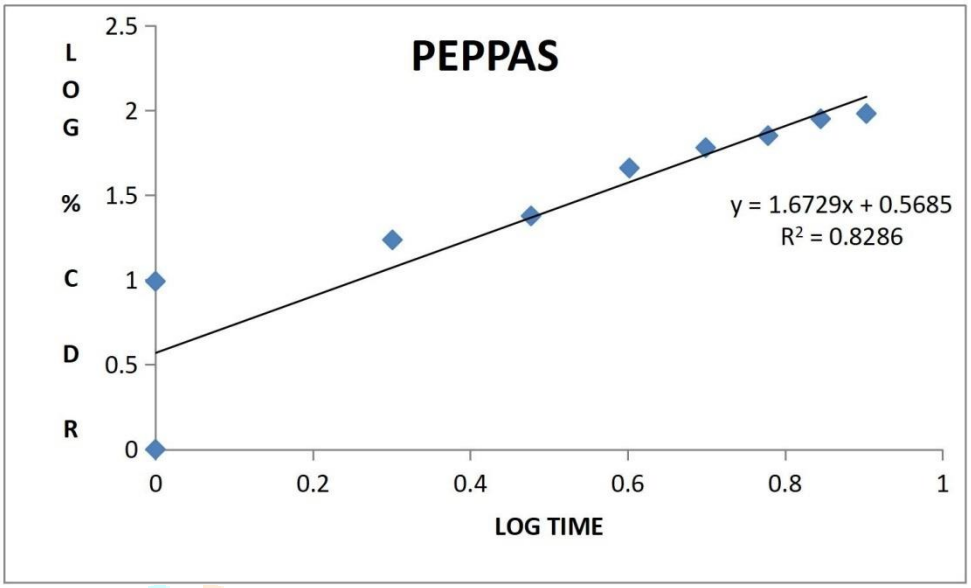


Fig 10: Peppas plot for formulation F2.

Fig 11: First Order graph for Formulation F2.

***Ex-vivo* drug permeation studies for F2.**

Table 5: *Ex-vivo* drug permeation studies for F2.

Time (hr)	F2
1	9.03
2	13.8
3	26.18
4	35.27
5	44.89
6	58.76
7	70.04
8	84.01

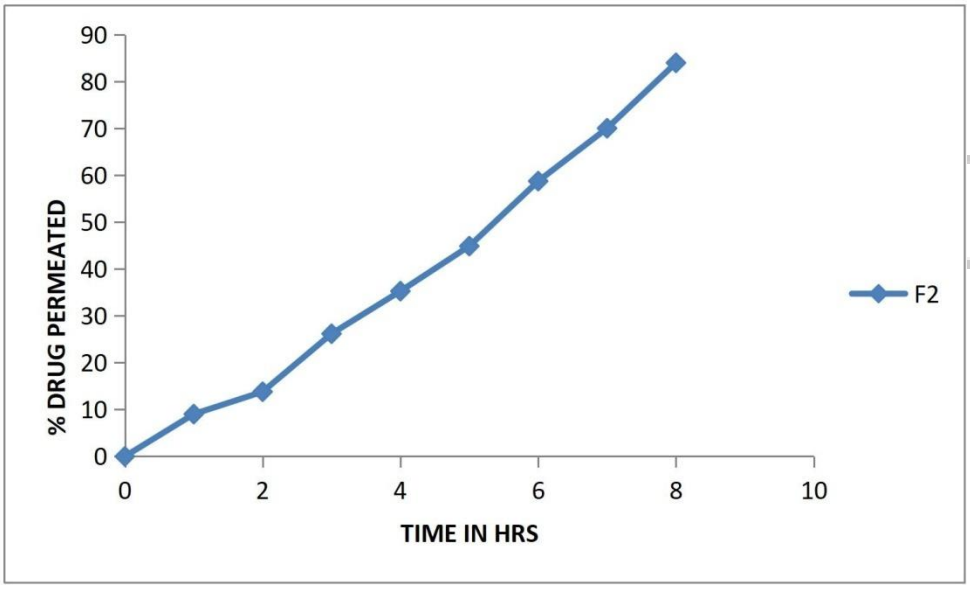


Fig 12: Graph showing permeation studies of formulation F2.

The drug permeation was slow and steady, 84.01% of drug could permeate throughthe buccal membrane in 8 hours.

Drug release kinetics

In-vitro drug release data of all the buccal tablet formulations was subjected to goodness of fit test by linear regression analysis according to zero order, first order, Higuchi's and Korsmeyer-Peppas models to ascertain the mechanism of drug release. From the above data, it can be seen the formulation, F2 have displayed zero order release kinetics ('r^2 value of 0.9842). From Peppas data, it is evident that the

drug is released by non-Fickian diffusion mechanism. This is because as the proportion of polymers in the matrix increased there was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer. Zero-order release from swellable hydrophilic matrices occurs as a result of constant diffusional path lengths.

Stability studies:

Table 6: Stability studies of Ivabradine buccoadhesive tablet (F2) at room temperature

Time	Colour	Assay		Cumulative % drug release		Surface PH	
		25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH	25±2^{0}c and 65±5%RH	40±2^{0}c and 75±5%RH
First day	White	99.48	99.48	97.6	98.6	6.6	6.6
30 days	White	99.40	99.30	99.1	97.9	6.6	6.6
60days	White	99.31	99.2	97.2	97.1	6.6	6.6
90 days	White	98.5	98.0	98	97.8	6.6	6.6

Results from stability studies indicate that the formulated Ivabradine buccoadhesive tablets are stable for a period of 3 months under 2 different conditions at 25±2^{0}c and 65±5%RH and 40±2^{0}c and 75±5%RH. There were no remarkable changes were observed during the period of storage.

Conclusion

Mucoadhesive buccal tablets of Ivabradine HCL can be prepared by direct compression method using HPMC K4M, Xanthan gum and guar gum as mucoadhesive polymers. FT- IR spectroscopic studies indicated that there are no drug-excipient interactions. Post compression parameters of Ivabradine HCL were within the limits according to IP standards. Among all the 12 formulations, F2 formulation is optimized, as it shows maximum drug release at the end of 8hrs and have displayed good bioadhesion strength. Optimized formulation (F2) follows zero order release kinetics and drug release follows non-Fickian diffusion mechanism.

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