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Formulation and evaluation of Ivabradine buccal tablets

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Abstract
In the present study, an attempt was made to prepare buccal tablets of Ivabradine HCL (an anti-anginal drug), in order to overcome bioavailability problems, to reduce dose dependent side effects and frequency of administration. Buccal tablets containing the drug were prepared by direct compression method using combinations of polymers (such as sodium CMC, HPMC K200M and karaya gum). Estimation of Ivabradine HCL was carried out spectrophotometrically at 292 nm. The Buccal tablets were evaluated for various physical and biological parameters, drug content uniformity, *in-vitro* drug release, drug- excipient interactions (FTIR). IR spectroscopic studies indicated that there are no drug-excipient interactions. The formulations F9 (containing 30mg of HPMC K200M) were found to be promising, which showed maximum drug release within 8 h. These formulations have displayed good bioadhesion strength (4.66 gm respectively).

Keywords: Ivabradine HCL, FTIR, sodium CMC, HPMC K200M and karaya gum

Introduction
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 bioa dhesion 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].
Corlanor (Ivabradine) is a hyperpolarization-activated cyclic nucleotide-gated channel blocker indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting heart rate ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use [10].

Materials and Methods
Ivabradine HCL of pharma grade was obtained from BMR chemicals. Hyderabad. Hydroxypropyl methyl cellulose K200M, sodium CMC, Karaya gum were obtained from Otto chemicals, Mumbai, India. Mannitol was obtained from Concord Drugs Ltd, Hyderabad. Micro crystalline cellulose was obtained from Loba Chemie pvt ltd, Mumbai. Talc and magnesium stearate were obtained from Rankem. All other chemicals, reagents and solvents were used are of analytical grade.

Drug-excipient compatibility study using ftir
Drug and excipients interaction was checked by comparing the FT-IR spectra of pure drug Ivabradine HCl and FT-IR spectra of the physical mixture of drug and excipients.

The IR spectra were taken from FT-IR-8400S (Shimadzu Corporation, Tokyo, Japan). In the present study, potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered KBr crystals. The mixture was compressed to form a disc. The disc was placed in the IR Spectrophotometer and the spectrum was recorded.
Physical compatibility studies were assured by FT-IR studies. The IR spectrums of the mixed powders were taken by preparing Potassium bromide pellets under dry condition by using pellet press. Spectra are superimposed. The transmission minimal (absorption maxima) in the spectra obtained with the sample corresponded in position and relative size to those in the spectrum obtained with the working/reference standards.

Method of Preparation of Buccal Tablets
Direct compression method has been employed to prepare buccal tablets of Ivabradine using Sodium CMC, HPMC K200M and karaya gum as polymers. All the ingredients including drug, polymer and excipients were weighed accurately. The drug is throughly mixed with mannitol on a butter paper with the help of a stainless steel spatula. Then all the ingredients except lubricants 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 [11]. Compositions of the designed buccal tablets are given Table-6.4.

Flow properties of API
A. Bulk Density (Db)
It is the proportion of aggregate mass of powder to the mass volume of powder. It was estimated by pouring the measured powder (went through standard sieve#20) into an estimating barrel and the underlying volume was noted. This underlying volume is known as the mass volume. From this, the mass thickness is computed by the equation specified beneath. It is communicated in g/cc and is given by

$$Db = m/Vo$$

Where,
m = mass of the powder
Vo = bulk volume of powder

B. Tapped density (Dt)
It is the proportion of aggregate mass of powder to the tapped volume of powder. The volume was estimated by tapping the powder for 500 times. At that point the tapping was improved the situation 750 times and the tapped volume was noticed (the contrast between the two tapped volumes ought to be under 2%). In the event that it is over 2%, tapping is proceeded for 1250 times and tapped volume was noted. It is communicated in g/cc and is given by

$$Dt = m/Vi$$

Where,
m = mass of the powder
Vi = tapped volume of powder

C. Angle of Repose (θ)
This is the most extreme edge conceivable between the surface of a heap of powder or granules and the flat plane. The powders were permitted to move through the pipe settled to a remain at positive stature (h). The edge of rest was then ascertained by estimating the stature and sweep of the pile of granules framed.

$$\tan \theta = h/r$$
(Or)
$$\theta = \tan^{-1} (h/r)$$

Where,
θ = angle of repose
h = height of the heap
r = radius of the heap

D. Compressibility Index
The flowability of powder can be evaluated by comparing the bulk density (Db) and tapped density (Dt) of powder and the rate at which it packed down. Compressibility index is calculated by:

$$\text{Compressibility index (\%)} = Dt - Db/Dt \times 100$$

Where,
Db = Bulk density
Dt = Tapped density

Hausner's Ratio: It is the proportion of tapped density to the bulk density. It is given by:

$$\text{Hausner's ratio} = Dt / Db$$

Where,
Dt = Tapped density
Db = Bulk density

The flow properties of API alone and along with excipients i.e., powder blend was calculated by using the above formulae and the type of flow can be compared by using the following standard specifications.

Post compression parameters of buccal tablets of Ivabradine HCL
Hardness test: The crushing strength (kg/cm^2) of tablets was determined by using Pfizer hardness tester.
Friability test: This was determined by weighing 10 tablets after dusting, placing them in the friabilator and rotating the plastic cylinder vertically at 25 rpm for 4 min. After dusting, the total remaining weight of the tablets was recorded and the percent friability was calculated (% loss in weight) [12].
Uniformity of content: The weight (mg) of each of 20 individual tablets was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation from the mean [13].
Uniformity of drug content: Five tablets were powdered in a glass mortar and the powder equivalent to 10 mg of drug is placed in a stoppered 100 ml conical flask. The drug is extracted with 25 ml water with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 2 h and filtered into

50 ml volumetric flask through Whatman No.1 filter paper (Mean pore diameter 1.5 µm) and more solvent is passed through the filter to produce 50 ml. Aliquots of the solution are filtered through 0.22 µm membrane filter disc (Millipore corporation) and analyzed for drug content by measuring the absorbance at 292 nm against solvent blank [14].

Surface pH study: The surface pH of the buccal tablets is determined in order to investigate the possibility of any side effects *in vivo*. As an acidic or alkaline pH may irritate the buccal mucosa, we sought to keep the surface pH as close to neutral as possible. A combined glass electrode is used for this purpose. The tablet is allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.8 ± 0.05) for 2 h at room temperature. The pH is identified by bringing the electrode into contact with the tablet surface and allowing to equilibrate for 1 min.

Swelling Index: The swelling rate of the buccal tablet is evaluated by using of pH 6.8 phosphate buffer. The initial weight of the tablet is determined (w_1). The tablets is placed in pH 6.8 phosphate buffer (6 ml) in a petridish placed in an incubator at 37 ± 1º C and tablet is removed at different time intervals (0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 h), blotted with filter paper and reweighed (w_2) [15].

The swelling index is calculated by the formula:

$$\text{Swelling index} = 100\ (w_2 - w_1) / w_1.$$

Mucoadhesion strength: The apparatus used for testing bioadhesion was assembled in the laboratory. Mucoadhesion strength of the tablet was measured on a modified physical balance using bovine cheek pouch as model mucosal membrane.

A double beam physical balance was taken, the left pan was removed. To left arm of balance a thick thread of suitable length was hanged. To the bottom side of thread a glass stopper with uniform surface was tied. A clean glass mortar was placed below hanging glass stopper. In this mortar was placed a clean 500 ml glass beaker, within which was placed another glass beaker of 50 ml capacity in inverted position and weighted with 50 gm to prevent floating. The temperature control system involves placing thermometer in 500 ml beaker and intermittently adding hot water in outer mortar filled with water. The balance was so adjusted that right hand-side was exactly 5 gm heavier than the left.

Method: The balance adjusted as described above was used for the study. The bovine cheek pouch, excised and washed was tied tightly with mucosal side upward using thread over the base of inverted 50 ml glass beaker. This beaker suitably weighted was lowered into 500 ml beaker, which was then filled with pH6.8 phosphate buffer kept at 37º C such that the buffer reaches the surface of mucosal membrane and keeps it moist. This was then kept below left hand side of balance. The buccal tablet was then stuck to glass stopper through its backing membrane using an adhesive (Feviquick). The 5gm on right hand side is removed, this causes application of 5 gm of pressure on buccal tablet overlying moist mucosa. The balance was kept in this position for 3 minutes and then slowly weights were increased on the right pan, till tablet separates from mucosal membrane. The total weight on right pan minus 5 gm gives the force required to separate tablet from mucosa. This gives bioadhesive strength in grams. The mean value of three trials was taken for each set of formulations. After each measurement, the tissue was gently and thoroughly washed with isotonic phosphate buffer and left for 5 minutes before reading a new tablet of same formulation to get reproducible multiple results for the formulation [16].

***In vitro* drug release study**

The prepared buccal tablets were subjected to *in vitro* dissolution. Dissolution test was carried out using USP type 2 paddle method [apparatus 2]. The stirring rate was 50 rpm, pH 6.8 phosphate buffer was used as dissolution medium and dissolution medium was maintained at 37±0.5oC. Samples of 5 ml were withdrawn at regular intervals of time, filtered and replace with 5 ml of fresh dissolution medium, dilutions were made wherever necessary and were analyzed for Ivabradine at 292 nm by using UV-visible spectrophotometer.

Release Kinetics

In the present study, data of the *in vitro* release were fitted to different equations and kinetic models to explain the release kinetics of ivabradine from the buccal tablets. The kinetic models used were Zero order equation, First order, Higuchi release and Korsmeyer-Peppas models [17].

The results of *in vitro* release profiles obtained for the BDDS formulations were fitted into four models of data treatment as follows [18].

1. Cumulative percent drug released versus time (zero order kinetic model).
2. Log cumulative percent drug remaining versus time (first-order kinetic model).
3. Cumulative percent drug released versus square root of time (higuchi's model).
4. Log cumulative percent drug released versus log time (korsmeyer - Peppas equation).

Results and Discussion

Drug-Excipient compatibility studies

The IR spectrum of pure drug was found to be similar to the standard spectrum of Ivabradine.

The spectrum of Ivabradine shows the following functional groups at their frequencies shown in Figure 6.1. From the spectra of Ivabradine, combination of Ivabradine with polymers, it was observed that all characteristic peaks of Ivabradine were not altered and present without alteration in the combination spectrum, thus indicating compatibility of the drug and excipients.

FTIR spectra of Ivabradine, and Optimized formulation are shown in Figures below.

Drug-Excipients compatability studies

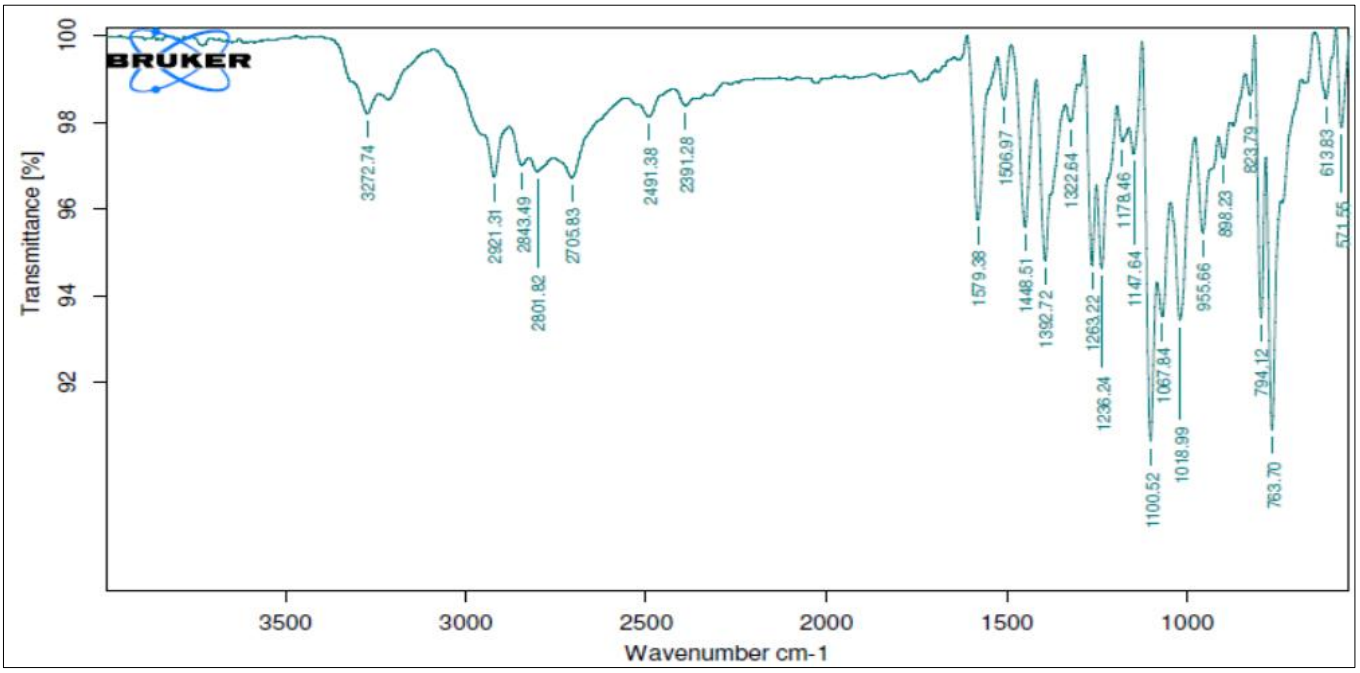

Fig 1: FTIR spectrum of Ivabradine

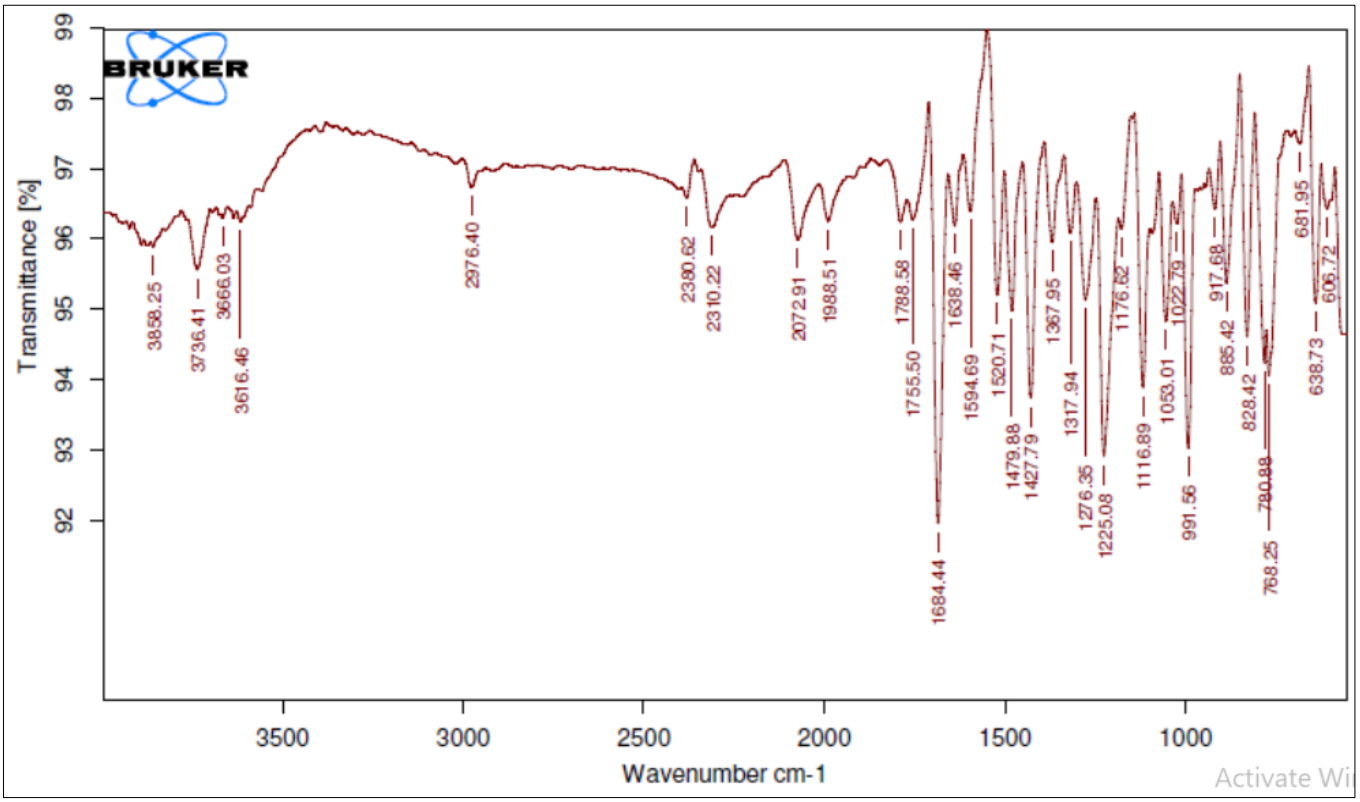

Fig 2: FTIR Spectrum of drug and polymers in optimized formulation

Standard graph

The standard calibration curve of Ivabradine was developed in pH 6.8 phosphate buffer

Standard Calibration Curve in 6.8 pH phosphate buffer

Standard graph of Ivabradine in pH 6.8 phosphate buffer shows linearity in the concentration range of 5-30µg/ml with correlation coefficient of 0.999. Table 6.6 gives data of the standard graph and Figure 6.9 shows the standard graph in pH 6.8 phosphate buffer.

Table 1: Data for calibration curve of Ivabradine in pH 6.8 at 292nm

Concentration (µg/ml)	Absorbance
0	0
5	0.167
10	0.305
15	0.468
20	0.602
25	0.768
30	0.899

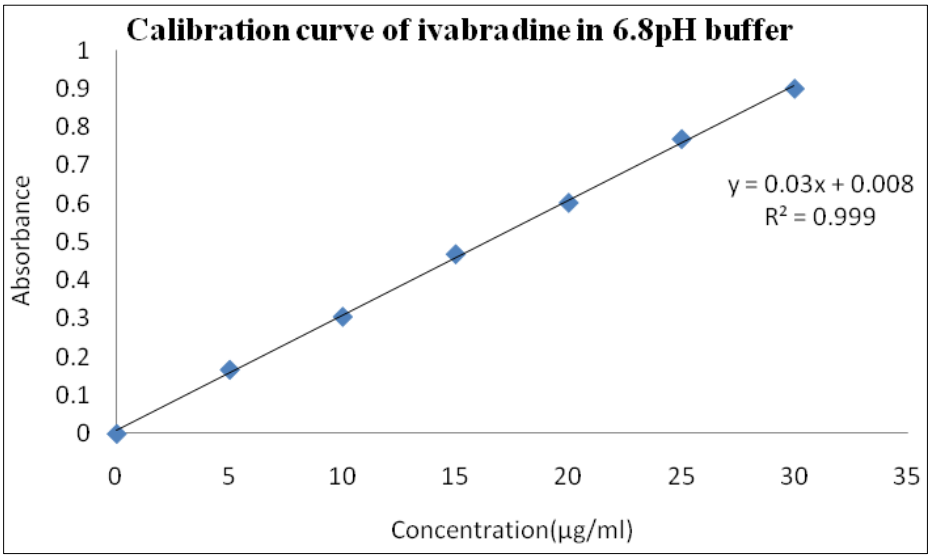

Fig 3: Standard Calibration Curve of Ivabradine in pH 6.8 at 292 nm

Flow properties of powder blend

Table 2: Flow properties of powder blend

Code	Angle of Repose±SD	Bulk Density (g/ml)	Tapped Density (g/ml)	Carr's Index. (%)	Hausner's ratio
F1	28.16±0.03	0.458±0.26	0.521±0.45	12.09±0.26	1.14±0.26
F2	29.30±0.26	0.453±0.23	0.521±0.56	13.05±0.23	1.15±0.35
F3	27.02±0.15	0.354±0.12	0.41±0.14	13.66±0.15	1.16±0.14
F4	28.16±0.45	0.376±0.02	0.432±0.23	12.96±0.48	1.15±0.52
F5	29.41±0.53	0.371±0.14	0.429±0.64	13.52±0.51	1.16±0.85
F6	25.16±0.63	0.363±0.52	0.416±0.74	12.74±0.26	1.15±0.74
F7	27.50±0.15	0.452±0.63	0.516±0.85	12.40±0.32	1.14±0.63
F8	26.15±0.47	0.395±0.25	0.468±0.54	15.60±0.46	1.18±0.12
F9	26.03±0.56	0.386±0.42	0.448±0.26	13.84±0.85	1.16±0.20

Post compression parameters of Ivabradine buccal tablets

Table 3: Post compression parameters of Ivabradine buccal tablets

Formulation code	Hardness (kg/cm2)	Thickness (mm)	Weight variation	Friability (%)	% Drug content (CV)	Surface pH	SI (after8h)	Mucoadhesiv sterngth (gm)
F1	6.6± 0.15	2.03± 0.04	149± 0.30	0.51±0.26	92.26±0.76	6.26±0.02	21.16±2.26	4.01±0.15
F2	6.7± 0.26	2.23± 0.09	151± 0.50	0.12±0.14	94.14±0.86	6.66±0.16	35.02±1.52	4.06±0.25
F3	7.1± 0.51	2.02± 0.13	148± 0.63	0.26±0.52	93.52±1.02	5.98±0.41	46.42±1.15	4.26±0.16
F4	6.1± 0.89	2.16± 0.05	149± 0.25	0.16±0.65	95.63±1.46	6.15±0.15	19.15±1.23	4.13±0.02
F5	6.0± 0.85	2.21± 0.06	150± 0.40	0.41±0.15	94.15±0.89	6.16±0.56	39.46±2.12	4.29±0.15
F6	6.1± 0.49	2.15± 0.04	149± 0.10	0.52±0.41	96.45±1.10	6.02±0.47	47.85±1.15	4.44±0.41
F7	7.1± 0.74	2.20± 0.08	150± 0.20	0.36±0.02	93.12±0.36	6.15±0.26	26.52±1.20	4.36±0.52
F8	6.4± 0.89	2.17± 0.09	148± 0.25	0.14±0.06	95.16±0.52	5.63±0.89	41.16±1.23	4.51±0.26
F9	6.6± 0.84	2.13± 0.04	149± 0.40	0.16±0.04	97.14±1.15	5.98±0.74	50.02±2.15	4.66±0.18

The appearance of buccal tablets was smooth and uniform on physical examination. The hardness of prepared buccal tablets of Ivabradine was found to be 6.0 to 7.1 kg/cm^2.

The thickness and weight variation were found to be uniform as indicated by the low values of standard deviation. The thickness and weight of the prepared buccal tablets were found to be in the range of 2.02 to 2.21 mm and 148 to 151 mg respectively. Friability values less than 1% indicate good mechanical strength to withstand the rigors of handling and transportations.

The drug content of buccal tablets was quite uniform. The average drug content of the buccal tablets was found to be within the range of 92.26 to 97.14 % and the low values of standard deviation and coefficient of variation (< 2) indicate uniform distribution of the drug within the prepared buccal tablets.

The surface pH was determined in order to investigate the possibility of any side effects, in the oral cavity as acidic or alkaline pH is bound to cause irritation to the buccal mucosa. Surface pH of all formulations was found to be in the range of 5.63 to 6.66. Hence it is assumed that these formulations cause no any irritation in the oral cavity.

The swelling profile of different batches of the tablets is shown in Table-7.4. These profiles indicate the uptake of water into the tablet matrix, producing an increase in weight. The swelling state of the polymer (in the formulation) was reported to be crucial for its bioadhesive behavior. Adhesion occurs shortly after the beginning of swelling but the bond formed between mucosal layer and polymer is not very strong. The adhesion will increase with the degree of

hydration until a point where over-hydration leads to an abrupt drop in adhesive strength due to disentanglement at the polymer/tissue interface. In formulations maximum swelling was seen with the formulation containing higher concentration of HPMC K200M. Results indicate that as the concentration of polymers increases the swelling index increases.

The mucoadhesion of all the buccal tablets of varying ratios of polymers were tested and weight required to pull off the formulation from the mucous tissue is recorded as mucoadhesion strength in grams and results are given in Table-7.4. The mucoadhesivity of buccal tablets was found to be maximum in case of formulation F9 i.e. 30mg of HPMC K200M.

In vitro dissolution of Ivabradine buccal tablets F1 to F9

Table 4: *In vitro* dissolution data of formulations F1 to F9

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
0.5	29.86±0.52	26.18±0.41	20.78±0.52	27.56±0.26	23.18±0.61	10.36±0.02	19.26±0.51	15.05±0.26	8.96±0.18
1	35.16±0.63	30.15±0.96	26.48±0.63	32.18±0.25	28.62±0.85	19.26±0.23	25.18±0.32	20.56±0.35	15.02±0.15
2	57.16±0.21	50.16±0.86	39.26±0.14	52.63±0.36	31.05±0.42	27.26±0.25	46.96±0.56	32.18±0.18	30.56±0.25
3	79.18±0.45	68.28±0.56	59.28±0.5	76.18±0.14	59.18±0.15	36.18±0.14	62.59±0.48	39.15±0.52	46.28±0.56
4	98.15±0.25	82.62±0.53	73.48±0.26	89.26±0.52	71.28±0.32	48.62±0.58	79.18±0.52	47.26±0.14	59.86±0.14
5		97.16±0.26	86.18±0.85	98.05±0.56	85.15±0.39	69.48±0.56	86.17±0.01	69.48±0.56	72.61±0.85
6			98.42±0.45		98.17±0.26	82.62±0.32	97.08±0.26	85.18±0.99	80.56±0.15
7						99.18±0.14		97.12±0.51	89.17±0.35
8									98.36±0.26

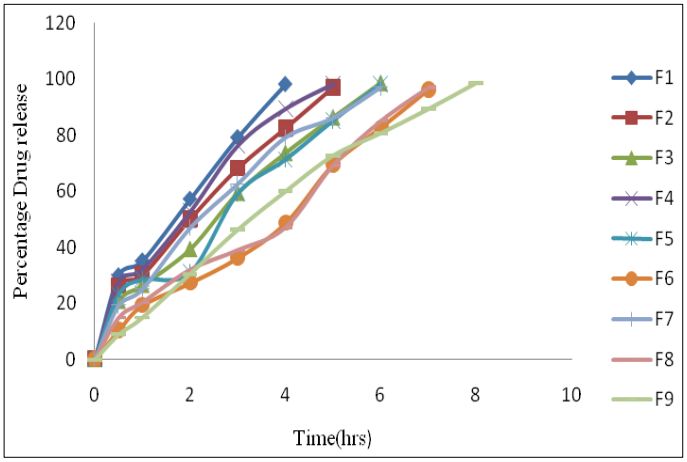

Fig 4: *in vitro* drug release profiles of F1-F9

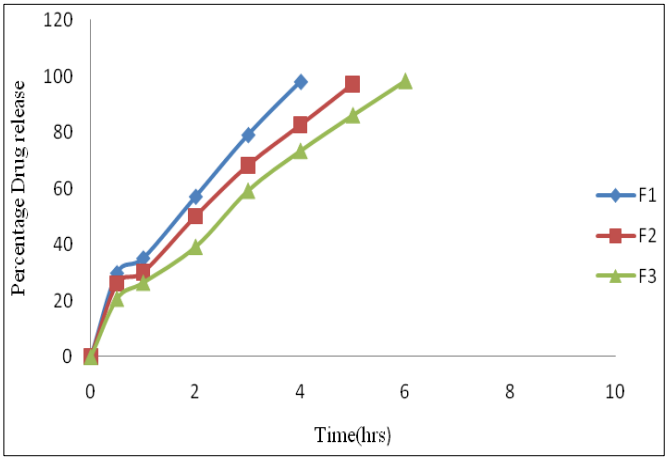

Fig 5: *in vitro* drug release profiles of F1-F3

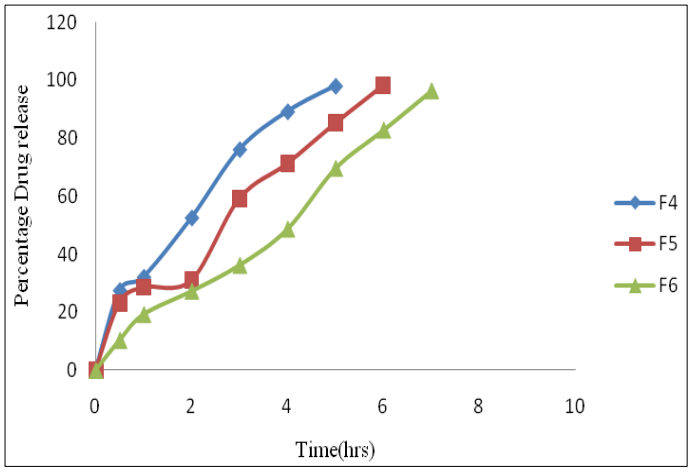

Fig 6: *in vitro* drug release profiles of F4-F6

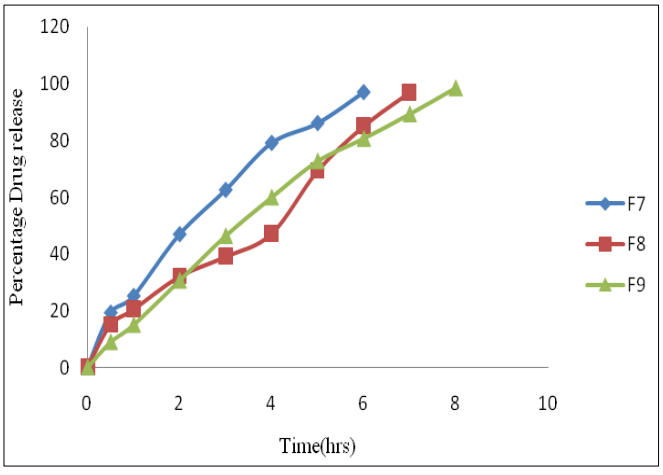

Fig 7: *in vitro* drug release profiles of F7-F9

Discussion

All the 9 formulations of Ivabradine buccal tablets were subjected to dissolution studies.

Formulations F1, F2, F3 containing the sodium CMC with drug: polymer ratio i.e., 1:1, 1:2, 1:3 F1 formulation containing 1:1 ratio shows 98% drug release at the end of 4hrs. Where as F2 formulation containing 1:2 ratio shows 97% drug release at the end of 5hrs. While the F3 formulation containing 1:3 ratio shows 98% drug release at the end of 6hrs. As the concentration of polymer increasing release rate is slow down. So further trails were performed using Karaya gum with different rations.

Formulations F4, F5, F6 containing the Karaya gum with drug: polymer ratio ie., 1:1, 1:2, 1:3 F4 formulation containing 1:1 ratio shows 98% drug release at the end of 5hrs. Where as F5 formulation containing 1:2 ratio shows 98% drug release at the end of 6hrs. While the F6 formulation containing 1:3 ratio shows 99% drug release at the end of 7hrs. As the concentration of polymer increasing release rate is slow down. So further trails were performed using HPMC K200M with different ratios.

Formulations F7, F8, F9 containing the HPMC K200M with drug: polymer ratio ie., 1:1, 1:2, 1:3 F7 formulation containing 1:1 ratio shows 97% drug release at the end of 6hrs. Where as F8 formulation containing 1:2 ratio shows 97% drug release at the end of 7hrs. While the F9 formulation containing 1:3 ratio shows 98% drug release at the end of 8hrs. As the concentration of polymer increasing release rate is slow down.

Among all the 9 formulations F9 formulation is optimized, as it shows maximum drug release at the end of 8hrs which suits the buccal drug delivery system criteria as per our studies.

Further drug release kinetics were performed to F9 formulation.

Drug release kinetics

Zero Order

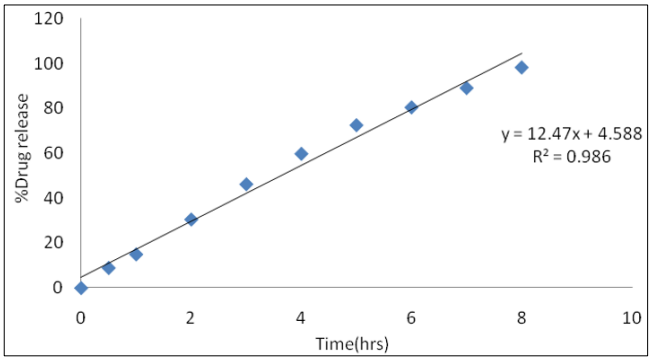

Fig 8: Zero order graph of F9 formulation

First Order

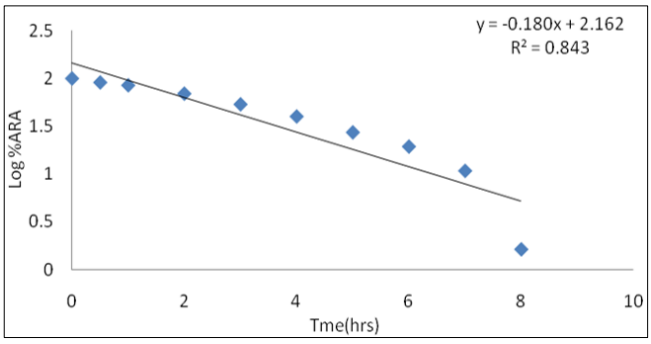

Fig 9: First order graph of F9 formulation

Higuchi Plot

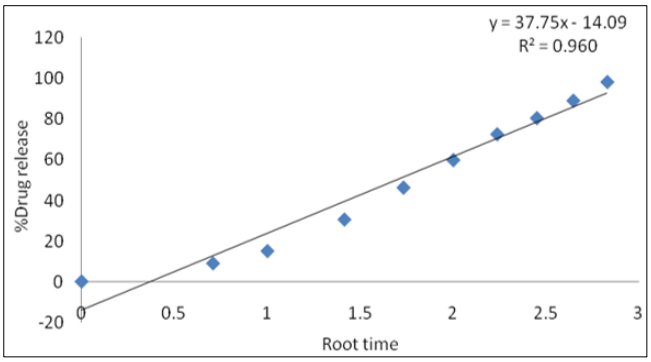

Fig 10: Higuchi plot of F9 formulation

Peppas Plot

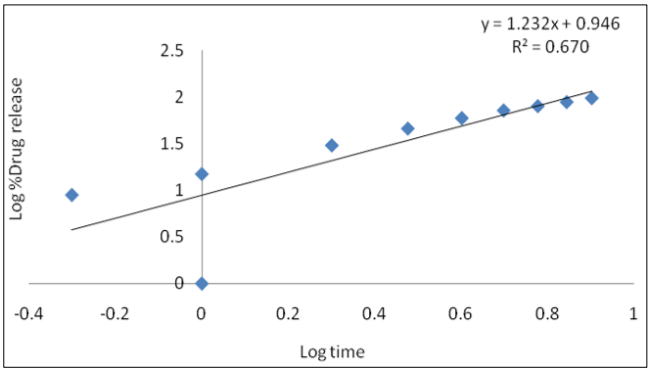

Fig 11: Peppas plot of F9 formulation

The *in vitro* dissolution data for best formulation F9 were fitted in different kinetic models i.e, zero order, first order, Higuchi and Korsemeyer-Peppas equation. Optimized formulation F9 shows R^2 value 0.986. As its value nearer to the '1' it is confirmed as it follows the zero order release. The mechanism of drug release is further confirmed by the korsmeyer and peppas plot, if n = 0.45 it is called Case I or Fickian diffusion, 0.45 < n < 0.89 is for anomalous behavior or non-Fickian transport, n = 0.89 for case II transport and n > 0.89 for Super case II transport.

The mechanism of release is anomalous, that is both diffusion and erosion are involved and the data was shown in the table 5.

Table 5: Drug release kinetics

	R^2 values				n values
Formulation	**Zero order**	**First order**	**Higuchi**	**Korsmeyer – Peppas**	**Korsmeyer-Peppas (n)**
F9	0.986	0.834	0.960	0.670	0.982

Conclusions

From the present study, the following conclusions can be drawn:

- Mucoadhesive buccal tablets of Ivabradine HCL can be prepared by direct compression method using Sodium CMC, HPMC K100M and Karaya gum as mucoadhesive polymers.
- All the prepared tablet formulations were found to be good without capping and chipping.
- 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.
- As the amount of polymer in the tablets increases, the drug release rate decreases, whereas swelling index and mucoadhesion strength increase.
- Among all the 9 formulations F9 formulation is optimized, as it shows maximum drug release at the end of 8hrs which suits the buccal drug delivery system criteria as per our studies. These formulations have displayed good bioadhesion strength (4.66 gm).
- Optimized formulation (F9) displayed that it follows zero order release kinetics and drug release follows non-Fickian diffusion mechanism.

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