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Research Article

FORMULATION AND EVALUATION OF IVABRADINE BUCCAL PATCHES

Boya Shivaranjani[1], B.Sandhya Rani[2], MD Iftekhar Ahamed Khan[3], Dr. MD Sultan Ali Basha[4]

[1]Research scholar, Dept. of Pharmaceutics, Safa College of Pharmacy, Kurnool.
[2]Associate Professor, Dept. of Pharmaceutics, Safa College of Pharmacy, Kurnool.
[3]Associate Professor, Dept. of Pharmaceutics, Safa College of Pharmacy, Kurnool.
[4]Professor and Principal, Dept. of Pharmacology, Safa College of Pharmacy, Kurnool.

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ABSTRACT:
Ivabradine is a HCN channel blocker used to reduce the risk of hospitalization for worsening heart failure in adult patients. The present investigation is concerned with the development of the Ivabradine buccal films, which were designed to prolong the buccal residence time, to increase penetration through buccal mucosa and thus increase the bioavailability and its half life. Various formulations were developed by using release rate controlling film forming polymers like, Sodium carboxymethyl cellulose, Eudragit and Chitosan in various combinations using plasticizer Propylene Glycol. The prepared films were evaluated for number of parameters like physical appearance and surface texture, weight uniformity, thickness of the films, folding endurance, swelling index, tensile strength, drug excipients interaction study, content uniformity, in-vitro drug release study. The FTIR studies indicate that Ivabradine showed complete entrapment within the polymer carrier bonding is suggested and there were no chemical interaction. From all the formulations, F12 shows maximum drug release at the ends of 8 hrs and chosen as optimized formulation and which follows zero order release with super case II transport mechanism.
Keywords: Ivabradine, Chitosan, Propylene Glycol, FTIR, super case II transport.

INTRODUCT ION

The oral route is the most preferred route for the administration of therapeutic agents because of its low cost, ease of administration and high level of patient compliance. However, many therapeutic drugs have been reported which undergoes extensive presystemic elimination by gastrointestinal degradation and or hepatic metabolism results in less systemic bioavailability, short duration of therapeutic action, and formation of inactive or highly toxic metabolites. The choice of another route of drug administration via parenteral, transdermal, mucosal route may avoid presystemic elimination or hepatic first-pass metabolism and the plasma level of drug can be maintained effectively or efficiently in the systemic circulation [1,2,3,4] . Transdermal route is unsuitable for maintaining drug plasma level in systemic circulation because of skin the main barrier. In the parentral administration drug directly enter into the systemic circulation and efficiently maintain plasma level of drug. However, parentral route is not prefer because of the pain during the parentral administration, can't reverse a toxic dose, may be expensive and specialized trained person is required for administration [5,6,7,8] . Therefore the Oral mucosal drug delivery system is widely applicable as novel site for administration of drug for immediate and controlled release action in various body cavities, like the nasal, buccal, ocular, rectal and vaginal mucosae has the benefit of bypassing the hepatic first-pass elimination associated with oral administration. Because of the dual biophysical and biochemical nature of these mucosal membranes drugs with hydrophilic and lipophillic nature can be rapidly absorbed [9,10]. Piroxicam (PX) is one of the most effective non-steroidal, anti-inflammatory drug of the oxicam derivative which also having antipyretic activity in numerous types of pains such as used in the treatment of rheumatoid arthritis and osteoarthritis. Even though the drug is well absorbed through oral route, gastric irritation is still the most serious adverse effect. Thus there is a need for another drug delivery system with improved GI tolerability. Buccal administration of drugs provides a useful route of administration for both systemic and local actions and bypasses first-pass effects and avoids GI side effects [11,12] .

MATERIALS & METHODS USED:

Ivabradine API was procured from Everlyn Healthcare, and Eudragit, Chitosan, Sodium (NaCMC), Aspartame were procured from Loba Chemical Pvt. Ltd., Mumbai., Propylene Glycol was procured from SD Fine Chem., Mumbai., and Methanol was procured from Narmada chemicals, Hyderabad.

Address for Correspondence: Boya Shivaranjani. Research scholar, Dept. of Pharmaceutics, Safa College of Pharmacy, Kurnool., **Email:** shivaranjaniboya1@gmail.com.

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Solubility:

Solubility of Ivabradine was determined in Methanol, Ethanol, 0.1N HCl, pH 7.4 and pH 6.8 phosphate buffers. Solubility studies were performed by taking excess amount of Ivabradine in different beakers containing the solvents. The mixtures were shaken for 48hrs in rotary shaker. The solutions were centrifuged for 10mins at 1000 rpm and supernatant were analyzed at 286 nm.

Drug-excipients interaction study of films:

There is always a possibility of drug-excipients interaction in any formulation due to their intimate contact. The technique employed in this study to know drug-excipients interactions is IR spectroscopy; IR spectroscopy is one of the most powerful analytical techniques which offer the possibility of chemical identification. Infra-red spectra of pure drug Ivabradine and formulations were scanned by using Jasco FTIR 410, by a thin film method.

Analytical methods for the estimation of Ivabradine:

Preparation of Reagents

A. Potassium Dihyrogen Phosphate (0.2M)

27.218 gm of potassium dihyrogen phosphate is dissolved in distilled water and makeup to 1000 ml with the same.

B. Sodium Hydroxide Solution (0.2M)

8 gm of sodium hydroxide was dissolved in 1000 ml of distilled water.

C. Phosphate buffer pH 6.8 buffer

50 ml of 0.2M of potassium dihydrogen phosphate solution and 22.4ml of 0.2M sodium hydroxide solution were mixed and made up to 200 ml with distilled water.

Determination of λ max for Ivabradine

10mg of Ivabradine was dissolved in 3ml of methanol and made upto 10ml with 6.8 pH buffers so as to get a stock solution of 1000 µg/ml concentration. From this 1ml solution was withdrawn and diluted to 10ml with same to get a concentration of 100µg/ml (SS-II). From this stock solution pipette out 0.5 ml of the solution and makeup the volume to 10ml using same buffer to get the concentration of 5µg/ml concentration, this solution was scanned under UV Spectroscopy using 200-400nm.

Preparation of standard calibration curve of Ivabradine

The standard calibration curve for Ivabradine was prepared using pH 6.8 phosphate buffer.

Standard solution

10 mg of Ivabradine was dissolved in 3ml of methanol and made upto 10 ml with pH 6.8 phosphate buffer to give a concentration of 1000 µg/ml.

Stock solution

From standard solution take 1ml of solution in 10 ml volumetric flask. The volume was made up to mark with pH 6.8 phosphate buffer to produce concentration 100 µg/ml of Ivabradine respectively. From the working standard solution take 0.1, 0.2, 0.3, 0.4, 0.5, 0.6ml of the solution and make upto the mark with 6.8 pH buffer to get the concentrations of 1, 2, 3, 4, 5, and 6 µg/ml.

The absorbance data for standard calibration curve and plotted graphically. The standard calibration curve yields a straight line, which shows that drug obeys Beer's law in the concentration range of 1-6 µg/ml.

Ivabradine Buccal Patchesby Solvent Casting Method:

Initially, polymer was dissolved in methanol under constant stirring till clear solution was obtained. Then to this solution, 4 drops of propylene glycol was added. To this solution Ivabradine was added by stirring. The resultant solution was then poured on the petri dish of area 36 sq.cm and allowed to dry undisturbed at room temperature. The dried film was cut into discs of 2x2 cm (4sq.cm of area) diameter. The compositions of films are reported in table.

Table.1 Formulation Details of Drug Incorporated Buccal Films

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Ivabradine (mg)	45	45	45	45	45	45	45	45	45	45	45	45
Sodium carboxymethyl cellulose(mg)	45	60	75	90	-	-	-	-	-	-	-	-
Eudragit(mg)	-	-	-	-	45	60	75	90	-	-	-	-
Chitosan(mg)	-	-	-	-	-	-	-	-	45	60	75	90
Aspartame(mg)	10	10	10	10	10	10	10	10	10	10	10	10
Propylene Glycol (ml)	4	4	4	4	4	4	4	4	4	4	4	4
Methanol (ml)	5	5	5	5	5	5	5	5	5	5	5	5

Note: 4 sq.cm buccal films containing 5 mg of Ivabradine.

Calculation of dose for Ivabradine:

The dose of Ivabradine is 45 mg. Therefore, amount of Ivabradine required in 4 cm2 film is 5 mg.

- Length of glass plate =6 cm.
- Width of glass plate =6 cm.
- Area of the plate =36 cm2.
- No. of 4 cm2 films present whole plate =36/4 =9 films.
- Therefore, Each films contains 10 mg of drug
- 9 films contain 45 mg drug (9*5).
- So, the Labelled claim of drug = 5 mg

Evaluation of films

Evaluation of Ivabradine buccal films

The Ivabradine buccal films were evaluated for the following properties:

Physical appearance and surface texture of film:

This parameter was checked simply with visual inspection of films and evaluation of texture by feel or touch.

Weight uniformity of films:

Three films of the size 4sq.cm were weighed individually using digital balance and the average weights were calculated.

Thickness of films:

Thickness of the films was measured using screw gauge with a least count of 0.01 mm at different spots of the films. The thickness was measured at three different spots of the films and average was taken.

Folding endurance of films:

The flexibility of films can be measured quantitatively in terms of what is known as folding endurance. Folding endurance of the films was determined by repeatedly folding films at the same place till it broke. The number of times films could be folded at the same place, without breaking gives the value of folding endurance.

Swelling index of films:

The swelling index of the films was determined by immersing preweighed film of size in 50 ml water. The films were taken out carefully at 0.5, 1, 2 upto 3hrs. intervals, blotted with filter paper and weighed accurately.

The swelling index calculated by,

Surface pH of films:

Surface pH was determined by the films were allowed in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min.

Tensile strength of films:

Tensile strength of the film was determined with digital tensile strength tester (Tinius-Olsen). The sensitivity range of the machine is 1-10 Newton's. It consists of two load cell grips. The lower one was fixed and upper one was movable. The test film of size (1x4 cm2) was fixed between these cell grips and force was applied till it breaks. The tensile strength of the film was directly taken from the dial reading in Newton's, which was converted into kilogram.

Drug content uniformity study of films:

The films were tested for drug content uniformity by UV-Spectrophotometric method. Films of 4sq.cm were cut from three different places from the casted films. Each film was placed in 100 ml volumetric flask and dissolved in pH 6.8 phosphate buffer and 1 ml is taken and diluted with pH 6.8 phosphate buffer upto 10 ml. The absorbance of the solution was measured at 286 nm using UV/visible spectrophotometer (Shimadzu UV-1700). The percentage drug content was determined using the standard graph and the same procedure was repeated for three films.

Determination of Moisture Content and Moisture Absorption

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss (%) using the formula:

Moisture Content (%) = Initial weight – Final weight/Initial weight*100

The buccal patches were weighed accurately and placed in the desiccators containing 100 ml of saturated solution of aluminum chloride, which maintains 76% and 86% relative humidity (RH). After 3 days, the films were taken out and weighed. The percentage moisture absorption was calculated using the formula:

Moisture Absorption (%) = Final weight – Initial weight/Initial weight*100

In-vitro drug release of films:

In-vitro release studies were carried out by attaching dialysis membrane, prepared buccal films containing drug was placed inside donor compartment which is agitated continuously using magnetic stirrer at 50 rpm and then temperature was maintained at 37 ± 0.5ºC. Receptor compartment consist of 40 ml of pH 6.8 phosphate buffer, sample of 1 ml were withdrawn at periodic intervals from receptor compartment and replaced with fresh pH 6.8

phosphate buffer immediately, and drug release was analyzed spectrophotometrically at 286 nm. Release rate was studied for all prepared formulations.

Drug Release Kinetics:

In order to predict and correlate the release behavior of Ivabradine from different patches, it is necessary to fit into a suitable mathematical model. The in vitro Ivabradine release data from buccal patches were evaluated kinetically using various mathematical models like zero-order, first-order, Higuchi, and Koresmeyer–Peppas model equations.

Zero-Order Kinetics

$$F = Kot$$

where F represents the fraction of drug released in time t, and Ko is the zero-order release constant.

First-Order Kinetics

$$\ln (1 - F) = -K1t$$

where F represents the fraction of drug released in time t, and K1 is the first-order release constant.

Higuchi Model

$$F = KHt1/2$$

where F represents the fraction of drug released in time t, and KH is the Higuchi dissolution constant.

Koresmeyer–Peppas Model

$$F = Kptn$$

where F represents the fraction of drug released in time t, Kp is the Koresmeyer–Peppas release rate constant, and n is the diffusion exponent.

RESULTS AND DISCUSSION

Solubility studies:

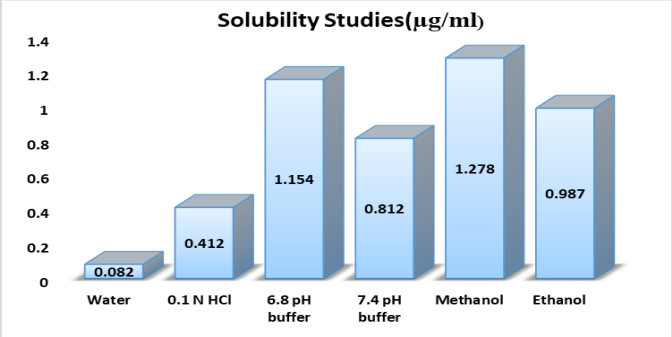

Figure.1 Solubility studies of Ivabradine

Discussion: From the solubility studies it was observed that Ivabradine was found to be more soluble in water and 6.8 pH Buffer among buffers and among Organic solvents it was found to be more soluble in methanol.

UV Spectrum of Ivabradine:

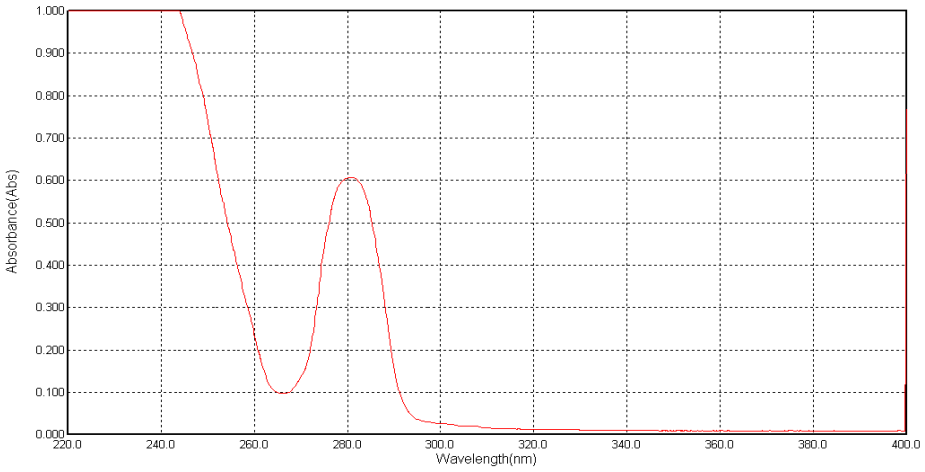

Figure.2 UV- spectrum of Ivabradine

Discussion: A solution of Ivabradine containing the conc. 10 µg/ ml was prepared in 6.8 pH Buffer and UV spectrum was taken using PG Instruments T60 double beam spectrophotometer. The solution was scanned in the range of 200 – 400 nm. The maximum absorbance was found to be at 286 nm.

Calibration Curve of Ivabradine in 6.8 pH Buffer

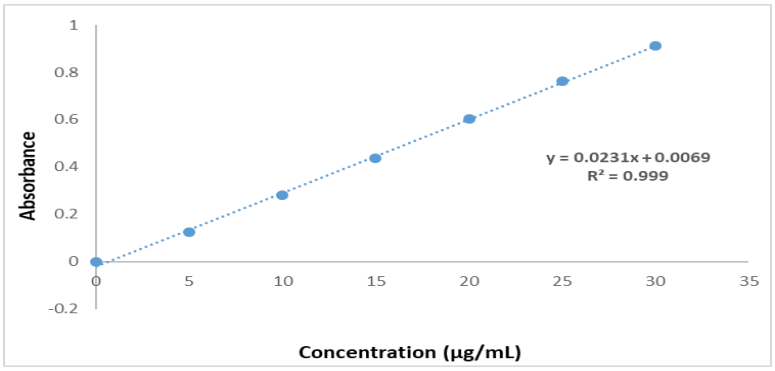

Figure.3 Standard calibration curve of Ivabradine in 6.8 pH Buffer

Discussion:

The linearity was found to be in the range of 5-30 µg/ml in 0.1N HCl buffer. Regression analysis was selected because it minimizes the deviation and correct the variance heterogeneity. The regression line was defined by its slope (m) and its intercept (C) for normal regression analysis was found as 0.0231 and 0.0069, with regression coefficient of 0.9999 respectively. The regression value was closer to 1 indicating the method obeyed Beer-lamberts' law.

Drug-excipients interaction studies of films:

Pure Drug:

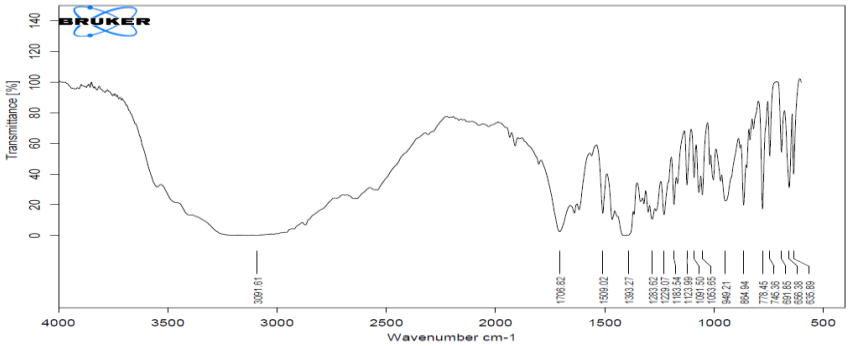

Figure.4 FTIR Spectra of Ivabradine (pure drug)

Optimized Formulation

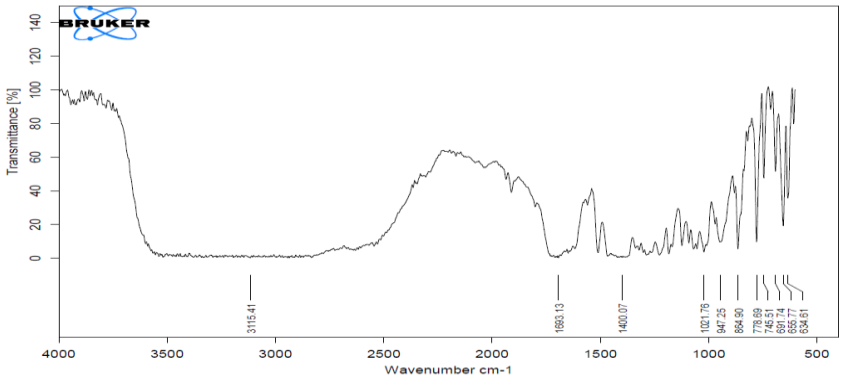

Figure.5 FTIR Spectra of optimized formulation

Discussion:

From the compatibility studies it was concluded that the functional groups that were present in the pure drug were also found in the optimized formulation with very minute changes, from this we can conclude that the drug and excipients have no interactions

Physical appearance and surface texture of films:
These parameters were checked simply with visual inspection of films and by feel or touch. The observation reveals that the films are having smooth surface and they are elegant in appearance.

Weight uniformity of films:
The weight of the films was determined using digital balance and the average weight of all films was given in table.

Folding endurance of films:
The folding endurance gives the idea of flexible nature of films. The folding endurance was measured manually, films were folded repeatedly till it broke, and it was considered as the end point. The folding endurance was found optimum and the films exhibited good physical and mechanical properties and the average folding **endurance of all films**

Surface pH of films:
Surface pH was determined by bring the films in contact with 1ml of distilled water. The surface pH was noted by bringing a combined glass electrode or pH paper near the surface of films and allowing equilibrate for 1 min and the average surface pH of all films.

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa and influence the degree of hydration of polymer, the surface pH of the buccal films was determined to optimize both drug permeation and mucoadhesion. Attempts were made to keep the surface pH as close to buccal /salivary pH as possible, by the proper selection of the polymer for developing the buccal films. The surface pH of all the films was within the range of salivary pH. No significant difference was found in surface pH of prepared films.

Table.2 Evaluations of Buccal Films

Formulation code	Thickness (mm)	Folding endurance	Surface pH	Average Weight variation of film (mg)
F1	0.12±0.01	161±1	6.8±0.1	11.21±1.24
F2	0.15±0.02	178±2	6.7±0.1	13.25±1.36
F3	0.18±0.01	181±1	6.8±0.2	15.06±1.47
F4	0.19±0.02	189±2	6.7±0.1	17.12±1.25
F5	0.16±0.01	178±2	6.8±0.1	11.45±1.02
F6	0.17±0.01	185±1	6.7±0.2	13.81±1.69
F7	0.15±0.02	178±2	6.6±0.1	15.37±1.34
F8	0.17±0.02	185±2	6.8±0.2	17.46±1.74
F9	0.16±0.01	168±1	6.7±0.1	11.75±1.26
F10	0.17±0.01	172±2	6.8±0.1	13.12±1.45
F11	0.15±0.02	185±2	6.7±0.2	15.09±1.84
F12	0.13±0.01	191±1	6.8±0.1	17.45±1.27

Swelling index of films:
The swelling index of the films was determined by immersing preweighed film of size 10 mm in 50 ml water. The films were taken out from petridish carefully at 0.5, 1, 2, upto 3hrs intervals, blotted with filter paper and weighed accurately and the average swelling index of all films was given in Table.6.5 From all these films F12 formulation buccal film films shows high percent swelling index.

Tensile strength of films:
The tensile strength of all the films were evaluated by using standard tensile strength tester and the average tensile strength of all films was given in Table . In all the cases the calculated standard deviation values are very low which suggest that, the prepared films shows uniform tensile strength.

Drug content uniformity of films:
Ivabradine buccal films prepared with various polymers were subjected to the evaluation for uniform dispersion of drug throughout the film. In each case three films were used and the average drug content was calculated, the results were shown in Table-6.5. The drug was dispersed in the range of 93.98±1.24 to 99.45±1.45%. Suggesting that drug was uniformly dispersed throughout all prepared films.

Table.3 Evaluation of Ivabradine Buccal Patches

FC	Avg. Swelling index (%)	Moisture content (%)	Moisture absorption (%)	Tensile strength	Drug content (%)
F1	12.76±1.24	1.76±0.02	4.09±0.02	3.83±1.02	93.98±1.24
F2	19.86±1.67	1.07±0.01	3.87±0.03	4.26±1.04	95.16±1.20
F3	25.02±1.32	1.32±0.03	4.56±0.02	4.79±1.03	97.09±1.69
F4	25.85±1.10	1.08±0.02	3.46±0.01	5.02±1.02	98.78±1.45
F5	19.67±1.27	0.98±0.01	4.23±0.02	3.76±1.15	92.45±1.53
F6	29.72±1.35	1.05±0.02	3.09±0.04	4.98±1.27	93.75±1.42
F7	25.98±1.69	0.89±0.04	3.42±0.02	5.13±1.03	95.65±1.75
F8	29.76±1.45	1.02±0.03	3.96±0.01	5.24±1.26	96.53±1.36
F9	34.12±1.06	1.05±0.02	3.45±0.02	4.31±1.10	95.34±1.06
F10	26.48±1.42	0.97±0.01	3.11±0.02	5.39±1.02	97.18±1.48
F11	22.14±1.37	1.32±0.02	3.18±0.01	3.28±1.39	98.36±1.24
F12	30.24±1.69	1.14±0.03	3.05±0.01	3.14±1.12	99.45±1.45

In-vitro drug release of films:

The detailed in vitro drug release data were plotted between percent drug released from the formulation and time. The present study indicates a good potential of erodible mucoadhesive buccal films containing Ivabradine for systemic delivery with an added advantage of circumventing the hepatic first pass metabolism. The result of the present study shows that therapeutic levels of Ivabradine can be delivered buccally. It may be concluded that the formulations F12 shows promising controlled drug release.

Table.4 Drug release data of Ivabradine buccal films

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
0.5	48.21 ±1.27	31.24 ±1.78	20.24 ±1.02	30.21 ±1.45	42.27 ±1.26	48.98 ±1.25	36.65 ±1.24	19.24 ±1.27	42.67 ±1.24	39.58 ±1.24	45.76 ±1.27	25.58 ±1.27
1	60.96 ±1.69	45.15 ±1.36	34.68 ±1.45	38.34 ±1.23	55.18 ±1.45	57.98 ±1.45	47.58 ±1.02	27.87 ±1.42	65.09 ±1.45	45.85 ±1.74	58.98 ±1.47	38.64 ±1.46
2	68.47 ±1.02	59.86 ±1.45	49.67 ±1.26	46.78 ±1.27	68.69 ±1.02	65.69 ±1.37	58.98 ±1.36	36.98 ±1.02	79.65 ±1.20	56.56 ±1.34	67.86 ±1.36	46.12 ±1.20
3	76.38 ±1.45	67.14 ±1.02	52.74 ±1.42	55.28 ±1.45	74.39 ±1.45	72.35 ±1.45	62.38 ±1.45	48.72 ±1.69	85.16 ±1.37	62.85 ±1.20	71.64 ±1.75	59.74 ±1.74
4	82.64 ±1.36	80.45 ±1.45	67.63 ±1.36	67.41 ±1.02	86.65 ±1.02	81.76 ±1.02	75.54 ±1.20	56.24 ±1.54	96.64 ±1.52	74.34 ±1.24	78.98 ±1.20	63.46 ±1.20
5	98.45 ±1.10	88.24 ±1.67	79.24 ±1.74	74.36 ±1.52	98.22 ±1.63	88.96 ±1.54	84.69 ±1.45	78.57 ±1.25	98.45 ±1.69	86.65 ±1.95	85.09 ±1.24	82.99 ±1.20
6		98.62 ±1.34	83.38 ±1.02	85.36 ±1.34		97.82 ±1.74	98.96 ±1.02	86.56 ±1.75		95.09 ±1.43	91.56 ±1.34	89.79 ±1.34
7			98.26 ±1.26	91.24 ±1.05				98.52 ±1.02			97.76 ±1.26	93.68 ±1.74
8				96.85 ±1.87								99.78 ±1.25

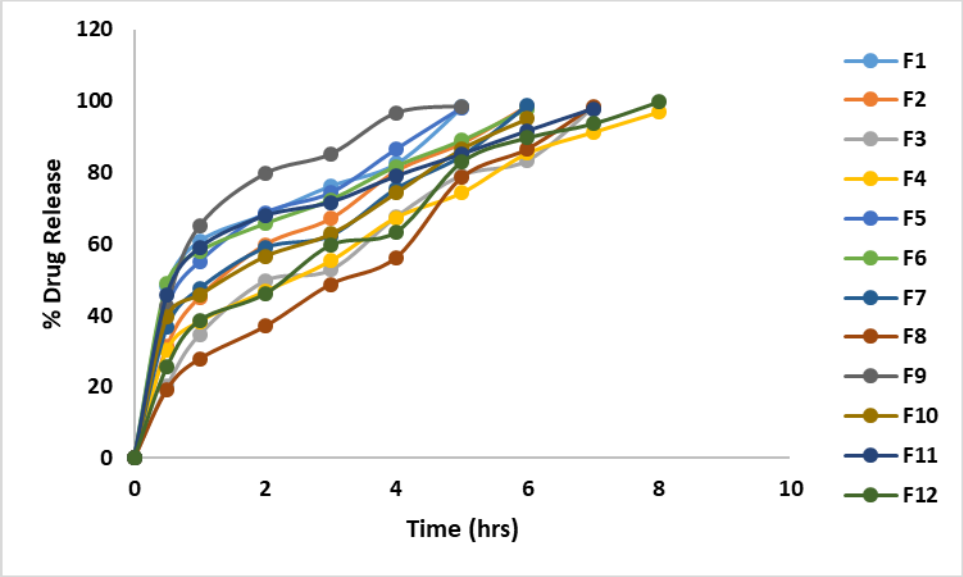

Figure.6 In vitro Drug Release of Formulations (F1-F12)

Kinetic Data of Ivabradine Mucoadhesive Buccal Films:

Zero Order:

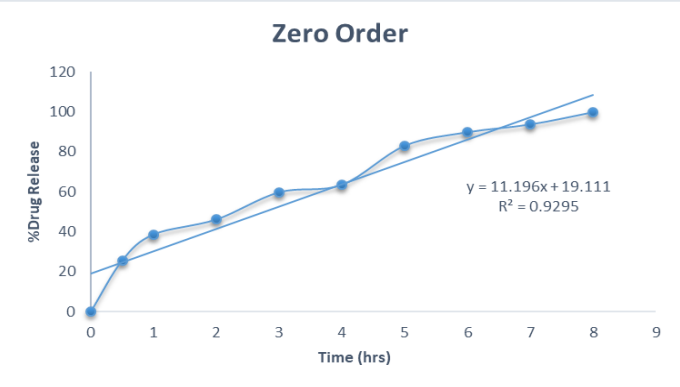

Figure.7 Zero order of F12 formulation

First Order:

Figure.8 First order of F12 formulation

Higuchi Plot:

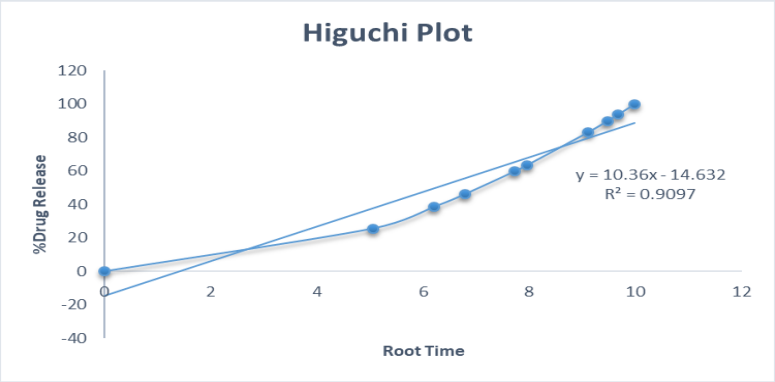

Figure.9 Higuchi plot of F12 formulation

Peppas Plot:

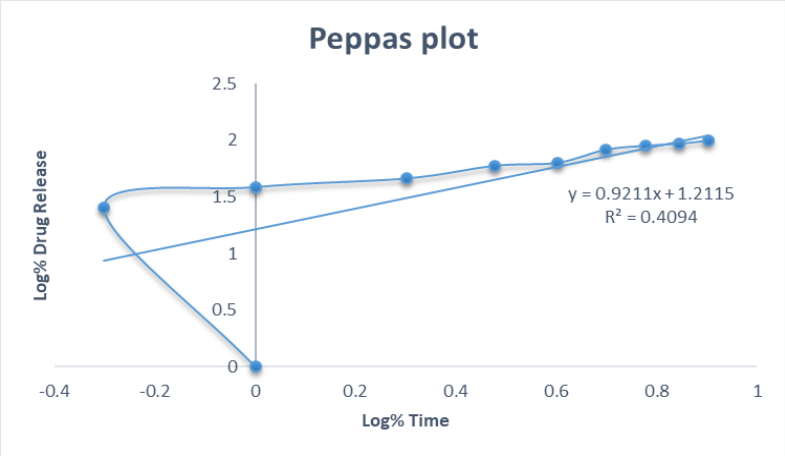

Figure.10 Peppas plot of F12 formulation

Discussion:

The invitro dissolution data for best formulation F12 were fitted in different kinetic models i.e, zero order, first order, Higuchi and korsemeyer-peppas equation. Optimized formulation F12 shows R2 value 0.929. As its value nearer to the '1' it is conformed 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 'n' value is 0.921 for the optimised formulation (F12) i.e., n >0.89 which indicates Super case II transport.

SUMMARY AND CONCLUSION

Recently the buccal patch has been increasingly used for administration of drug mainly because of advantages like the drug is directly available to the systemic circulation, avoidance of first pass metabolism and easy removal of patch from the site etc.

Among the various drug delivery systems development buccal drug delivery system is one by which one can improve the bioavailability of the drug by avoiding hepatic metabolism.

So, in the present research work we have prepared Ivabradine buccal patches with an objective of improving its bioavailability. Ivabradine buccal patches were prepared by solvent casting technique using Sodium carboxymethyl cellulose, Eudragit and Chitosan. The detailed formulation compositions.

The prepared patches were evaluated for number of parameters like physical appearance and surface texture, weight uniformity, thickness of the patches, folding endurance, swelling index, tensile strength, drug excipients interaction study, content uniformity, in-vitro drug release study.

The results are quoted in different section from the result of various evaluation parameters, we can summarize:

The patches prepared were checked visually for its appearance and surface texture. All the prepared patches were of smooth surface and elegant texture.

- Weight variation of all the prepared patches using different concentration are in between 11.21±1.24mg to 17.45±1.27mg.
- The patches show thickness values in between 0.12±0.01 to 0.19±0.02 mm.
- The patches show folding endurance values are below 161±1 to 191±1. The patches show swelling index values in between 12.76±1.24% to 30.24±1.69%.
- Similarly surface pH of all the patches prepared is ranging in between 6.7±0.1 to 6.8±0.2 pH.

- The tensile strength of all the patches prepared is ranging in between 3.14±1.12 to 5.24±1.26 Kg/cm2 respectively.
- The FTIR studies indicate that Ivabradine showed complete entrapment within the polymer carrier bonding is suggested and there were no chemical interaction.
- Similarly, the patches are also subjected to drug content uniformity study and it lies in between 92.45±1.53% to 99.45±1.45%, which suggest that uniform dispersion throughout the buccal patches.
- Finally the in-vitro drug release study was carried out for all the patches and release profile were subjected to various kinetic equations like Higuchi diffusion equation and Peppas exponential equation. The regression coefficient values of this kinetic equation are very nearer to one (1) suggesting that plots are fairly linear and slope values of the Peppas equation is (>0.89) suggest that drug was released by Super case II transport mechanism.
- From the above results it can be concluded that Ivabradine F12 can be delivered in the form of buccal patches. Release pattern of drug from these patches can be altered by using different formulation variables.

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