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DEVELOPMENT AND CHARACTERIZATION OF MUCOADHESIVE BUCCAL FILM OF IVABRADINE HYDROCHLORIDE FOR ANGINA PECTORIS

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ABSTRACT

The objective of this study was to develop and evaluate mucoadhesive buccal film of Ivabradine hydrochloride using mucoadhesive polymer HPMC E5 LV for angina pectoris. During study polyvinylpyrrolidone considered as a thickening agent, film former. PEG 4000 and PEG 6000 use as a plasticizer as well as solubilizing agent. Tween 80 use as a permeation inhancer. A total number of six formulations were prepared by a solvent casting method. The prepared mucoadhesive film were evaluated for drug content, in-vitro dissolution, Ex Vivo Permeation folding endurance, mucoadhesive strength, swelling index, and drug-polymer interaction study. From the present study, it found that formulation F3 and F5 show in vitro drug release 94.08% ± 0.15, 98.51% ± .612 respectively within 3hr. Ex vivo drug permeation found to be 65.87% and 71.48% within 4 Hr. by using goat oral mucosa. There was no any physical and chemical interaction between drug and polymer based on physical and FTIR data interpretation.

KEYWORDS: Ivabradine hydrochloride; Mucoadhesive film; HPMC E5 LV; Ex Vivo Permeation.

INTRODUCTION

Buccal delivery is an choice for the drug which required immediate action. This is widely use for potent medicines for life threatening disease such as angina pectoris, heart attack, COPD etc. Muccoadhesive drug delivery avoids the destruction and biotransformation of drug by gas-trointestinal contents or hepatic first-pass effect by applied in the buccal area. Oral film formulation prepared by using hydrophilic polymer hold the all promises regarding the drug delivery of potent drug in life threatening disease.[17]

Ivabradine is a novel heart rate lowering medicine for management of stable angina pectoris and chronic heart failure. Buccal delivery refers to a topical route of administration by which drugs held or applied in the buccal area, diffuse through the oral mucosa and enter directly into the systemic circulation. Dosage form retained at the site of action by intimate contact.[1] Amongst various routes of drug delivery, oral route is perhaps the most preferred route to the patient and the clinician alike. However, oral route presents some problems for few drugs. The enzymes in the GI fluids, GIT-pH conditions, and the enzymes bound to GIT membranes are the few factors responsible for the bioavailability problems. The blood that drains the GIT carries the drug directly to the liver leading to first-pass metabolism resulting in poor bioavailability.[2,3] Over the decades mucoadhesion has become popular for its potential to optimize localized drug delivery by retaining a dosage form at the site of action (e.g. within the gastrointestinal tract) or systemic delivery by retaining the formulation in intimate contact with the absorption site.[4] The use of mucoadhesive polymers in buccal drug delivery has a greater application. Buccal route of drug delivery provides the direct access to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability.[5] Ivabradine hydrochloride 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 oral bioavailibility is 40 %.[6]

MATERIAL AND METHODS

Material

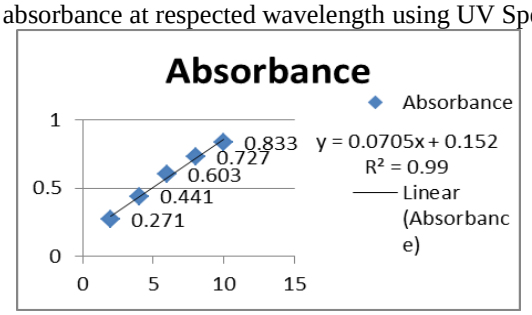
Ivabradine Hydrochloride was procured as gift sample from Intas Pharmaceutical Ltd. Ahmedabad, India. HPMC E52V, Polyvinylpyrrolidone (PVP), PEG 4000 & PEG 6000 were purchased from Loba Chemie, Mumbai. All chemical and solvent were used are of the high analytical grade.

Methods of Preparation

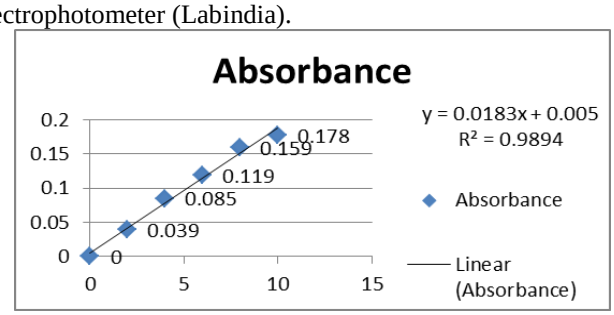
The film of respective composition, as shown in Table 1 prepared by the solvent casting method. The buccal mucoadhesive patch was prepared using HPMC E5 LV, PVP as polymers, two different grade PEG 400 and PEG 6000 in three level of concentration as a plasticizer and solublising agent. Tween 80 use as a permeation enhancer. The solvent system was used 50:50 ratios of methanol and water. The drug was dispersed uniformly in the solvent with continuous stirring on the magnetic stirrer. All polymers were added in the drug solution with continue stirring. In order to avoid entrapment of the air bubble inside the patch, the entire drug polymer-solvent system was subjected to sonication with ultrasonic bath sonicator. The solution was poured into moulds for casting and dried at (room temperature) for a period of 24 hrs. After drying the medicated patches of 2.5×2.5 cm^2 area were cut using a sterilized stainless steel blade which containing 5mg ivabradine hydrochloride.

For the calibration curve take 100mg drug in respected medium and prepare 2, 4, 6, 8, 10µg/ml separately in methanol and phosphate buffer pH 6.8.

Take absorbance at respected wavelength using UV Spectrophotometer (Labindia).



C.C. of Ivabradine HCL in Methanol.



C.C. of Ivabradine HCL in Phosphate buffer 6.8.

Table No.1.

Formulation code	Ivabradine hcl. (mg)	HPMC E5 LV (mg)	Polyvinyl pyrolidone (PVP) (mg)	PEG 4000. (mg)	PEG 6000. (mg)	Glycerol (ml)	Aspartame (mg)
F1	10	250	10	10	-	0.06	1
F2	10	250	10	15	-	0.06	1
F3	10	250	10	20	-	0.06	1
F4	10	250	10	-	10	0.06	1
F5	10	250	10	-	15	0.06	1
F6	10	250	10	-	20	0.06	1

RESULTS AND DISCUSSION

1. Compatability study

The present work investigated for drug excipient compatibility study by using physicochemical changes and IR study. It was show good compatibility between drug, polymer, and excipients as there was change in the principal peaks nor presence or absence of any peaks of the drug/ polymer. The formulations were evaluated for various parameters, and the results obtained were within the range.

Table No. 2.

Functional Groups	Wavenumber (cm-1)	Functional Groups	Wavenumber (cm-1)
Aliphatic C‑H Stretch:	3054.14	Alkene C=C Strech	1674.32
C=C Stretch:	1860.63	Aromatic C‑H stretch	1453.87
Aliphatic C-N Strech	3450.75		

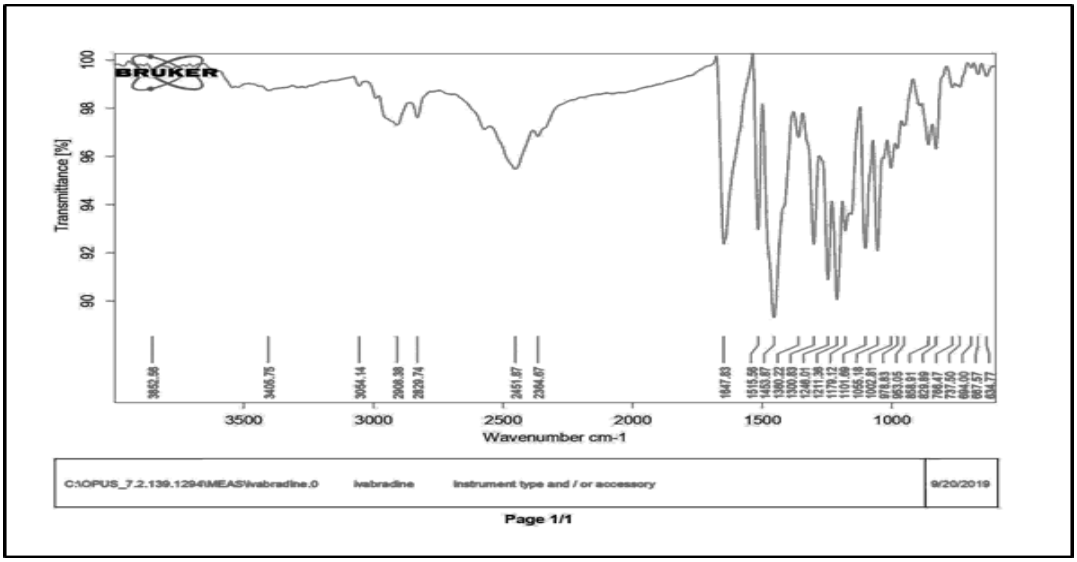


Fig. No.1: FTIR Spectra of F5 Formulation.

2. Physical appearance and surface texture

Characterized by visual inspection and film texture by feel or touch. All formulation from F1 to F6 having smooth texture and transparent appearance as shown in figure.

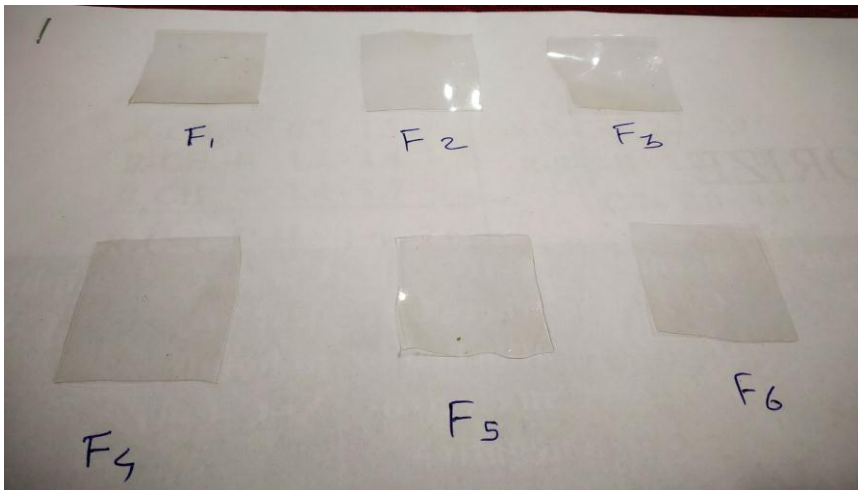


Fig No.2: Film Formulation F1 to F6.

3. Folding endurance

Folding endurance of the film was determined by repeatedly folding one film at the same place till it broke or folded up get break manually and repetition of folding was noted down. All formulation >200 time folding endurance as given in table no.3.

4. Thickness variation test

From each formulation, six films were chosen, and thickness was measured at five different places with the help of digital thickness gauze. The average film thickness were computed.[6,7]

All formulation having mean thickness between 0.228 mm to .355 mm shown in table no 3. The optimized formulation F3 and F5 having mean thickness 0.300 mm, 0.334 mm respectively as given in table no.3.

5. pH study

The pH of the patch was determined in order to dissolving the each formulation film in 5 ml distilled water at room temperature, and pH was noted down by bringing the electrode in contact with solution and allowing it to equilibrate to give stable reading on display.[8] The average surface pH of all film as given in table no.3.

6. Weight variation test

From each formulation, six films of similar specifications have been chosen and subjected to weight variation test as per the IP procedure using Citizen digital balance. The average weight of six buccal films was subtracted from individual film weight. The mean ± SD values were calculated for all the formulations as given in table no.3.

7. Content uniformity of film

To ensure uniform distribution of Ivabradine in film, a content uniformity test was performed. The film was added to 100 ml of methanol contained in a 250 ml beaker, which was placed on temperature controlled magnetic stirrer maintained at 37± 2 °C. The medium was stirred at 300 rpm with a Teflon coated magnetic bead for 3 hrs. Then, the solution was filtered through whatman filter paper, and the filtrate was examined for the drug content at 241 nm using UV Spectrophotometer.[6,7] As given in table no.3.

Table No.3.

Formulation code	Folding Endurance	Mean Thickness (Mean)	pH study	Weight (mg)	Content uniformity	% Moisture	
						Absorption	Loss
F1	>278	0.228	6.982	100±0.354	97.32±0.73	4.24	3.12
F2	>260	0.254	6.893	95±0.294	95.74±0.88	4.28	3.45
F3	>234	0.300	6.782	97±0.431	96.61±0.76	4.67	3.93
F4	>290	0.279	6.917	92±.304	96.13±0.89	4.87	3.95
F5	>275	0.334	6.821	94±0.253	98.03±0.89	4.95	3.93
F6	>264	0.355	6.948	98±0.386	96.15±1.49	5.13	4.16

8. Percentage moisture absorption and loss

Buccal films were pondered and placed in a desiccator containing 100 ml of saturated solution of aluminum chloride, and 75 ± 5% RH was maintained. After three days, the buccal films were taken out and reweighed. The percentage moisture absorption was calculated using the formula specified below. Buccal films were weighed and kept in a desiccator containing anhydrous calcium chloride. After three days, the patches were taken out and reweighed. The percentage moisture loss was calculated using the formula.[9]

$$\% \text{ Moisture absorption} = \frac{\text{Final weight - Initial weight} \times 100}{\text{Initial weight}}$$

$$\% \text{ Moisture loss} = \frac{\text{Initial weight - Final weight} \times 100}{\text{Initial weight}}$$

9. Drug Content

A 2.5 cm^2 of a film is to be dissolved in methanol specific volume of 10 ml. Then the solution is to be filtered through whatman filter medium and analyzed by using UV spectrophotometer (Lab India) against the corresponding blank solution at 241nm, each value represents an average of four different values.[16] Shown in the Table no.4.

10. Swelling Index

Were determined by putting the film in stainless still sieve (10 mm) into beaker containing phosphate buffer pH 6.8. After an hour the devices were removed from the media, blotted with tissue paper to remove excess water, and weighed. Swelling index of the each film calculated by using formula given below.

$$\text{Swelling index (\%)} = \frac{Ws - Wd}{Wd} * 100$$

Where Wd and Ws are the weights of dry and hydrated film. Shown in the Table no.4

Table No. 4.

Formulation Code	Drug Content. (mg)	Mucoadhesive Strength (gm)	% Swelling Index		
			10min.	30min.	60min.
F1	4.89	15	2.12	2.35	2.35
F2	4.60	19	2.36	2.41	2.56
F3	4.97	23.5	3.04	3.13	3.18
F4	4.86	13	2.26	2.86	2.90
F5	4.98	16.5	2.76	3.16	3.78
F6	4.82	21	3.56	3.84	4.19

11. *Ex vivo* Mucoadhesive strength

Bio adhesive strength of the patch was measured on a one arm physical balance. The device was mainly composed of aone‑arm balance. The arm of the balance was replaced by a small plastic cap vertically suspended through a wire and fix the goat oral mucosal membrane.[9,12] The goat buccal mucosa was cut into pieces and washed with phosphate buffer pH 6.8. A piece of buccal mucosa was tied to the open mouth of a diffusion cell, which was placed and tightly fitted in the center of glass beaker. The phosphate buffer (pH 6.8, 37 ± 2^0c) was filled in to the glass beaker in such a way that it makes contact with buccal mucosal surface. The patch was stuck to the lower side of flat surface plastic cap with cyanoacrylate adhesive. The balance was kept in this position for 5 min contact time, and then slowly the weights were increased on weight bar till the patch separated from the mucosal surface.[10,11] Note down the

weight of detachment of pin from buccal mucosa. Shown in the Table no.4.[13]

12. *In vitro* drug release studies

The patches containing Ivabradine were evaluated for in vitro release. As there was no official method prescribed for in vitro drug release study for film. Each six formulation buccal film of 2.5 × 2.5 cm^2 (containing 5 mg of drug) cut and placed directly over the diffusion apparatus (Dolphin-diffusion cell apparatus) containing phosphate buffer 6.8 without starring. Periodically samples were withdrawn, diluted with same solvent and assayed for drug content by spectrophotometrically at 286 nm.[11,12]

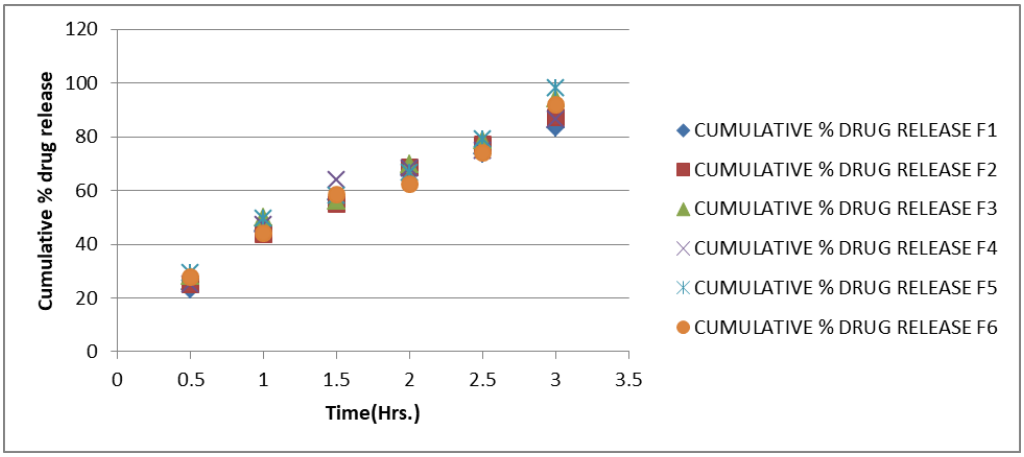
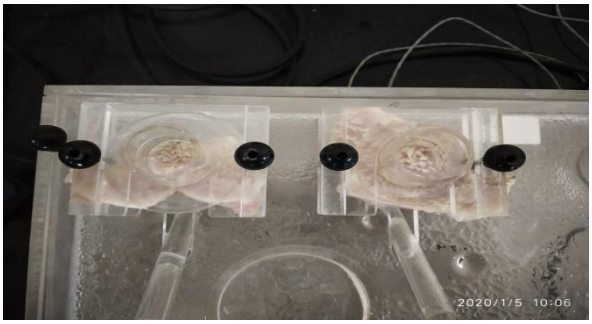


Fig No. 3: *In vitro* drug release of F1 to F6 Formulation Batches.

13. *Ex vivo* studies

The Dolphin-diffusion cell apparatus was used for permeation studies. The receptor compartment filled with 25ml phosphate buffer 6.8 and covered with water jacket to maintain temperature at 37°C. A Teflon coated magnetic bead was placed in the receptor compartment. The separated fresh goat buccal epithelium was mounted over the receptor compartment adjust the 100 rpm by knob of respected cell and buccal epithelium was allowed to stabilize. After stabilization; place the film over buccal epithelium. 2 ml were withdrawn at regular intervals, suitably diluted, and were analyzed spectrophotometrically at 286 nm.[13,14]



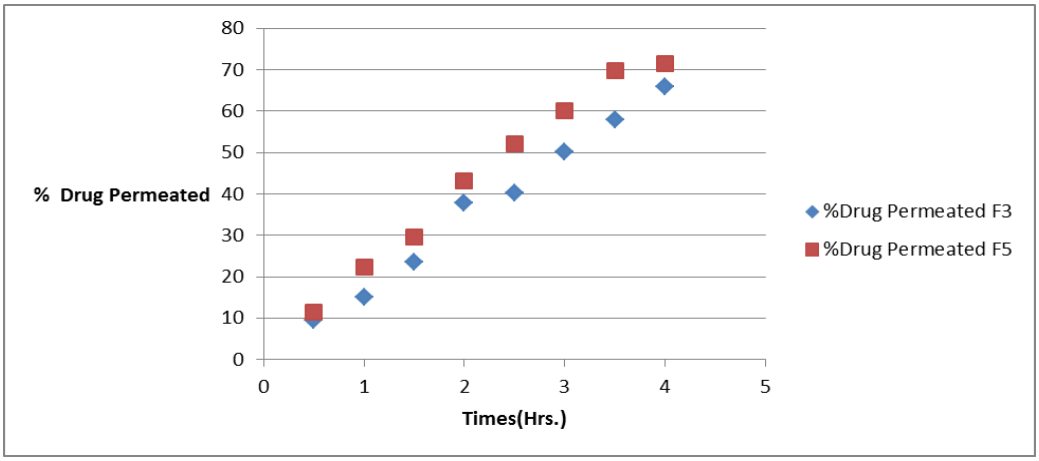


Fig. No. 5: *Ex- Vivo* Permeation of F3 & F5 Formulation.

CONCLUSION

In this research work, buccal patch of ivabradine hydrochloride were prepared by solvent casting method using HPMC E5 LV, Polyvinyl pyrolidone (PVP), PEG 4000, PEG 6000 at different concentration. Among this F3 and F5 was optimized formulation on the basis of in vitro drug release 94.08% ± 0.15, 98.51% ± .612 respectively within 3hr and Ex Vivo Permeation study found to be 65.87% and 71.48% within 4 Hr. followed zero‑order model of drug release. The present study indicated enormous potential of mucoadhesive buccal patches containing Ivabradine for systemic delivery. Having advantage of immediate bioavailability, immediate action and circumventing hepatic first pass metabolism. Future work is recommended to support long‑term pharmacokinetic and pharmacodynamics studies in human beings.

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