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Research Article

FORMULATION AND EVALUATION OF MUCOADHESIVE PATCHES OF IVABRADINE HYDROCHLORIDE

Harekrishna Roy *, P Sowmya, I Srija, K Nagaraju, K Srinivas
Department of Pharmaceutics, Nirmala College of pharmacy, Atmakur (Vill.), Mangalagiri, Guntur, Andhra Pradesh, India
*Corresponding Author Email: hareroy@gmail.com

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ABSTRACT

The objective of this study was to develop a mucoadhesive buccal patch of Ivabradine hydrochloride using mucoadhesive polymers such as carbopol, poloxamer, and HPMC 15LV. During this study polyvinylpyrrolidone, ethyl cellulose considered as a thickening agent or rate controlling polymer. A total number of five formulations were prepared by a solvent evaporation method. The prepared mucoadhesive patches were evaluated for in-vitro dissolution, drug content, folding endurance, mucoadhesive strength, swelling index, and drug-polymer interaction study. From the present study, it found that the mean thickness of the buccal polymeric patches increased with an increase in the amount of polymer percent. Percent swelling index determined at 2, 4, 6 and 8 hrs increased with time and with an increase in the polymer. The in-vitro study was performed by phosphate buffer PH 6.8 in Franz diffusion cell. During the study, it was also found that an increase in the amount of polymer retarded the release of the drug. Formulation F3 released 100% of the drug in 10 hrs of time. There was no such interaction found between drug and excipients.

Keywords: mucoadhesive, Ivabradine hydrochloride, carbopol, polyvinyl pyrrolidine.

INTRODUCTION

Historically, the oral route of drug administration has been the one used most for both conventional as well as novel drug delivery. Major limitations of the oral route of drug administration are some drugs irritate the gastrointestinal tract and this is partially counteracted by coating. The oral route may not be suitable for drugs targeted to specific organs. The conventional type of buccal dosage forms is buccal tablets, troches and lozenges, and mouthwashes. [1] 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. [2] Well defined bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. The biological surface can be epithelial tissue or it can be the mucus coat on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion. [3, 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 selectively inhibits the pacemaker if the current in a dose-dependent manner. Blocking this channel reduces cardiac pacemaker activity, slowing the heart rate and allowing more time for blood to flow to the myocardium. Ivabradine is biological half-life is about 2 hrs and is eliminated rapidly, the repeated daily administration is needed to maintain effective plasma level. [6, 7] The short half-life and severe first pass metabolism of ivabradine makes it suitable for administration via a buccal delivery system that provides controlled drug delivery. Hence, in the current study mucoadhesive patch was developed with mucoadhesive and rate controlling polymer. Also, the effect of poloxamer on release rate was also studied and reported.

MATERIALS AND METHODS

Materials: Ivabradine hydrochloride was procured as gift sample from, Ahmedabad, India. HPMC K15 LV, Carbopol 934P (CP), polyvinylpyrrolidone (PVP), ethyl cellulose (EC), Poloxamer 808, PEG 400 were purchased from Signet chemical corporation Mumbai, India. All chemicals and solvents were used are of the high analytical grade.

Method of preparation: The patches of respective composition, as shown in Table 1 prepared by the solvent casting method. [8] The buccal mucoadhesive patch was prepared using HPMC K15LV, PVP as polymers and CP as a mucoadhesive polymer, PEG 400 as a plasticizer and permeation enhancer and poloxamer as a surfactant. The solvent system used was 50:50 ratios of methanol. The drug was then dispersed uniformly in the viscous solution with continuous stirring on the magnetic stirrer. 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 2×2 cm^2 area were cut using a sterilized stainless steel (Table 1).

Table 1: Formulation batches for Ivabradine hydrochloride mucoadhesive patch

Ingredients	Formulation batches				
	F1	F2	F3	F4	F5
Drug (mg)	50	50	50	50	50
HPMC K15 LV (gm)	1.5	1.5	-	1.5	1.5
Carbopol 934 P (mg)	50	50	50	-	-
PVP (mg)	150	-	150	-	-
EC (mg)	-	150	1.5	-	5
Poloxamer (mg)	50	50	50	50	-
PEG 400 (3%)	2	2	2	2	2
Methanol (ml)	3	3	3	3	3

Evaluation parameters of the patch

Thickness: The thickness of the drug-loaded patch is measured in different points by using a digital micrometer and the average thickness and standard deviation are determined to ensure the thickness of the prepared patch.

Mucoadhesive Strength: In this test, the force required to remove an adhesive coating form a test substrate is referred to as peel adhesion. The molecular weight of an adhesive polymer, the type and amount of additives are the variables that determined the peel adhesion properties. A single tape is applied to a stainless steel plate or a backing membrane of choice and the tape is pulled from the substrate at a 180 degrees angle and the force required for the tape removed is measured. [9]

Swelling Index: Weight and area increase due to swelling was measured. Weight increase due to swelling: A drug-loaded patch of 1x1 cm^2 was weighed on a preweighed coverslip. It was kept in a Petri dish and 50 ml of phosphate buffer, pH 6.8 was added. After every five min, the coverslip was removed and kept for 30 min. The difference in the weights gives the weight increase due to absorption of water and swelling of the patch. Area increase due to swelling: A drug loaded patch size of 1x1 cm2 was cut and placed in a petridish. A graph paper was placed beneath the Petri dish, to measure the increase in the area. Fifty ml of phosphate buffer, pH 6.6, was poured into the Petri dish. [10, 11] An increase in the length and breadth of the patch was noted at five min intervals for 60 min and the area was calculated. The percent swelling, % S, was calculated using the following equation.

Swelling (%)= S_T-S_0/S_0 X 100……(1)
Where, S_T is final weight of patch and S_0 is the initial weight of patch

Folding Endurance: Three patches of each formulation of bigger size, i.e., 2 x 2 cm, were cut using a sharp blade. Folding endurance was determined by repeatedly folding a small strip of the patch at the same place until it ruptured. The number of times the patch could be folded at the same place without breaking resulted in the folding endurance value. The mean value was calculated and recorded. [12]

Surface pH of Patches: To determine surface pH, three patches of each formulation were allowed to swell for two hours on the surface of an agar plate. Surface pH was measured by using pH paper placed on the surface of the swollen patch as per reported method. A mean of three readings was recorded. [13]

Drug Content: A specified area of a patch is to be dissolved in a suitable solvent in a specific volume of 10 ml. Then the solution is to be filtered through a filter medium and analyzed the drug contain with the suitable method (UV spectrophotometer) against the corresponding blank solution at 287 nm, each value represents an average of three different values. [10]

Dissolution Test: Franz diffusion cell is taken .it contains donor and receptor, the donor is tied with egg membrane, on that place 2 mm of drug patch is placed. The receptors was filled with phosphate buffer with a small magnetic bead, and placed on a magnetic stirrer. Samples were collected up to 10 hrs, with a specific and predetermined time interval. Finally, absorbance values are taken by using UV spectrophotometer. [10, 13]

The drug release was performed at 37 ± 0.5°C, at a stirring speed of 50 rpm using a magnetic stirrer. Five milliliters of the sample from the receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of drug released into the receptor medium was quantified by using UV–Visible spectrophotometer at 287 nm against a blank.

RESULTS AND DISCUSSION

The prepared patches were found to be good without any manufacturing defects. All prepared patches were white in color and smooth in texture there was no sign of defect

The thickness of the patches were found to be 0.107+_0.021 to 0.118+_0.05 mm within minimum deviation by which the weight variation of the patch was controlled within the limits.

Mucoadhesion is commonly defined as the adhesion between two materials, at least one of which is a mucosal surface. The mucoadhesive strength ranged between 2.43 to 3.97 dyne/cm^2. The result showed that the presence of carbopol along with PVP had higher mucoadhesive strength as seen in F1. Whereas the presence of hydrophobic polymer such as EC decreased mucoadhesive strength to 2.43 for F3. In case F5 showed only 1.76 as contained only EC and HPMC K15 LV. [14, 15]

Drug content of all formulations was in the range of 79.76% to 99.15% it complies with official specifications.
Swelling index study is a scientific approach for the study of polymer and excipients behavior in presence with the exposed environment. The formulated batches were performed and studied in phosphate buffer 6.8 for the time range of 2 hrs to 8 hrs. From the result, it observed that the presence of polymers such as carbopol, PVP has a direct relationship with swelling index [16] as seen in F1, F2 and F3 have more than 70 % in 8 hrs. In F5 the least value of 65 as it did not contain carbopol and PVP. The swelling properly was achievable only on the presence of HPMC K15LV.

The surface pH value is to predict the possibility of sensitivity or any kind of interaction with the mucosal membrane. From the evaluation, it observed the surface pH value of all patches within 6.4 to 7.1.

The folding endurance was found between 52 to 81. It observed the least value of 52 found for F5. A comparison was made between the patches and result showed that the patches contained hydrophilic polymer had the more folding endurance that patch containing hydrophilic polymer as seen in F3, F1 and F2. [17] The patch contained a hydrophobic polymer such as EC had lesser folding endurance as seen in F5.

Table 2: Characteristics of buccal mucoadhesive patches containing ivabradine hydrochloride

Formulation	Drug content (%)	Mucoadhesive strength(dyne/cm²)	Surface pH	Folding endurance	Swelling index (%)			
					2 hrs	4 hrs	6 hrs	8 hrs
F1	89.8 ± 2.87	3.97 ± 1.02	6.5	71	25	39	46	73
F2	96.6 ± 3.01	2.68 ± 0.92	6.8	65	26	42	57	74
F3	99.15 ± 3.15	2.43 ± 1.01	7.1	81	31	44	61	78
F4	80.57 ± 2.86	3.72 ± 0.98	6.4	59	25	37	51	67
F5	79.76 ± 1.75	1.76 ± 1.03	6.6	52	27	41	54	65

In vitro dissolution study was performed in phosphate buffer 6.8. It observed all the patches released 10 % drug in 0.5 hrs. Among patches, F3 released 99.06 % in 10 hrs. A comparison was made between F1 and F3. F1 released 89.41 % in 10 hrs, whereas F3 released 99.06 % in 10 hrs. A fact was that F1 contained HPMC K15 LV but F3 contained EC at an equal amount. Hence from the result, it can be concluded that the HPMC K15 LV has a major contribution in extending the drug release as compared to EC. [18, 19] It might be the reason that HPMC K15 LV had formed a gel-like layer surrounding the drug molecule which delayed the drug release. Similarly, a study was made between F4 and F5. F4 released faster 80.77 % as compared to F5 for 78.52 in 10 hrs. It might be that, the poloxamer because of emulsification character released more drug than F5 contained only EC.

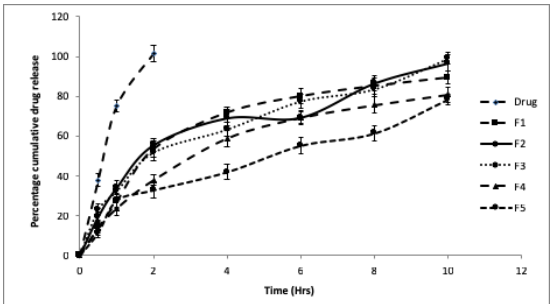

Figure 1: In-vitro release study for pure drug and all patches

Table 3: Release kinetic model for different formulations

Formulations	Zero-order	First order	Higuchi kinetic	Korsmeyer peppas	
				R^2	n value
F1	0.989	0.873	0.924	0.746	0.721
F2	0.992	0.831	0.932	0.643	0.79
F3	0.993	0.91	0.892	0.854	0.784
F4	0.986	0.86	0.912	0.832	0.81
F5	0.992	0.921	0.973	0.741	0.8

In order to study the exact mechanism of drug release from buccal patch drug release data was analyzed according to Zero order kinetics, first-order kinetics, Higuchi and Korsmeyer Peppas model. It observed all formulations followed zero order kinetics. The diffusion mechanism was studied by Korsmeyer and Peppas model and found the value between 0.72 to 0.81, which represented drug is released by a diffusion-based and swelling-based mechanism (Table 3).

Pure Ivabradine HCl mixed with excipients and polymer with IR grade KBr and pellets were prepared by applying a pressure of 10 tons in a hydraulic press. [20] The pellets were scanned over a wavelength range of 450 to 4,500 cm^{-1} using an FTIR IR Spirit, Schimazu. There was no chemical interaction between the drug and the polymers used which are obtained by employing I.R. spectral studies. The FTIR spectra of pure ivabradine HCl showed a sharp peak at 1547, 1411 (O-CH3 stretching), 2919 (symmetric CH stretching), 1511 (CH-) and 1639 (C=C stretching). There was no such remarkable change in peak was observed in formulation F3.

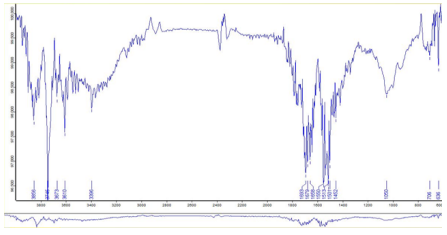

Figure 2: FTIR Spectrum of pure ivabradine hydrochloride

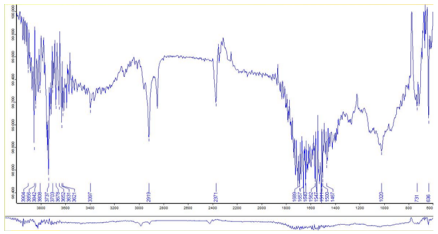

Figure 3: FTIR Spectrum of patch F3

Differential scanning calorimetry (DSC) has shown to be an important tool to quickly obtain information about possible interactions between the active and the excipients, according to the appearance, shift or disappearance of endothermic or exothermic peaks. DSC study was performed using Perkin Elmer DSC to determine the drug excipient compatibility study. [21] During the study, a sharp endothermic peak for Ivabradine HCl was obtained at 54.32 ^{0}C corresponding to melting point (figure 5). But in the formulation there was a slight change in peak temperature and appearance of other peaks, peak shape and area observed at 76.43 ^{0}C, 145.37 ^{0}C and 192.80 ^{0}C (figure 6), which might be due to reduction of the purity percentage of component, appearance of adjacent polymer, interaction with solvent excipients.

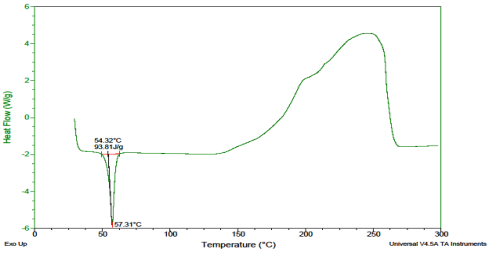

Figure 4: DSC spectra of ivabradine hydrochloride

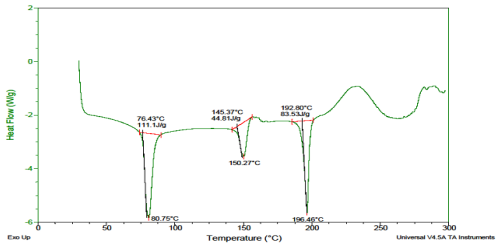

Figure 5: DSC spectra of patch F3

CONCLUSION

During this study mucoadhesives, patches of Ivabradine HCl was prepared with HPMC K15 LV, Carbopol 934P (CP), polyvinylpyrrolidone (PVP), ethyl cellulose (EC), Poloxamer 808. It was observed patch F3 released 99.09 % in 10 hrs and followed zero order. The effect of various polymers on the release of drug from dosage form was assessed and studied. Furthermore, industrial grades of reproducible batches of F3 and in-vivo pharmacokinetic study have to carry out.

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