AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Formulation and *Ex Vivo* Evaluation of Buccal Tablets of Eletriptan Hydrobromide

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ABSTRACT

The objective of this study was to develop effective buccoadhesive bilayered tablets of Eletriptan hydrobromide containing bioadhesive layer and drug free backing layer, expected to release the drug in unidirectional for extended period of time. Buccoadhesive tablets were prepared by using HPMC K4M, Carbopol 941NF and Carbopol 974p as mucoadhesive polymers with varying concentrations. The formulations were tested for *in-vitro* drug release, bioadhesive strength, moisture absorption, residence time and drug permeation through porcine buccal mucosa. Optimized formulation F3 of HPMC K4M showed maximum release of the drug (97.83±0.41), best fit in the peppas model and permeated 73.52% of the drug through porcine buccal membrane.

Keywords: Eletriptan Hydrobromide, ex vivo permeation studies, mucoadhesive buccal tablet, mechanical properties, in vitro studies, buccoadhesive

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Received 25 April 2012, Accepted 13 May 2012

Please cite this article in press as: Shayeda S *et al.*, Formulation and *Ex Vivo* Evaluation of Buccal Tablets of Eletriptan Hydrobromide. American Journal of PharmTech Research 2012.

INTRODUCTION

Buccal delivery of drugs provides an attractive alternative to the oral route of drug administration, particularly in overcoming deficiencies associated with the latter mode of dosing[1-3]. Problems such as first pass metabolism and low bioavailability can be circumvented by administering the drug via buccal route. Buccal delivery involves the administration of drug through buccal mucosal membrane (the lining in the oral cavity). Buccal drug delivery is the safer method of drug utilization because; drug absorption is terminated in case of toxicity by removing the dosage form from the buccal cavity. The drug directly reaches to the systemic circulation through the internal jugular vein and bypasses the drugs from the hepatic first pass metabolism, which leads to high bioavailability[4]. The other advantages of buccal drug delivery include: low enzymatic activity, suitable for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless drug administration, easy drug withdrawal, possible to include the permeation enhancer/enzyme inhibitor or pH modifier in the formulation. A suitable buccal drug delivery system should be flexible and should possess good bioadhesive properties, so that it can be retained in the oral cavity for the desired duration.

Eletriptan hydrobromide is a selective 5-hydroxytryptamine 1B/1D (5-HT1B/1D) receptor agonist, used in the treatment of migraine attacks. Eletriptan is chemically designated as (R)-3-[(l-Methyl-2-pyrrolidinyl) methyl]-5-[2-(phenylsulfonyl)ethyl]-lH-indole monohydrobromide. The empirical formula is $C_{22}H_{26}N_2O_2S.HBr$, representing a molecular weight of 463.40. Eletriptan hydrobromide is a white to light pale colored powder that is readily soluble in water. The terminal elimination half-life of Eletriptan is approximately 4 hours, and is primarily metabolized by cytochrome P-450 enzyme CYP3A4 after oral administration. Although Eletriptan is well absorbed after oral administration, it undergoes first pass metabolism leading to a mean absolute oral bioavailability of approximately 50%. Eletriptan dosing guidelines generally call for a dose of 20 mg or 40 mg to relieve symptoms of a migraine attack. Usually, the higher dose is more effective, but it can cause more side effects[5]. Moreover, a substantial proportion of patients suffer from severe nausea or vomiting during their migraine attacks, leading to the loss of dosage form. The above mentioned limitations of oral administration make buccal route a suitable alternative for the systemic delivery of Eletriptan , leading to improved bioavailability and reduction in dose dependent side effects[6].

MATERIAL AND METHODS

Eletriptan hydrobromide was obtained as a gift sample from Aurobindo Pharma Ltd, Medak A.P, India. Hydroxyl Propyl Methylcellulose (HPMC K4M) Carbopol 941NF and Carbopol 974p

were procured from Loba chemicals Pvt Ltd., India. All other reagents used were of analytical grade.

Methods

Formulation of buccal tablets

Bilayered buccal tablets were prepared by a direct compression method, before going to direct compression all the ingredients were screened through sieve no.100. Eletriptan was mixed manually with different ratios of HPMC K4M, Carbopol 941NF and Carbopol 974P as mucoadhesive polymers and Perlitol S.D 200 as diluent for 10 min. The blend was mixed with sodium stearyl fumerate (SSF) for 3-5 min. Final lubricated blend equivalent to 120mg was compressed into tablets using 8 mm flat punches and corresponding dies on 16 station rotary compression machine (Riddhi, Ahmedabad, India). Upper punch was raised and the backing layer of ethyl cellulose was placed on the above compact. Then 2 layers were compressed into a mucoadhesive bilayer tablet with a total weight of 140 mg/tablet. Composition of tablets shown in Table 1.

Table 1: Composition of Eletriptan buccal tablets

Formulation Code	Drug(mg)	HPMCK4M	Carbopol 941NF	Carbopol 974P	Filler (Perlitol SD 200)	SSF	Ethyl cellulose
F1	20	10	-	-	88	2	20
F2	20	20	-	-	78	2	20
F3	20	40	-	-	58	2	20
F4	20	60	-	-	38	2	20
F5	20	80	-	-	18	2	20
F6	20	-	10	-	88	2	20
F7	20	-	20	-	78	2	20
F8	20	-	30	-	68	2	20
F9	20	-	40	-	58	2	20
F10	20	-	50	-	48	2	20
F11	20	-	-	5	93	2	20
F12	20	-	-	10	88	2	20
F13	20	-	-	15	78	2	20
F14	20	-	-	20	68	2	20
F15	20	-	-	30	58	2	20

Tissue Isolation

Buccal tissue was collected from pigs at a slaughter-house. It was isolated within 10 minutes after slaughter of the pig and tissue was kept in Krebs buffer solution. It was transported immediately to the laboratory and was mounted within 2 hours of isolation of buccal tissue. The tissue was rinsed thoroughly using phosphate buffer saline to remove any adherent material. The

buccal membrane from the tissue was isolated using surgical procedure. Buccal membrane was isolated and buccal epithelium was carefully separated from the underlying connective tissue. Sufficient care was taken to prevent any damage to the buccal epithelium.

***Ex vivo* permeation studies through porcine buccal mucosa**

The buccal epithelium was carefully mounted in between the two compartments of a Franz diffusion cell with an internal diameter (ID) of 2.4cm (4.52 cm^2 area) and with a receptor compartment volume of 24 ml. 24 ml of mixture of phosphate buffer solution (PBS) pH (7.4) and methanol (70:30) was placed in the receptor compartment. The donor compartment contained a mixture of 5 ml of PBS pH (6.6) and in which 4 mg of Eletriptan hydrobromide was dissolved. The donor compartment also contained phenol red at a concentration of 20µg/ml. This is because phenol red acts as a marker compound and is not expected to permeate through the porcine buccal membrane[7]. Absence of phenol red in the receiver compartment indicates the intactness of the buccal membrane. The entire setup was placed over magnetic stirrer and temperature was maintained at about 37^0c. The samples were collected at 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5 and 4.0 hr and stored under refrigerated conditions till the analysis was carried out by using UV-Visible spectrophotometer (Elico, India) at 225 nm. All the experiments were performed in triplicates[8].

Estimation of Drug Content in the Sample by HPLC Method

Analysis of samples was performed using a Shimadzu HPLC system equipped with a shimadzu (Japan), LC-20AT pump with Spectrophotometric detector and a Grace C18 column (250mm, 4.6mm ID, particle size 5µ) at ambient temperature. The mobile phase used was a mixture of (40:20:40) of acetonitrile, methanol, 0.01M Phosphate buffer. The pH was adjusted to 4.3 with orthophosphoric acid. The flow rate is 1 ml per minute. The detection was carried out at 225nm wavelength. A calibration curve was plotted for Eletriptan in the range of 50-500 ng/ml. A good linear relationship was observed between the concentration of Eletriptan and the peak area of Eletriptan with a correlation coefficient (r2 = 0.999). The required studies were carried out to estimate the precision and accuracy of the HPLC method of analysis of Eletriptan. Typical chromatogram for Eletriptan Hydrobromide is shown in Figure 1.

Assay of phenol red

To 250 µl of sample solution, 250 µl of acetonitrile was added and vortexed to precipitate the proteins. To this 1 ml of 0.2 M NaoH was added, vortexed and to this 3.5 ml of distilled water was added to make the volume to 5 ml, vortexed, centrifuged and absorbance of supernatant was measured at 563 nm using UV-Vis Spectrophotometer.

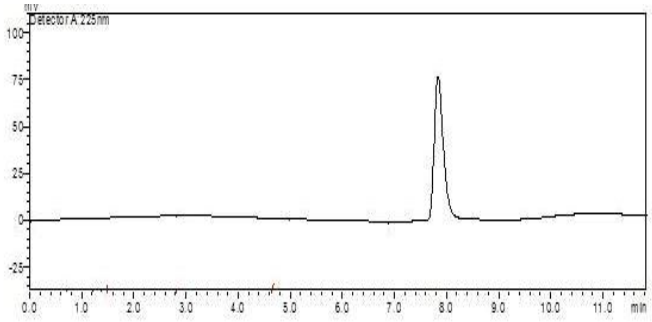

Figure 1: Typical chromatogram for Eletriptan Hydrobromide

Physico-chemical parameters of tablets

Weight variation test was performed for tablets (*n*=20) from each batch using an electronic balance (DENVER APX 60, Denver Instrument GmbH, Germany) and average values were calculated, thickness was calculated with digital micrometer (Mitutoyo, Japan). Crushing strength (*n*=6) was measured with Monsanto hardness tester (Pharmalab, Ahmedabad, India), friability (*n* =6) with Roche type friabilator (Pharmalab, Ahmedabad, India). The drug content in each formulation was determined by triturating 20 tablets in a mortar and powder equivalent to average weight was added to 100 ml of water, followed by shaking for 30 minutes. The solution was filtered through 0.45 µm membrane filter, diluted suitably and analyzed by using HPLC method.

Moisture absorption studies of buccal tablet

Agar (5% w/v) was dissolved in hot water. It was transferred into petri dishes and allowed to solidify. Six buccal tablets (pre-weighed) from each formulation were placed in vacuum oven overnight to remove moisture and laminated on one side with a water impermeable backing membrane[9]. Then they were placed on the surface of the agar and incubated at 37°C for one hour. Then the tablets were removed and weighed and the percentage of moisture absorption was calculated by using following formula:

% Moisture absorption = [(final weight – initial weight)/initial weight] x100.

Surface pH Study

The bioadhesive tablet was allowed to swell by keeping it in contact with 1 ml of distilled water for 2 hr at room temperature[10]. The pH was measured by bringing the pH-meter electrode, in contact with the surface of the tablet and allowing it to equilibrate for 1 min

Swelling Index

Buccal tablets were weighed individually (designated as W1) and placed separately in petri dishes containing 15 ml of phosphate buffer (pH 6.6) solution. At regular intervals (0.5, 1, 2, 3, 4,

5 and 6hr), the buccal tablets were removed from the petridishes and excess surface water was removed carefully using the filter paper. The swollen tablets were then reweighed (W2) .This experiment was performed in triplicate. The swelling index (water uptake) calculated according to the following equation

%Swelling index= (W2-W1)/W1 X 100

W1---initial weight of tablet,

W2--- weight of swollen tablet

In vitro dissolution studies

The United States Pharmacopoeia (USP) II method was used to study the drug release from the tablets. Each tablet was attached on a glass plate with cyanoacrylate adhesive. The glass plate was then placed in a dissolution tester. The experiments were performed at 37±0.5°C using the paddle method at 50 rpm with 500 ml of phosphate buffer of pH 6.8 as a dissolution medium. Samples equivalent to 5 ml was withdrawn for every one hour, filtered and analyzed at 225 nm using UV-Visible spectrophotometer (Elico, India). Release data were fitted to various mathematical models like zero order, first order, Higuchi release model and Korsmeyer-Peppa's model in order to determine the release mechanism from tablet.

In vitro Bioadhesive Strength

The bioadhesive strength of the buccal tablets was determined using an ultra test (Mecmesin, west Sussex UK) equipped with a 5-kg load cell. The fresh porcine buccal mucosa obtained from slaughterhouse was stored in simulated saliva solution (2.38 g Na2HPO4, 0.19 g KH2PO4 and 8.00 g NaCl in 1000 ml of distilled water at pH 6.75). The porcine buccal mucosa was secured tightly to a circular stainless steel adapter of a diameter 2.2 cm provided with the equipment. This was fixed to advanced force gauze. The buccal tablet to be tested was placed over another cylindrical stainless steel adaptor of similar diameter and mounted on the platform of motorized test stand. Buccal tablet with a backing membrane was adhered on to it using a solution of cycnoacrylate adhesive. All measurements were conducted at room temperature. During Measurement 100µl of 1% mucin solution of crude mucin procured from sigma chemicals was used to moisten the porcine buccal membrane. The upper support was lowered at a speed of 0.5 mm/s until contact was made with the tissue at the predetermined force of 0.5 N for a contact time of 180 sec. At the end of the contact time upper support was withdrawn at a speed of 0.5mm/s to detach the membrane from the tablet. Data collection and calculations were performed using the data plot software package of the instrument. Two parameters, namely the work of adhesion and peak detachment force were used to study the buccal adhesiveness of

tabletss[5]. The work of adhesion was determined from the area under force distance curve while the peak detachment force required detaching from tissue.

Stability of buccal tablets

Stability studies of buccal tablets were performed for optimized formulation. The human saliva was collected from humans and filtered. Buccal tablets were placed in separate Petri dishes containing 5 ml of human saliva and placed in a temperature controlled oven for 8 hr at 37°C ± 0.2°C. At regular time intervals (0, 2, 4 and 6 hr), the buccal tablets were examined for change in color, surface area and integrity. The experiment was repeated in triplicate.

RESULTS AND DISCUSSIONS

Drug Penetration Studies through the Porcine Buccal Membrane

The cumulative amount of Eletriptan that had penetrated through the buccal epithelium was determined. This model, which was aimed at simulation of *in vitro* drug penetration, was found to be useful. The tissue could be isolated successfully because no detectable levels of Phenol red, which was used as marker compound, was not found in the receiver compartment. Hence it did not show any penetration whereas Eletriptan could penetrate freely. This indicated that the membrane was intact. The result is shown in Figure 2. The flux was calculated to be 0.156 mg/hr.cm^2.

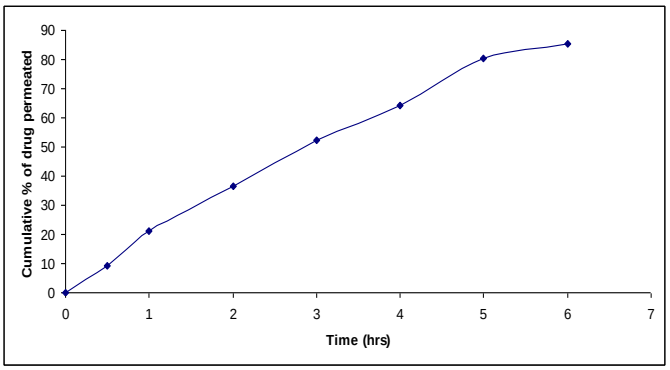

Figure 2: Cumulative % drug permeated through porcine buccal mucosa

Physico-chemical properties

The hardness of prepared buccal tablets was found to be in the range of 3.8 Kg/cm^2 to 4.5Kg/cm^2.The thickness was found to be 3.02 mm to 3.42 mm, the friability of all tablets was less than 1% i.e., in the range of 0.06 – 0.38 %. The percentage deviation from mean weights of all the formulations of tablets was found to be within the prescribed limits. The low values in standard deviation indicates uniform drug content in all the formulations prepared as observed from table given Table 2.

Table 2: Physico-chemical parameters of buccal tablets.

Formulation Code	Thickness (mm)	Weight Variation (mg)	Friability (%)	Hardness (Kg/cm^2)	%Drug Content
F1	3.02±0.07	138±0.23	0.06	3.9±0.12	105.4
F2	3.3±0.1	141±0.16	0.14	4.1±0.26	107.8
F3	3.3±0.06	141±0.20	0.12	4.2±0.13	107.6
F4	3.22±0.08	139±0.13	0.18	4.5±0.18	93.4
F5	3.24±0.01	140±0.18	0.21	4.5±0.2	99.6
F6	3.32±0.2	139±0.19	0.09	3.8±0.17	90.7
F7	3.27±0.22	142±0.23	0.13	3.8±0.41	98.3
F8	3.42±0.04	140±0.31	0.18	4.3±0.21	107.4
F9	3.4±0.06	141±0.81	0.31	4.6±0.34	104.6
F10	3.32±0.07	138±0.22	0.28	4.4±0.45	103.8
F11	3.3±0.2	137±0.17	0.17	4.0±0.14	94.6
F12	3.02±0.09	140±0.13	0.22	4.1±0.16	98.2
F13	3.22±0.04	142±0.16	0.45	4.0±0.12	106.3
F14	3.3±0.06	142±0.21	0.16	4.3±0.41	101.4
F15	3.3±0.07	139±0.31	0.38	4.3±0.17	103.2

***In vitro* drug release of buccal tablets**

Release of drug from the tablet varied according to the type and ratio of matrix-forming polymer. HPMC is a hydrophilic swellable polymer, which is able to form a viscous gel layer which controls the drug release via diffusion through the gel and erosion of gel barrier. Carbopol has excellent mucoadhesive, gelling properties and also helps in sustaining effect. For all formulations the cumulative drug release at the end of 6th hour was calculated. From formulations F1-F5, drug release was good for F3 (97.83%), from formulations F6-F10, drug release was good for F7 (89.68%), from formulations F11-F15, drug release was good for F12 (82.63%).

The results indicate that the rate of drug release (Table 3, Table 4, Table 5 & Figure 3) was higher for F3 formulation. The rate of drug release decreased by increase in the concentration of HPMC K4M which may be due to the increase in viscosity produced by the gelling of the hydrophilic polymer HPMC K4M. For non-Fickian release, the value of n falls between 0.5 and 1.0, while in the case of Fickian diffusion, n=0.5; for zero order release (case II transport), n=1; and for supercase II transport, n is greater than 1. All of these formulations exerted fickian diffusion mechanism with *n* value varied from 0.434-0.497. Based on these results F3 formulation was selected for further studies.

Swelling studies of buccal tablets

In formulations containing HPMC K4M, F3 (selected optimized formulation) -shows swelling index of 102.8; the formulations containing carbopol-941NF and 974P show maximum swelling

index i.e. 138.6, 149.4 respectively. The formulation containing carbopol shows higher swelling index values than HPMC containing formulation. Results were shown in Table 6.

Table 3: In vitro cumulative percentage drug release data of formulations with HPMCK4M

Time(hr)	F1	F2	F3	F4	F5
0.5	32.79±0.2	32.54±0.12	38.91±0.06	37.39±0.28	30.13±0.1
1	39.14±0.13	40.68±0.26	46.28±0.03	43.18±0.22	39.16±0.3
2	56.87±0.3	55.42±0.14	60.84±0.08	58.31±0.36	42.63±0.23
3	68.31±0.42	68.58±0.05	71.35±0.12	65.67±0.33	57.32±0.3
4	80.36±0.22	82.16±0.06	88.71±0.24	81.39±0.12	69.48±0.26
5	84.52±0.34	89.43±0.03	93.67±0.02	88.62±0.2	75.28±0.25
6	91.83±0.33	92.67±0.14	97.83±0.04	90.61±0.16	83.48±0.2

Table 4: In vitro cumulative percentage drug release data of formulations with Carbopol 941NF

Time(hr)	F6	F7	F8	F9	F10
0.5	17.15±0.24	13.63±0.22	20.19±0.2	20.16±0.32	19.62±0.1
1	20.65±0.11	21.14±0.24	24.14±0.23	28.41±0.3	26.11±0.38
2	24.58±0.1	28.67±0.31	32.38±0.33	41.81±0.26	32.92±0.27
3	38.16±0.1	50.68±0.3	54.93±0.3	58.28±0.16	41.26±0.25
4	59.36±0.01	62.58±0.13	70.14±0.12	62.37±0.1	49.73±0.13
5	68.12±0.03	76.38±0.3	81.45±0.2	69.18±0.18	53.62±0.3
6	78.48±0.13	89.68±0.23	85.32±0.2	72.39±0.1	60.36±0.1

Table 5: In vitro cumulative percentage drug release data of formulations with Carbopol 974P

Time(hr)	F11	F12	F13	F14	F15
0.5	25.28±0.1	29.16±0.13	23.78±0.3	19.26±0.23	15.74±0.3
1	31.82±0.27	32.48±0.2	28.84±0.32	23.68±0.3	19.42±0.39
2	40.72±0.18	43.62±0.1	38.62±0.3	37.85±0.1	26.67±0.27
3	43.91±0.33	50.59±0.26	45.25±0.22	43.92±0.13	37.55±0.14
4	52.74±0.38	61.93±0.3	56.38±0.24	50.11±0.1	45.32±0.16
5	69.13±0.26	73.12±0.1	68.19±0.26	63.26±0.15	57.63±0.18
6	80.40±0.3	82.63±0.33	76.79±0.3	72.91±0.29	68.14±0.19

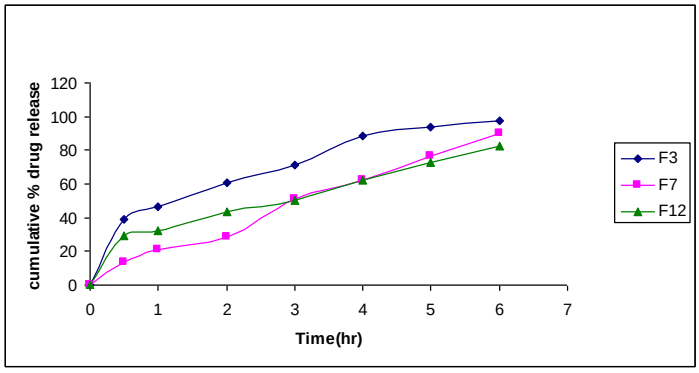

Figure 3: Cumulative % drug release of selected formulations

Table 6: % swelling index profile of selected Formulations

Time (hr)	F3	F7	F12
0	79.2	92.4	95.8
0.5	82.4	97.4	99.6
1	87.6	99.9	104.6
2	93.2	102.4	112.4
3	95.4	119.2	125.2
4	97.2	129.3	137.6
6	102.8	138.6	149.4

***Ex-vivo* permeation of Eletriptan Hydrobromide through porcine buccal membrane from buccal tablet**

The results of drug permeation from buccal tablet of Eletriptan Hydrobromide through the porcine buccal mucosa reveal that drug was released from the formulation and permeated through the porcine buccal membrane, hence they can possibly permeate through the human buccal membrane. The results indicated that the drug permeation was more in F3 among the selected formulations and about 73.14% of Eletriptan Hydrobromide could permeate through the buccal membrane in 6 hrs. (Table 7 & Figure 4)

Table 7: *Ex vivo* drug permeation (Cum % Drug permeated) data of drug solution and selected formulations

Time(hr)	Drug Solution	F3	F7	F12
0	0	0	0	0
0.5	9.32±0.1	3.12±0.48	1.92±0.42	0.98±0.14
1	21.22±0.13	8.07±0.33	4.16±0.46	1.72±0.25
2	36.46±0.26	21.06±0.42	8.53±0.24	3.54±0.24
3	52.28±0.24	38.86±0.28	19.01±0.23	7.20±0.17
4	64.26±0.16	56.14±0.26	27.32±0.26	16.14±0.18
5	80.42±0.18	70.48±0.53	41.33±0.64	19.68±0.14
6	85.48±0.32	73.14±0.13	44.73±0.45	21.01±0.26

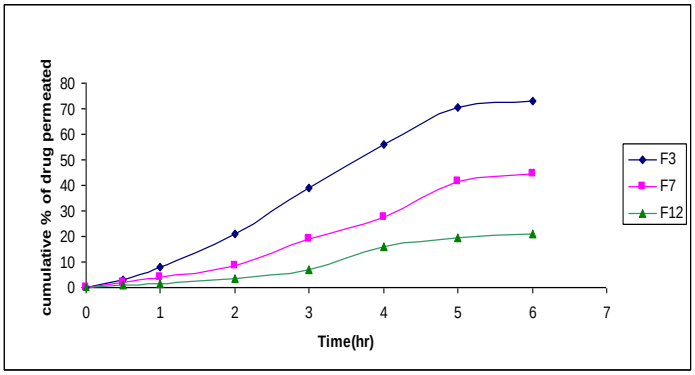

Figure 4: Cumulative % drug permeation of selected formulations

Measurement of bioadhesion strength

This test was conducted for selected formulations (F3, F7 and F12); there is a gradual increase in bioadhesion strength from F3 to F12. The order of bioadhesion was HPMCK4M <Carbopl 941NF<Carbopol 974p. Buccal tablets formulated with carbopol showed stronger mucoadhesion than HPMCK4M formulations. Very strong bioadhesion could damage the epithelial lining of the buccal mucosa. Optimized tablet (F3) showed 38.22±0.328 g of bioadhesion strength. Results are shown in Table 8.

Moisture Absorption

These studies give an indication of the relative moisture absorption capacities of polymers and whether the formulation maintained their integrity after its absorption. The order of increasing moisture absorption was HPMCK4M< Carbopol 941NF< Carbopol 974P, as shown in Table 8.

Surface pH study

Surface pH of the optimized formulations F3, F7 and F12 was found to be near to the neutral, so the formulation does not cause any irritation on the mucosa. Surface pH values for all the formulations shown in Table 8.

Table 8: The bioadhesive strength, moisture absorption and surface pH values of selected tablets

Formulation Code	Bio adhesion Strength (gm)	Surface pH	%Moisture absorbance
F3	24.64±0.246	6.1±0.24	36.73±0.62
F7	38.22±0.328	5.82±0.33	45.92±0.48
F12	49.46±0.624	6.22±0.53	56.64±0.53

Stability of buccal tablets

Stability study was conducted only for optimized formulations (F3, F7 and F12). There was no change in the color and integrity of the tablets for all formulations. From the stability results, it was known that formulations were stable in human saliva.

CONCLUSIONS

Developed bilayered buccal tablets of Eletriptan hydrobromide may overcome the disadvantage of poor oral bioavailability by eliminating the first pass effect and also provide prolonged release. The formulation (F3) containing HPMC K4M was found to be an optimized formulation, which satisfies all physico-chemical properties, bioadhesion strength, surface pH, moisture absorption and *ex vivo* drug release. So there is a need to develop bilayered buccal tablets of Eletriptan hydrobromide and to carryout *in vivo* studies.

ACKNOWLEDGEMENT

The authors are thankful to University Grants Commission (UGC), New Delhi, India for providing fellowship.

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