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Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF MUCOADHESIVE BUCCAL PATCHES OF ZOLMITRIPTAN

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ABSTRACT

In the present study, buccal patches of zolmitriptan were formulated by solvent casting method using HPMC E 15, aloe vera, Na CMC and eudragit RS100 as film forming polymers. The developed patches were evaluated for the thickness, folding endurance, bioadhesion strength, *in-vitro* residence time, mucoadhesive strength, *in vitro* drug release studies and *ex-vivo* drug permeation characteristics. Formulation F10 (contains HPMC E 15 & eudragit RS 100) has shown optimum *ex-vivo* mucoadhesion strength (19.4±0.9 g), *in vitro* residence time (6.0±0.14 hrs), *in vitro* drug release (75.06±1.12%) for 8hrs and satisfactory surface PH (6.8±0.02), *ex vivo* drug permeation (94.04±1.04%). The IR spectroscopic studies revealed that there is no evidence for chemical interaction between drug and polymers.

Keywords: Zolmitriptan, Propylene glycol, Buccal patches, Mucoadhesive strength, *Ex vivo* permeation, First pass metabolism, Migraine.

INTRODUCTION

Over the last few decades' pharmaceutical scientists throughout the world are trying to explore transdermal and transmucosal routes as an alternative to injections. Among the various transmucosal sites available, mucosa of the buccal cavity was found to be the most convenient and easily accessible site for the delivery of therapeutic agents for both local and systemic delivery as retentive dosage forms, because it has expanse of smooth muscle which is relatively immobile, abundant vascularization, rapid recovery time after exposure to stress.[1]

The buccal route of administration has a number of advantages including bypassing the gastrointestinal tract and hepatic first pass effect and prolonged residence time of the dosage form at the site of absorption. Due to an increased residence time one can expect enhanced absorption as well the therapeutic efficacy of the drug. As the dosage form is adhered to buccal cavity, drug can be protected from degradation in the acidic environment of the GIT. Within the oral mucosal cavity, the buccal region offers more advantages than other modes of administration for systemic purposes.[2]

In the present study, zolmitriptan is the drug of choice, because it has a high first pass metabolism (60%). Zolmitriptan an anti migraine agent requires to elicit its action rapidly and continuously. Film formers HPMC and eudragit RS 100 and mucoadhesive agents aloe and Na CMC were used at various concentrations.

MATERIALS AND METHOD

Zolmitriptan, Eudragit RS 100 and HPβCD were obtained as a kind gift samples from Dr. Reddys laboratories, Hyderabad. HPMC E 15(SD fine chemicals, Mumbai), aloe vera powder (madvik laboratories, Hyderabad), Na CMC (SD fine chemicals, Mumbai), propylene glycol (SD fine chemicals, Mumbai) were procured.

Preparation of Mucoadhesive Buccal patch of zolmitriptan

An accurately weighed amount of polymers (table 1) were taken in a clean and dry boiling tube. The chosen solvent was accurately measured and transferred to the boiling tube. The polymer was allowed to swell/dissolve by keeping aside for 4-6 hours based on the degree of interaction of polymer with respective solvent/mixture of solvents. The boiling tube was covered with an aluminum foil to prevent evaporation of the solvent.

Accurately measured quantity of selected plasticizer was added to the polymeric solution. The drug was first dissolved in water and added to the polymeric solution containing the plasticizer. The contents were stirred on cyclo mixer until the contents were uniformly mixed and allowed to deaerate by keeping aside. The resultant mixture was poured onto the anumbra petri plates allowed for controlled drying using inverted funnel with cotton plug at room temperature. The dried films were removed from the plates carefully by lifting the edges along the periphery of the plate using a sharp knife.

Table 1: Formulation composition of zolmitriptan patches

Formulation	Zolmitriptan (mg)	HPMC E 15 (mg)	Aloe vera (mg)	Na.CMC (mg)	Eudragit Rs 100 (mg)	PG (w/v)	Solvent (ml)	Penetration enhancer
F1	79	300	_	_	_	30%	water	_
F2	79	_	300	_	_	30%	water	_
F3	79	_	_	300	_	30%	water	_
F4	79	300	_	_	200	40%	water & ethanol	_
F5	79	300	_	_	300	40%	water & ethanol	_
F6	79	_	300	_	200	40%	water & ethanol	_
F7	79	_	300	_	300	40%	water & ethanol	_
F8	79	_	_	300	200	40%	water & ethanol	_
F9	79	_	_	300	300	40%	water & ethanol	_
F10	79	300	_	_	300	40%	water & ethanol	HPβCD
F11	79	_	300	_	200	40%	water & ethanol	HPβCD
F12	79	_	_	300	200	40%	water & ethanol	HPβCD

Film Thickness

The thickness of each film was measured at four corners and in the centre of film (total five locations using dial gauge.). Average of all five readings was taken as thickness of one film.[3]

Folding Endurance

The folding endurance was measured manually for the prepared films. Films were repeatedly folded at the same place till it breaks. The number of times the film could be folded at the same

place without breaking will gives the exact value of folding endurance.[3]

Surface pH Study

Bucco-adhesive films were allowed to swell for 2 hrs in pH 6.8 phosphate buffer solution. pH meter placed on the core surface of the swollen film. A mean of three readings was recorded.[6]

***In vitro* Residence Time**

The *In vitro* residence time was determined using a modified USP disintegration apparatus. The disintegration medium composed of 800 ml of pH 6.8 phosphate buffer solution. The bucco-adhesive patch was hydrated from one surface using phosphate buffer and then the hydrated surface was brought into contact with the glass slab. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for complete erosion or detachment of the patch from the glass slab was recorded as the *In-vitro* residence time.[1]

***Ex Vivo* Muco-adhesive Strength**

A modified balance method was used for determining the *Ex vivo* muco-adhesive strength. Fresh porcine buccal mucosa was obtained from a local slaughterhouse and used within two hours of slaughter. The mucosal membrane was separated by removing the underlying fat and loose tissues. The membrane was washed with distilled water and then with phosphate buffer pH 6.8. A piece of buccal mucosa was pasted to the glass beaker using an instant adhesive, and held on the right side of the balance. The patch was stuck to the lower side of the glass petri dish with instant adhesive. The left and right pans were balanced by adding weights on the left hand pan. Weights were added slowly to the left-hand pan until the patch detached from the mucosal surface. The weight (in gram) required to detach the patch from the mucosal surface gave the measure of muco-adhesive or bio-adhesive strength. [4]

***In Vitro* Drug Release**

The i*n vitro* drug release study of the prepared patches through the dialysis membrane was performed using a Franz diffusion cell at $37^0C \pm 0.5^0C$. Dialysis membrane mounted between the donor and receptor compartments. The buccal film was placed on the dialysis membrane, and two compartments were clamped together. The receptor compartment (20-ml capacity) was filled with phosphate buffer (pH 6.8) and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at 50 rpm. Three milliliter samples were withdrawn at predetermined time intervals and analyzed for drug content by UV spectrophotometer (shimadzu-1800) using 6.8 pH phosphate buffer as a blank.[7]

***Ex vivo* Buccal Permeation Study**

The *Ex vivo* buccal drug permeation study of zolmitriptan through the porcine buccal mucosa was performed using a Franz diffusion cell at $37^0C \pm 0.5^0C$. Fresh porcine buccal mucosa was obtained from local slaughter house and used within two hours of slaughter. Freshly obtained porcine buccal mucosa mounted between the donor and receptor compartments. The buccal film was placed on the mucosa, and the compartments were clamped together. The receptor compartment (20-ml capacity) was filled with phosphate buffer (pH 6.8) and the hydrodynamics in the compartment was maintained by stirring with a magnetic bead at 50rpm. Three milliliter samples were withdrawn at predetermined time intervals and analyzed for drug content by UV-visible spectrophotometer using blank.[7]

RESULTS AND DISCUSSIONS

Thickness

The thickness of each formulation (table 2) was measured using screw gauge (in triplicate). All the formulations were having the thickness in the range of 0.18 ± 0.02mm to 0.31 ± 0.05mm. Formulation F1, containing HPMC E 15, has the thickness of 0.21± 0.02mm and the formulations F4 & F5, containing combination of HPMC E 15 and Eudragit RS 100, have shown highest thickness compared to all other formulations which is ranging from 0.30 ± 0.03mm to 0.31± .05mm.

Formulation F3 has the thickness of 0.18±0.02mm, which contains Na CMC alone as a film former. Based on the quantities and combinations of the polymers, the thickness of different formulations was found to be varied.

Folding endurance

The folding endurance of different formulations was measured (table no2). formulation F1, was having highest folding endurance among the all other formulations, which contain HPMC E 15 (1:3, drug: polymer). In case of films prepared from Na CMC, has relatively lesser folding endurance than films prepared from HPMC, while films prepared using aloe alone, were having lesser folding endurance than that of HPMC & Na CMC.

The reason may be HPMC is good film former, NaCMC also a film forming polymer but not as good as HPMC. The aloe vera powder, which has a capability of mucoadhesion at lower concentrations, was failed to form films with acceptable physical properties, as it possess more mucoadhesion property rather films forming property. Na CMC having the low folding endurance compare to the HPMC and high folding endurance than aloe vera.

It was found that folding endurance values were decreased by the increasing the concentration of hydrophilic polymer. The folding endurance values were in the range of 159±2.0 to 213±2.0 folds.

Surface pH

Considering the fact that acidic or alkaline pH may cause irritation to the buccal mucosa. The surface pH of all formulations was within the desirable range (6.5±0.08 – 7.0±0.06) which is near to buccal pH and hence no mucosal irritation would be expected. No significant difference was observed in surface pH for different formulations. Results are shown as mean ± standard deviation in table no 2.

Table 2: Evaluation of zolmitriptan patches

Formulation	Folding endurance	surface PH	Mucoadhesion strength (g)	In vitro residence time (hrs)
F1	213±2.0	6.8±0.05	18.3±0.8	6.2±0.14
F2	183±3.6	6.7±0.03	16.4±0.4	4.0±0.24
F3	194±4.0	6.8±0.04	21.0±0.5	5.0±0.20
F4	182±2.0	6.8±0.02	20.5±0.3	6.2±0.31
F5	180±3.4	6.7±0.05	20.7±0.7	6.0±0.34
F6	168±1.0	6.7±0.03	17.0±0.7	4.3±0.18
F7	159±2.0	6.7±0.01	16.1±0.5	4.0±0.16
F8	177±3.3	6.5±0.08	21.3±0.4	4.1±0.27
F9	173±1.0	6.8±0.01	21.4±0.5	4.8±0.29
F10	171±2.0	6.8±0.02	19.4±0.9	6.0±0.14
F11	169±3.4	6.7±0.02	16.1±0.3	4.3±0.16
F12	176±4.0	7.0±0.06	21.2±0.8	5.6±0.32

*Values are expressed as mean ±S.D. (n=3).

In Vitro residence time

The *In vitro* residence time varied from 4.0±0.16 hrs to 6.6±0.31 hrs. Formulation F1 showed highest *In vitro* residence time (6.2±0.14 hrs), which contain HPMC E 15. Formulations F6 & F7, showed the lowest in vitro residence time (4.0±0.16 hrs), which contain aloe vera and eudragit RS 100. The order of decreasing in residence time is HPMC E 15 > Na CMC > aloe vera. The reason may be, HPMC is more hydrophilic and it can also posses integrity, whereas Na CMC which is a hydrogel, upon up taking the water it swells enormously and a surface erosion takes place. As a result, patches prepared with HPMC have shown longer residence time than patches prepared with Na CMC. Aloe vera which has a low swelling index than remaining two polymers has shown lesser residence time, because swelling can facilitate the mucoadhesive bond formation.

Mucoadhesion strength

The mucoadhesion strength values were found in between 16.1±0.39 g to 21.4±0.5g. Formulations F2 and F11 showed reduced mucoadhesion strength, which composed of aloe vera and eudragit RS 100. The mucoadhesion strength behavior seemed to be dependent on the kind of mucoadhesive polymer used for patch preparation. Formulations F3 & F9 showed higher mucoadhesion strength, which contain Na CMC and eudragit RS 100.

In vitro drug release

All the patches were tested for *In vitro* drug release. The release of drug from the buccal mucoadhesive patches varied according to the type and ratio of polymer. HPMC E 15 has excellent mucoadhesive, swelling properties and also helps in sustaining effect. Without eudragit RS 100 the drug release of all formulations between 4 to 6½ hrs. The combination of HPMC E15 and Eudragit RS 100 showed delay the drug release from the patch up to 8hrs. The Formulation F10, showed 75.06±1.12% of drug release in 8hrs.

Ex vivo permeation

The *Ex vivo* permeation study was conducted with porcine buccal mucosa. Formulations F10 to F12, subjected to *Ex vivo* permeation. Formulation F10, which contain HPβCD as a permeation enhancer, it showed up to 94.04±1.04% of drug release in 8 hrs, results are shown as mean ± standard deviation in table 3.

Table 3: *Ex vivo* Release of zolmitriptan from formulations

TIME (hrs)	WITH OUT PENETRATION ENHANCER			WITH PENETRATION ENHANCER HPβCD		
	HPMC E15 (F5)	Aloe vera (F6)	Na CMC (F8)	HPMC E15 (F10)	Aloe vera (F11)	Na CMC (F12)
	0	0	0	0	0	0
1	8.46±1.04	8.71±0.82	10.02±0.76	11.9±0.52	12.77±0.72	13.68±0.84
2	13.4±0.61	13.64±0.77	17.56±0.82	18.3±1.03	17.48±0.84	22.59±0.51
3	17.64±1.06	19.67±0.91	22.43±0.81	27.17±0.76	28.37±1.01	32.86±0.61
4	26.22±0.89	30.82±1.05	29.37±1.05	37.45±0.46	40.3±0.86	44.76±0.91
5	37.32±0.79	40.81±0.76	37.89±0.86	44.6±0.49	57.09±0.81	59.18±1.18
6	48.33±0.91	51.04±1.06	48.65±0.57	60.79±0.64	71.52±0.59	73.82±0.52
7	60.66±0.75	68.46±0.88	63.37±0.67	74.66±0.73	89.43±0.62	86.13±0.71
8	75.06±1.12	52.08±0.79	43.18±0.72	94.04±1.04	73.15±0.84	62.43±0.79

*Values are expressed as mean ±S.D. (n=3).

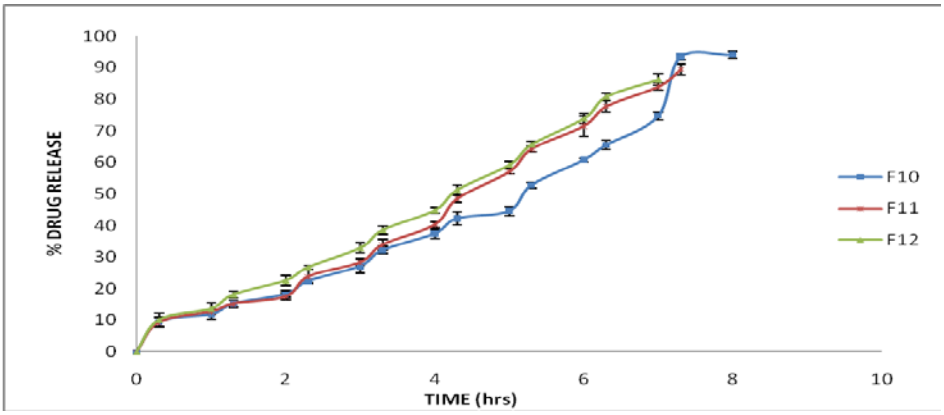
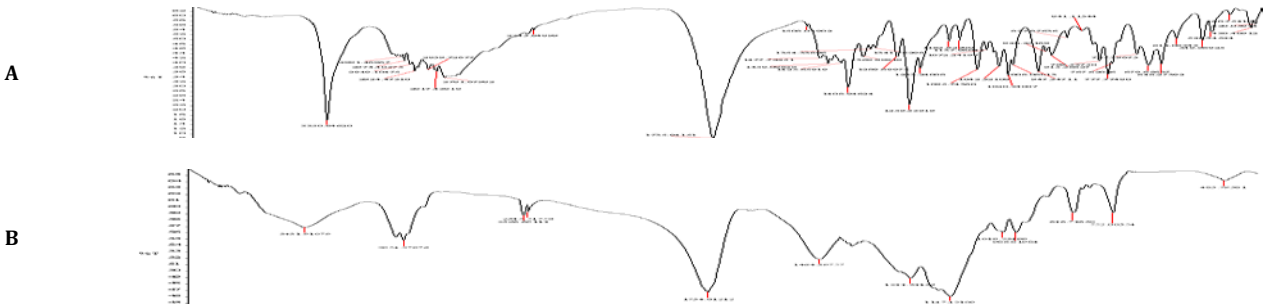


Fig. 1: *Ex vivo* permeation of zolmitriptan from buccal patches (F10- F12)



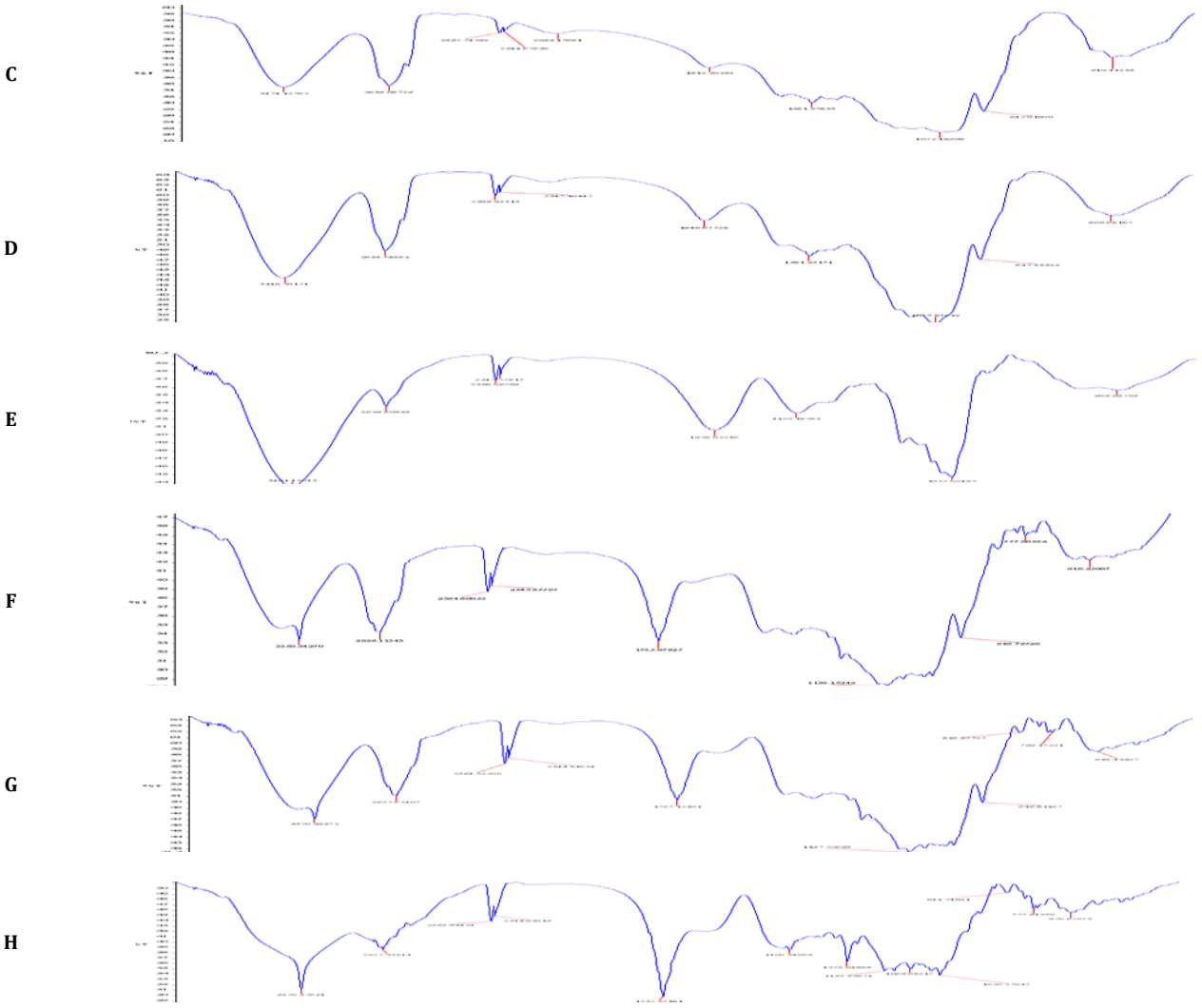


Fig. 2: FTIR of A) zolmitriptan pure, b) HPMC E15 pure, c) Eudragit RS100 pure, d) Na CMC pure, e) aloe vera pure, f) Formulation F10, g) Formulation F11, h) Formulation F12.

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