Research Article

Formulation and Evaluation of Mucoadhesive Buccal Patch for Treatment of Migraine

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ABSTRACT

A mucoadhesive buccal patch was designed particularly for treatment of migraine to obtain treatment effectiveness, reduction of drug dose, good residence time at the site and to avoid the first pass hepatic metabolism and gastrointestinal degradation with faster delivery of drug in circulation. Mucoadhesive buccal patches were prepared using solvent film casting method. The buccal patches of Diclofenac sodium were formulated using polymers HPMC and Ethyl cellulose. To improve the flexibility and to avoid brittleness of the buccal patch, Polyethylene glycol was selected as plasticizer. Then patches were characterized under following parameter like physical appearance, mass uniformity, thickness, folding endurance, surface pH, drug content uniformity, swelling, *in vitro* bio-adhesion test, *in vitro* residence time, *in vitro* buccal permeation study, *in vitro* drug release. Excellent adhesion and retention on the site observed by the prepared mucoadhesive buccal patches with better release. On the basis of the results among the polymeric combinations, the combination F5 was found to be most suitable. The formulation F5 comprising polymers HPMC and Ethyl cellulose in 1:1 ratios fulfill the requirement of good buccal patch. It showed good swelling as well as highest bioadhesive strength. It shows *in vitro* residence time up to 3 h. It follows *In vitro* drug release up to 90.61 % for 3 h and *In vitro* drug permeation up to 3 h.

Keywords: Buccal patch, Diclofenac sodium, Ethyl cellulose.

INTRODUCTION

Over the decades, controlled drug delivery and site-specific drug delivery have made rapid advances. Mucoadhesive systems now play a major role in this field, due to their interesting potentialities. Besides acting as platforms for sustained release dosage forms, mucoadhesive polymers can themselves exert some control over the rate and amount of drug release, and thus contribute to the therapeutic efficacy of mucoadhesive drug delivery system. Patches or films as dosage forms have gained relevance in the pharmaceutical area as novel, patient friendly, convenient and excellent accessible products. Due to the small size and thickness of buccal patches, they improved patient compliance, compared to tablets. Moreover, since mucoadhesion implies attachment to the buccal mucosa for extended period of time, patches can be formulated to exhibit a systemic or local action[1].

Buccal region is a part of the mouth bounded anteriorly and laterally by the lips and the cheeks, posteriorly and medially by the teeth and/or gums, and above and below by the reflections of the mucosa from the lips and cheeks to the gums. Maxillary artery supplies blood to the buccal mucosa and blood flow is faster and richer than that in the sublingual, gingival and palatal regions; thus facilitates passive diffusion of drug molecules across the mucosa. The thickness of the buccal mucosa is measured to be 500 - 800 µm and is rough textured, hence suitable for retentive delivery systems. The buccal mucosa has a surface lining consisting of non-keratinized squamous epithelium supported by a connective tissue lamina propria which has an abundant supply of blood and lymph vessels and beneath this is a thin layer of smooth muscle tissue. The primary function of the buccal epithelium is the protection of the underlying tissue. It is estimated that the permeability of the buccal mucosa is 4 - 4000 times greater than that of the skin.

Absorption of certain drugs across the oral mucosa provides a rapid onset of action, approaching that seen with intravenous administration. Additionally, oral mucosal drug delivery offers an alternative when enteral administration is impractical (e.g. in patients who have difficulty in swallowing, nausea or vomiting). Oral mucosal delivery is non-invasive and less intimidating for many patients compared with other routes of administration (e.g. intravenous and intramuscular) and elimination of the administered dosage form from the buccal area by natural clearance mechanisms is

possible. It offers an excellent route for the systemic delivery of drugs which undergo extensive first pass metabolism or degradation in the gastrointestinal environment. The oral mucosa is low in enzyme activity; hence, from the point of drug inactivation, the oral mucosal route would be preferred over the nasal or rectal routes[2].

MATERIALS AND METHODS

Materials

Diclofenac sodium was gift sample from Zim Laboratories, Kalmeshwar, Nagpur. Hydroxy propyl methyl cellulose was gift sample from Loba Pvt. Ltd., Mumbai. Ethyl cellulose was gift sample from Rohm Pharma, Mumbai. All other ingredients used throughout the study were of analytical grade and were used as received.

METHOD OF PREPARATION OF BUCCAL PATCH

Solvent casting method

The buccal patches of Diclofenac sodium were prepared by solvent casting method with HPMC in combination with polymer namely Ethyl cellulose with Polyethylene glycol as plasticizer.

Method of preparation of HPMC patches with copolymer

The Diclofenac sodium was weighed accurately and dissolved in suitable quantity of ethanol for 10-15 min on magnetic stirrer. After that, the suitable quantity of solvent dichloromethane was added. Then, the polymers (HPMC E15 and Ethyl cellulose) was weighed accurately and dissolved in solvents with stirring for 1-2 h on magnetic stirrer. Then polyethylene glycol was added as plasticizer and stirred for 30 min. Then mixture was poured on mercury in petri dish of suitable size and kept with inverted funnel on dish for overnight at room temperature. After 24 h, dried patches were obtained was taken out and stored on fused calcium chloride in a desiccator at room temperature for further use. The buccal patches of drug were prepared using polymer HPMC E15 in combination with Ethyl cellulose at 1:6, 1:8 drug: polymer ratio with Polyethylene glycol as plasticizer.

Table 1: Composition of various buccal patches

Formulation code	F1	F2	F3	F4	F5	F6
Diclofenac sodium (mg)	200	200	200	200	200	200
HPMC E15 (mg)	225	150	75	300	200	100
Ethyl cellulose (mg)	75	150	225	100	200	300
Ethanol (ml)	8	8	8	8	8	8
Dichloromethane ml)	8	8	8	8	8	8
Polyethylene glycol 400 (ml)	0.12	0.12	0.12	0.12	0.12	0.12

EVALUATION OF PREPARED BUCCAL PATCH

a) Physical appearance

The patches observed visually for their physical appearance such as color and transparency.

b) Surface texture

The surface texture of the patch was evaluated by simply touching the surface of the patch.

c) Mass uniformity

For the mass uniformity three patches from every formulation were taken and weighed individually on electronic balance. The average weights were calculated in table.

d) Thickness

Three patches of each formulation of different batches were selected randomly and the thickness of the each patch was measured at different places using screw guage. The average patch thickness and standard deviation performed in triplicate was computed in table.[3]

e) Folding endurance test

The folding endurance of the patch was determined by repeatedly folding one patch at same place till it broke. The number of times the patch could be folded at the same place without breaking gives the value of the folding endurance in the table.[4]

f) Surface pH

Considering the fact that the acidic or alkaline pH may cause irritation to the buccal mucosa; attempts were made to keep the surface pH as close as to that of the saliva. The pH values of all formulations were within the range of the salivary pH. No significant difference was observed in surface pH, consequently; these patches can be considered non-irritant to the

buccal cavity and could achieve patient complianceary pH (6-6.5).[5]

g) Drug content uniformity

Three patch units of each formulation were taken in separate 100 ml volumetric flasks, 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, diluted suitably and analyzed on a U. V. Spectrophotometer. The average of drug contents of three patches was taken as final reading.[5]

h) Swelling

The three patches were tested for each formulation. After determination of the original patch diameter, the sample was allowed to swell on the surface of an agar plate kept in an incubator (hot air incubator) maintained at 37°C. Measurement of the diameter of the swollen patch was done at 15 min intervals up to 75 min.[6]

i) *In vitro* bio-adhesion test

Fabrication of equipment

The equipment was fabricated in our laboratory and it was used for the determination of bioadhesive strength.

Procedure

A double pan physical balance was taken, both the pans were removed. The left pan was replaced with a thread, to which a Teflon block (A) was hung. Another Teflon block (B) was placed right below the suspended block upon the base of the balance merged in a beaker containing pH 6.8 phosphate buffer. The right pan was replaced with a lighter pan (C). The Teflon block (B) was intended to hold the mucosal tissue (D) of goat cheek pouch and it was placed in a beaker contained pH 6.8 buffer.[6]

j) *In vitro* residence time

The *in vitro* residence time was determined using USP disintegration apparatus. The disintegration medium was 900 ml of pH 6.8 phosphate buffer maintained at 37±2^{o}C. The segments of goat cheek mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three patches of each formulation were hydrated on one surface using phosphate buffer pH 6.8 and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The patch was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the patch from the mucosal surface was recorded (mean of triplicate) as given in table.[7]

k) *In vitro* buccal permeation study

The *in vitro* buccal permeation study of Diclofenac sodium through the goat buccal mucosa was performed using a Franz diffusion cell at 37.0±0.2°C. Goat buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments. The patch was placed on the mucosa, and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer (pH 6.8). The receptor compartment (15 ml capacity) was filled with phosphate buffer (pH 6.8), and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at 50 rpm. At predetermined time intervals, 0.5 ml sample was withdrawn and replaced with fresh medium and analyzed. The experiments were performed in triplicate, and average values were reported.[8]

l) *In vitro* drug release

In US Pharmacopoeia XXIII, rotating paddle method was used to study drug release from the buccal patch; 900 ml of phosphate buffer (pH 6.8) was used as the dissolution medium, at 37.0±0.5^{0}C, and a rotation speed of 50 rpm was used. One side of the buccal patch was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was put in the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at defined intervals and replaced with fresh medium. The samples were filtered through whatman filter paper and analyzed. The experiments were performed in triplicate, and average values were reported.[9]

m) Ageing

The optimized formulation F5 was subjected to accelerated stability testing. The ageing studies were conducted at 37^{o}C and 45^{0}C to investigate the effect of temperature on the drug content in formulation. Patches were packed in petri dish linked with aluminum foil and kept in an incubator maintained at 37.0±0.5^{0}C and 45.0±2.0^{0}C for 1 month. Changes in the appearance, drug content of the stored bioadhesive patches were investigated after 7, 14, 21, and 28 days. The data presented were the mean of three determinations.[10]

DISCUSSION

The present study aimed at preparing mucoadhesive buccal patches of Diclofenac sodium to improve its bioavailability by using different polymer in different concentration.

To assess any interaction between the drug and the polymer, FT-IR studies were performed. The data obtained suggested that there was no interaction between the drug and the polymer.

From the various lab scale methods available, solvent casting method was found convenient to prepare the buccal patches. Among various polymers tried, HPMC (E15) being selected as a base polymer while Ethyl cellulose were used in combination. To improve the flexibility and to avoid brittleness of the buccal patch, Polyethylene glycol was selected as plasticizer.

The prepared patches were subjected to various physicochemical characteristics.

The average weight of patch from each group of formulation was reported in Table 2 by using three patches for standard deviation. The weight of buccal patches ranges from 125.09±0.15 mg to 150.48±0.26 mg. Results indicated that formulation F5 having highest mass while formulation F2 having the least among the different formulations.

The thickness of the patches varied from 0.24±0.01 mm to 0.26±0.04 mm (Table 2). Formulation F5 having the highest thickness of 0.26±0.04 mm, because of F5 having highest mass among all formulations.

The folding endurance of the patches was measured manually and they were folded between 208±8.01 to 251±6.78 times without breaking or cracking (Table 2). It shows the flexibility of the patches. This test ensures that the prepared patches were suitable for large scale manufacture to produce long, continuous patch without breaking or tearing. The higher folding endurance was observed in the formulation F5.

The surface pH of all the patches exhibited almost uniformity in their values and they were found in between 6.31±0.07 to 6.42±0.09 indicating its compatibility with buccal pH (Table 2).

The drug content was estimated in all the formulations using standard method (Table 2). The drug content of all the patches was found to be uniform with low SD values, which indicates that the drug was distributed uniformly in all the patches.

Table 2: Physical evaluation of formulation f1-f6

Formulation	Surface texture	Mass uniformity (mg±SD)	Thickness (mm±SD)	Folding endurance (±SD)	Surface pH (±SD)	Drug content (mg±SD
F1	Smooth	125.55±0.30	0.24±0.01	208±8.01	6.34±0.06	49.71±0.15
F2	Smooth	125.09±0.15	0.25±0.02	235±3.58	6.32±0.12	49.56±0.09
F3	Smooth	125.15±0.42	0.24±0.01	241±4.75	6.35±0.11	49.80±0.21
F4	Smooth	150.42±0.32	0.25±0.03	223±4.57	6.31±0.07	49.38±0.22
F5	Smooth	150.48±0.26	0.26±0.04	251±6.78	6.33±0.24	49.81±0.14
F6	Smooth	150.06±0.25	0.25±0.01	216±7.15	6.42±0.09	48.92±0.27

Mean ± SD, n = 3

Any polymer with good swelling property is expected to be a good candidate for mucoadhesive application. When mucoadhesive comes in contact with aqueous medium they swell and form a gel. The rate and extent of water uptake by a polymer has been reported to be an important factor in determination of its relative mucoadhesive strength, uptake of water results in relaxation of originally stretched, entangled or twisted polymer chain resulting in exposure of all polymer mucoadhesive sites for bonding to occur. As the faster this phenomenon occurs, more rapidly will be the polymers adhering to its substrate. It was observed that there was proportionate increase in swelling of patch as the increased in concentration of polymer (Table 3).

Table 3: Swelling studies of buccal patches of diclofenac sodium

Formulation	Initial Diameter (cm)	Diameter after (min)					% Swelling (after 75 min)
		15	30	45	60	75	%
F1	3.0	3.1	3.1	3.2	3.3	3.4	13.33
F2	3.0	3.2	3.2	3.2	3.3	3.5	16.66
F3	3.0	3.0	3.1	3.2	3.3	3.4	13.33
F4	3.0	3.3	3.4	3.5	3.5	3.7	23.33
F5	3.0	3.2	3.3	3.5	3.6	3.8	26.66
F6	3.0	3.1	3.2	3.2	3.4	3.5	16.66

Mean ± SD, n = 3

The results for mucoadhesion indicated that the mucoadhesive strength of formulation F5 was more than the other formulations. Here, we conclude that, the HPMC base having good mucoadhesion properties in combination with Ethyl cellulose. As the concentration of Ethyl cellulose increases (1: 1 with HPMC E15), the mucoadhesive strength was found to increase, may be due to combination of hydrophilic and hydrophobic nature which gains the bond strength with mucosal surface. It can be seen that increasing the contact time for adhesion, increased the mucoadhesive force.

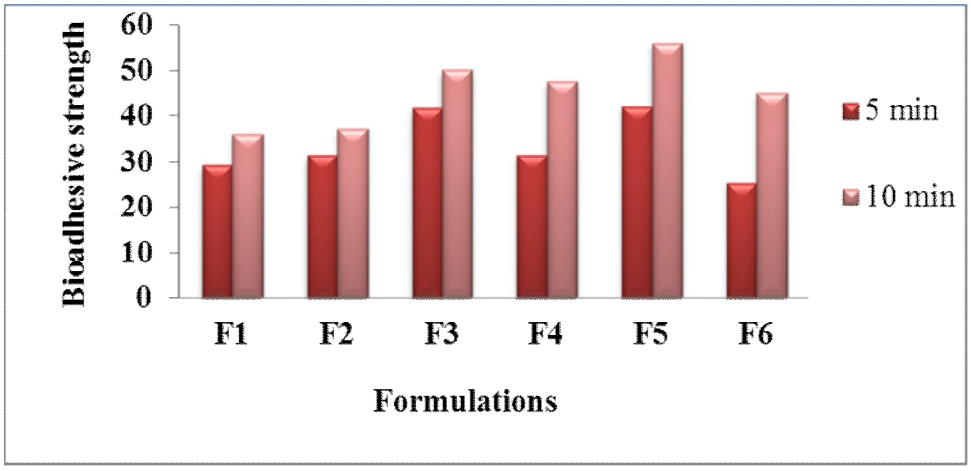

Fig. 1: Bioadhesive strength of formulation F1-F6

The values of the *in vitro* residence time were reported in the Table 4. Time required for the complete erosion or detachment of buccal patches from the mucosa was found satisfactory. The highest duration (2.32 h) was recorded for formulation F5. Patches of formulation F1; eroded completely in 2.06 h. This indicated that the water soluble hydrophilic additives dissolved rapidly introducing porosity. The void volume is expected to occupy by the external solvent diffusing into the patch and thereby accelerating the dissolution of the patch.

Table 4: *In Vitro* residence time (h) of formulation f1-f6

Formulation	Time (h±SD)
F1	2.06±0.14
F2	2.09±0.17
F3	2.16±0.23
F4	2.25±0.19
F5	2.32±0.42
F6	2.27±0.37

Mean ± SD, n = 3

Drug permeation from *in vitro* diffusion studies of formulation F1-F6 was indicated in Table 5. All the formulation F1-F6 follows Peppas model. Regression analysis of the *in vitro* permeation curves was carried out. The slope of the straight line obtained after plotting the mean cumulative amount diffused per patch Vs time was taken as the *in vitro* release for Diclofenac sodium. Formulation F5 has showed maximum release (91.89%) in 3 h and follows Peppas model and mechanism of release was non-fickian mediated with lowest diffusion coefficient.

Table 5: *In Vitro* buccal permeation of formulation f1-f6

Time (min)	Cumulative % drug release					
	Formulation					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	7.62±2.88	8.31±1.68	7.59±2.25	7.41±1.11	7.01±3.16	5.91±0.96
60	20.59±0.94	19.09±1.18	20.77±2.84	21.56±3.61	22.14±2.42	18.13±2.74
90	34.72±1.12	35.5±91.10	37.68±2.41	37.19±1.56	39.25±3.11	33.50±2.55
120	53.16±1.46	54.20±2.92	54.66±2.65	53.10±1.24	57.34±1.27	49.79±1.96
150	72.39±3.81	70.37±3.85	72.78±2.47	69.21±2.34	75.57±2.89	66.20±1.65
180	86.47±2.78	84.20±2.75	82.1±1.57	86.20±1.20	91.89±1.65	83.21±1.03

Mean ± SD, n = 3

All the formulations showed release up to 3 h. Formulation F5 showed maximum release (90.61%), while formulation F3 showed lowest release (81.76%). Formulation F5 has highest K Value (29.8957) and follows Peppas model rate release and mechanism of drug release was non-fickian mediated with lowest diffusion coefficient (0.6053). Hence, it was therefore chosen as an optimized formulation. Validation studies were performed for formulation F5.

The study of drug release kinetics showed that all the formulations F1-F6 were governed by Peppas model and mechanism of drug release was non-fickian mediated. Regression analysis of the *in vitro* permeation curves was carried out. The slope of the curve obtained after plotting the mean cumulative amount released per patch Vs time was taken as the *in vitro* release for Diclofenac sodium.

Table 6: *In Vitro* drug release of formulation f1-f6

Time (min)	Cumulative % drug release					
	Formulation					
	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
30	23.37±1.34	21.84±2.52	19.31±1.72	25.33±2.22	21.29±3.52	22.41±2.11
60	38.98±2.58	36.29±2.61	31.49±3.12	41.12±2.10	37.39±3.61	37.05±4.01
90	47.99±1.75	50.21±1.96	48.42±2.11	47.87±1.85	54.03±3.32	50.91±1.32
120	60.06±3.28	62.71±3.05	60.04±1.14	61.07±4.28	65.75±1.65	65.13±2.37
150	72.57±1.68	74.68±1.61	71.87±1.15	75.69±1.78	77.11±2.64	74.11±0.98
180	87.33±4.01	84.05±2.02	81.76±0.86	88.30±2.12	90.61±2.41	84.19±1.81

Mean ± SD, n = 3

Table 7: Kinetic assessments of buccal patches (f1-f6) containing diclofenac sodium

Formulation	Correlation coefficient (R) values				K value	Diffusion coefficient (n)
	Zero order	First order	Higuchi mattrixssss	Peppas model		
F1	0.9956	0.9569	0.8692	0.9933	22.2803	0.7541
F2	0.9950	0.9321	0.8750	0.9998	20.8540	0.7860
F3	0.9937	0.9352	0.8174	0.9961	18.8442	0.8731
F4	0.9926	0.9630	0.8814	0.9859	27.1882	0.6631
F5	0.9936	0.9233	0.8422	0.9986	29.8957	0.6053
F6	0.9912	0.9299	0.9988	0.8779	17.5623	0.8696

The stability studies were conducted for the optimized formulation F5 at 37°C and 45°C and results revealed that no significant changes in physical parameters of the formulations occurred at 37°C. No significant reduction in the drug content of patch over a period of one month at 37°C, but significant change was observed in the drug content when the patches kept at 45°C, which indicated that the temperature not exceeding 37°C essential to ensure the stability of the formulation.

The satisfactory results were shown for mass uniformity of patches when kept at 37°C, but varied at 45°C. The folding endurance was reduced significantly at 37°C and 45°C when kept for one month. That might be happened due to excess drying of dosage form which caused excess removal of moisture in absence of humidity.

For validation study formulation F5 was selected. All the five batches of formulation F5 were found to release the drug in 3 h. The

cumulative percentage release was found from 86.47% to 92.34 %. All five batches showed close similarity factor indicative of similarity in dissolution profile.

CONCLUSION

The mucoadhesive polymers can themselves exert some control over the rate and amount of drug release and thus contribute to the therapeutic efficacy of mucoadhesive drug delivery system. The buccal drug delivery bypasses the liver and avoids pre-systemic elimination in the GI tract and liver. The mucosa is relatively permeable with a rich blood supply. Six buccal formulations of HPMC were prepared along with co-polymer namely Ethylcellulose. Among the various polymeric combinations, the combination F5 was found to be most suitable. The formulation F5 comprising polymers HPMC and Ethyl cellulose fulfill the requirement of good buccal patch. It showed highest swelling as well as highest mucoadhesive strength. It shows *in vitro* residence time up to 2.32 h. It follows *In vitro* drug release up to 90.61 % for 3 h and *In vitro* drug permeation up to 3 h.

Thus, from the present study, it can be concluded that, mucoadhesive drug delivery system for Diclofenac sodium with HPMC and Ethyl cellulose meet the ideal requirement for buccal devices which can be good way to bypass the extensive hepatic first pass metabolism and increase bioavailability.

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