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Atenolol Buccal Patches: *Ex vivo* Evaluation

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ABSTRACT: Background: Buccal mucoadhesive systems among novel drug delivery systems have attracted great attention in recent years due to their ability to adhere and remain on the buccal mucosa and to release their drug content gradually. Buccal mucosdhesive patches can improve the drug therapeutic effect by increasing the drug absorption through buccal mucosa, increasing the drug bioavailability via reducing the hepatic first pass effect. **Aim:** The present study deals with the development and evaluation of buccal patches of Atenolol using isabgol husk mucilage with Hydroxyl Propyl Methyl Cellulose (HPMC K4M), Methyl Cellulose and backing membrane (Ethyl cellulose 6 % w/v). **Method:** The buccal patches were prepared by solvent casting technique. Prepared buccal patches were evaluated for average weight, thickness, drug content, folding endurance, surface pH and moisture content. **Result:** These evaluated parameters value were found satisfactory for all the prepared patches. *Ex vivo* Atenolol permeation from various Atenolol containing buccal patches showed that the drug permeated well across excised porcine buccal mucosa over a period of 24 h. **Conclusion:** Among all these formulated patches, maximum drug release (66.66 %) obtained with F1 buccal patches formulation and minimum drug release (50.47 %) obtained with F2.

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INTRODUCTIONS:

Recent focusing strategy in novel drug delivery system is the incorporation of drug dosage form in a specific region of the body for enhancing biological drug availability and reducing dose-dependent side effects [1,2]. Buccal delivery of drugs offers several advantages over other route of drug administration are relatively permeable with rich blood supply, excellent site for the absorption of drugs, facilitates a direct entry of drug molecules into the systemic circulation, avoiding the first-pass metabolism and drug degradation in the harsh gastrointestinal environment [3,4]. The buccal cavity is easily accessible for self medication, and hence it is safe

and well accepted by patients, since buccal patches can be very easily administered and even removed from the application site, terminating the input of drug whenever desired. Moreover, buccal patches provide more flexibility than other drug deliveries [5].

Atenolol is a β_1-receptor selective antagonist and therapeutically used in treating hypertension, angina, heart failure, and myocardial infarction. It is chemically, 4-(2-hydroxyl-3-isopropyl aminopropoxy) phenylacetamide. The Atenolol is slight water solubility, low molecular weight (266.336), and its elimination half-life ($t_{1/2}$ = 6 -7 h), make it a suitable candidate for administration by buccal route [6,7]. Thus an attempt was made to formulate and design Atenolol buccal patches.

MATERIALS AND METHODS:

Atenolol was procured as a gift sample from M/S. P.D.I.L, India. HPMC K4M, methyl cellulose and ethyl cellulose were obtained from Matrix Laboratories, India. Glycerin was purchased from Loba Chemie Pvt. Ltd., India. Isabgol husk *(Plantago ovate*) mucilage was isolated from the raw psyllium seeds.

Preparation of isabgol husk mucilage:

The isabgol husk mucilage (psyllium mucilage) is a white polysaccharide having sustained release properties obtained from the psyllium seeds of *Plantago ovate.* The psyllium seeds were mixed with 10 to 30 times their weight of water and allowed to stand for 24 h. The solution was then pressed through cloth and the mucilage was precipitated by adding double the quantity of 95 % ethanol. The precipitated material was dried in the oven at 40 °C, stored properly in controlled storage condition for further study [8,9].

Preparation of mucoadhesive buccal patches of Atenolol:

The buccal patches composed of different ratios of methyl cellulose, hydroxyl propyl methyl cellulose (HPMC K4M) and isabgol husk mucilage as containing Atenolol (~10 mg/cm^2 patches) were prepared using the 54 cm^2 petridish by solvent evaporation technique. Glycerin was incorporated as a plasticizer at a concentration of 15 % of dry weight of polymers. Backing membrane was casted by pouring and evaporating 6 % ethyl cellulose in 65: 35 acetone: isopropyl alcohol and 15 % of dry dibutyl phthalate of the polymer in room temperature for 12 h. Drug was transferred in different ratios of polymer and plasticizer mixture. The matrix was prepared by pouring 40 ml of the homogeneous solution on the backing membrane in a petridish and dried at 40 °C in the incubator. After 24 h the patch was removed from the petridish. The patch was dried at 37 ^{0}C for 1h. The dry patches were kept in desiccators until use [10,11].

Table 1. Formulation chart of Atenolol buccal patches.

FC	MC (mg)	HPMC (mg)	IHM (mg)	Drug (mg)	GL (%)	DW (ml)
F1	1000	-	-	50	15	40
F2	-	1000	-	50	15	40
F3	-		1000	50	15	40
F4	900		100	50	15	40
F5		900	100	50	15	40
F6	100		900	50	15	40

FC – Formulation code, MC- Methyl Cellulose, HPMC- Hydroxy Propyl Methyl Cellulose, IHM – Isabgul husk mucilage, GL – Glycerine and DW – Distilled water.

CHARACTERIZATION:

Measurement of average weight and thickness:

Six patches from each batch, as a whole (54 cm^2) were weighed individually, and the average weights were calculated. The thickness of these patches was assessed at six different points using thickness gauze (Mitutoyo, Japan). For each formulation, three randomly selected patches were used [12,13].

Determination of drug content:

The drug contents in each buccal patch were determined by dissolving 1 cm^2 of patches in 100 ml phosphate buffer saline (pH 6.8) and shaken vigorously for 24 h at room temperature. These solutions were filtered through Whatman® filter paper (No. 42). After proper dilution, optical density was measured spectrophotometrically using a UV–VIS spectrophotometer (UV-1700 Double beam spectrophotometer, SHIMADZU Corporation, Japan) at 274 nm against a blank. The drug content was estimated from the calibration curve, which was constructed between 1 and 5 µg/ml concentration ranges.

The method was validated for linearity, accuracy, and precision. The regression equation for the calibration curve was Y = 0.048 X + 0.002, R^2 value was 0.9990 [13,14].

Measurement of folding endurance:

The folding endurance was determined manually for the prepared buccal patches by repeatedly folding the film at the same place until it broke. The number of times the buccal patches could be folded at the same place without breaking or cracking gave the value of folding endurance [15].

Table 2. Weight variation, thickness and drug content studies of buccal patches formulations.

FC	WV (g) (X±SD)	Thickness (mm)(X±SD)	DC (%) (X±SD)
F1	2.063±0.056	0.62±0.03	97.8±0.63
F2	2.088±0.063	0.65±0.02	95.3±0.91
F3	2.101±0.059	0.67±0.05	93±0.86
F4	2.030±0.048	0.67±0.06	93±0.66
F5	2.019±0.044	0.66±0.05	96±0.82
F6	2.003±0.045	0.69±0.06	95.6±0.183

All values are represented as mean ± standard deviation. Standard error of mean < 0.525. FC – Formulation code, DC – Drug content, WV – Weight variation.

Determination of moisture content:

The buccal patches were weighed accurately and kept in desiccators containing anhydrous calcium chloride. After 3 days, the patches were taken out and weighed. The moisture content (%) was determined by calculating moisture loss (%) using the formula [16]:

Moisture content (%) = [(Wi–Wf)/Wi)]×100 ……..(1)

Where, Wi is initial weigh and Wf is final weight.

Table 3. Folding endurance, pH and moisture content studies of buccal patches formulations.

FC	FE (%) (X±SD)	Surface (pH)	MC (%)
F1	76	6.66±0.02	1.26±0.06
F2	84	6.52±0.01	1.31±0.09
F3	79	6.39±0.02	1.49±0.08
F4	78	6.33±0.03	1.45±0.08
F5	73	6.29±0.02	1.52±0.09
F6	80	6.33±0.01	1.59±0.06

All values are represented as mean ± standard deviation. Standard error of mean < 0.052. FC – Formulation code, FE – Folding endurance and MC – Moisture content.

Surface pH Study:

The surface pH of the prepared patches were determined by placing three patches of each formulation and allowed to swell for 2 h on the surface of an agar plate. The surface pH was measured by using a pH paper placed on the surface of the swollen patch. A mean of three readings was recorded [17].

***Ex vivo* studies:**

Preparation of porcine buccal mucosa:

The porcine buccal mucosa excised from porcine cheek pouch was obtained within 2 h of its death from the slaughter house and immediately transported to the laboratory in phosphate buffer solution. The buccal mucosa was separated from the full thickness of the tissue after immersion in distilled water and then in phosphate buffer saline, pH 6.8, at 37 ± 1°C for 2 min. The fatty layers were removed by scalpel, and the buccal mucosa was isolated from the underlying tissue. Finally, the mucosa was washed with phosphate buffer saline, pH 6.8 [18,19].

Statistical analysis:

Each parameter was studied in triplicate. All data are statistically verified using mean, standard deviation and standard error of mean [20].

RESULTS AND DISCUSSION:

The main goal of the research work was made to develop a new mucoadhesive bilaminated buccal patches of Atenolol using polymers like methylcellulose (MC), hydroxyl propyl methylcellulose (HPMC K4M), isabgol husk mucilage and ethyl cellulose (Table 1). The bilaminated drug delivery systems were designed as a matrix and the release was controlled by using polymeric rate controlling membrane. The physicochemical evaluation indicates (Table 1) the average weights of different formulations were found to be in the range of 2.0 ± 0.045 to 2.1 ± 0.059 g and the thickness of these films varied between 0.62 ± 0.03 to 0.69 ± 0.06 mm, of the thinnest being the formulation F1 and the thickest being the formulation F6 (Table 1). Good uniformity of distribution in drug content (%) among the batches was observed with all formulations and range from 93 ± 0.66 to 97.8 ± 0.63 % (Table 1). This indicates that the drug dispersed uniformly throughout the patch. Folding endurance was measured manually. The highest folding endurance was observed in case of F2 (84) and lowest, in case of F5 (73 %) as given in Table 2. The range of folding endurance study assured about its flexibility. The surface pH of the buccal patches varied between 6.29±0.02 to 6.66 ± 0.02 (Table 2). The surface pH of the buccal patches was

determined to optimize the drug release. The surface pH all formulations were close to the neutral pH and hence no mucosal irritation was expected and ultimately achieves patient compliance. The percentage of moisture content (%) of all the prepared Atenolol buccal patches was found to be within the range 1.26±0.06 to 1.59±0.06 % as shown in Table 2.

Table 3. *Ex vivo* drug permeation study of different Atenolol buccal patch formulations.

Time (h)	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0
1	1.1	0.2	0.8	0.8	1.1	0.9
2	2.1	1.6	1.7	1.8	1.9	1.8
3	3.2	3.6	3. 6	4.2	3.6	3.8
4	4.9	5.9	6.1	6.2	5.9	6.6
5	7.6	9.2	9.2	9.6	9.8	9.9
6	11.3	11.7	12.7	12.8	14.7	12.9
8	24.3	16.1	17.4	19.3	22.6	21.2
12	38.3	32.0	35.5	38.6	35.8	35.9
24	66.7	50.5	55.5	59.9	60.1	60.4

All values are represented as %.

The low moisture content well protects the patches from microbial contamination and also it gives stability from brittleness. The result of *Ex vivo* permeation study of Atenolol from the film is shown in Table 2 AND Fig 1. It was observed that formulation F1 shows highest release of 66.66 % and formulation F2 shows lowest release of 50.478 % for 24 h. Among 6 formulations, the release pattern is of the order of F1> F6> F5> F4> F3> F2. The drug release from the prepared films varied with respect to the polymer composition of films.

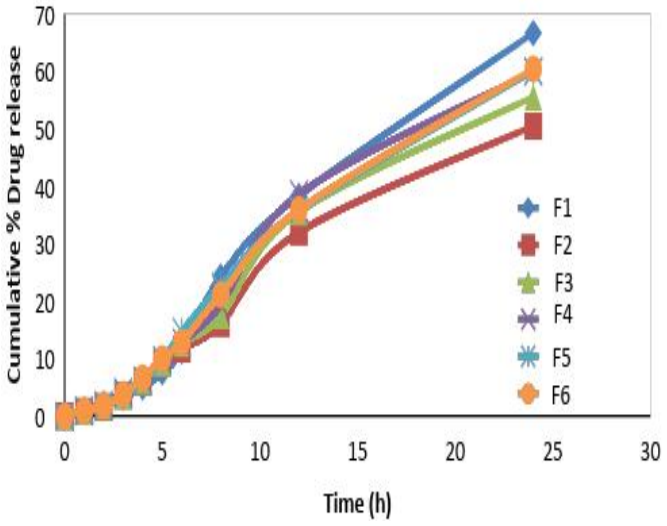

Fig. *Ex vivo* drug permeation comparative study of buccal patches formulations.

CONCLUSION:

The result of the study shows that feasibility for formulating new mucoadhesive bilaminated buccal patches of Atenolol using polymers like methyl cellulose, hydroxyl propyl methylcellulose, isabgol husk mucilage and ethyl cellulose. It could be concluded that the buccal patch formulation F1, containing methyl cellulose is the optimized buccal patch formulation as it shown maximum drug content and release, with good physico-chemical properties. The optimized formulation would be achieved maximum bioavailability. Thus this new mucoadhesive bilaminated buccal patch of Atenolol could be effectively used for safe and effective management of control and prophylaxis hypertension.

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