Research Article

Development and Evaluation of Buccal Patches containing Atenolol using Hydrophilic Polymers

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ABSTRACT

Buccal route of drug delivery is an attractive alternate to other conventional methods of systemic drug administration. It provides rapid and extensive drug absorption with bypassing fast pass metabolism, improving patient compliance, sustained drug delivery, ease of administration, significant reduction in dose and dosing frequency and increase bioavailability. The present investigation involves development and evaluation of atenolol containing buccal patches using various mucoadhesive polymers like xanthan gum, HPMC K4M, NaCMC in various proportions and combination prepared by solvent casting technique. Propylene glycol has been used as a plasticizer and tween 80 being a penetration enhancer. Atenolol is a β1- selective receptor antagonist used in the treatment of hypertension having t1/2 6-7 hours and undergoes hepatic first pass metabolism. Various physico mechanical parameters like weight variation, thickness, folding endurance, drug content, surface pH, moisture content, moisture absorption were evaluated. In vitro drug release study was carried out using commercial semi permeable membrane. All the prepared patches indicate sustained drug release profile for 24 hrs. Ex vivo drug permeation study was performed using goat buccal mucosa in Franz diffusion cell. The stability study of the optimized formulation F6 (atenolol-12.5 mg/cm 2, xanthan gum-125 mg, HPMC-125 mg, propylene glycol-10% w/w, tween 80 - 5%w/w) was performed according to ICH guidelines. The evaluation data revealed satisfactory physicomechanical characteristics. The drug content was found to be uniform in the range of 98.32 ± 0.13 (F1) to 99.66 ± 0.09 (F6) indicating uniformity with respect to drug content. The buccal patch formulation F6 having highest drug release (96.01%) and permeation (93.1%). Both in vitro drug release and ex vivo permeation study results indicate sustained drug release profile. The optimized buccal patch formulation was found to be stable with good surface morphology characteristics.

Keywords: Buccal Patches, Atenolol, Mucoadhesive, sustained release, *ex vivo* permeation.

INTRODUCTION

Increased research efforts have been made in recent years for placing a drug delivery system in a particular region of the body for increasing bioavailability and decreasing drug dependent side effects. Buccal drug delivery system acts as an attractive alternate to other conventional methods of systemic drug delivery. The well vascularised and large, smooth, immobile surface of buccal mucosa facilitates direct entry of drug in to the systemic circulation. The buccal route of drug delivery offers several advantages over other route of drug administration including: increasing bioavailability by bypassing the hepatic first pass metabolism and drug degradation in the harsh gastrointestinal environment that are often associated with oral route of drug administration, improved patient compliance due to elimination of associated pain with injections, sustained drug release, self medication, ease of terminating drug action by removing the patch from the buccal cavity when required and the more flexibility of the patch. Due to the ability to localize the dosage form in the specific regions of the body to enhance the bioavailability of drugs, in recent years mucoadhesive polymers drawn considerable attention as platforms for buccal delivery of drugs. [1,2]

Atenolol is a β1 selective receptor antagonist used widely in treating hypertension, heart failure, angina pectoris and myocardial infarction. Chemically, it is 4-(2-hydroxyl-3-isopropyl aminopropoxy) phenylacetamide. Its T_{max} is 2 to 4 hour and having short half life of 6 to 7 h. Atenolol is subjected to a very extensive first pass metabolism in the liver and having bioavailability only 40%. Atenolol have poor membrane permeability in the gastrointestinal tract due to its hydrophilic nature as it is sparingly soluble in water and low partion coefficient value of 0.23.The low molecular weight (266.336), low dose (25-50 mg), extensive first pass metabolism and short half life of atenolol makes it a suitable candidate for administration by the buccal route. The mucoadhesive polymers like xanthan gum, HPMC K4 M, NaCMC are release retardant polymers provide delayed release of drugs from buccal patches. [3]

The aim of the present research work was to develop and evaluate various buccal patch formulations containing drug (Atenolol), mucoadhesive polymers like xanthan gum, HPMC K4 M, NaCMC so that the prepared formulations possesses sustained drug release profile for prolonged periods with suitable mucoadhesive property that can be effectively used in the treatment of hypertension. Solvent casting technique was used to prepare the buccal patches .The drug free backing membrane composed of 6% ethyl cellulose to prevent back release of the drug from the prepared buccal patches[2, 3, 4].

MATERIALS AND METHODS

Materials

Atenolol was obtained from M/S. P.D.I.L, India. HPMC K4 M, NaCMC and ethyl cellulose were obtained from Matrix Laboratories, India. Xanthan gum was purchased from HiMedia Laboratories Pvt. Ltd. Mumbai, India. Propylene glycol was purchased from Burgoyne Burbides and Co., Mumbai, India. Dibutyl phthalate was obtained from Ranbaxy Laboratories, India. All other reagents used were of analytical grade.

Preparation of mucoadhesive buccal patches of atenolol

The mucoadhesive buccal patches composed of different ratios of xanthan gum, hydroxyl propyl methyl cellulose (HPMC K4M, Sodium carboxy methyl cellulose (NaCMC) and containing atenolol (~12.5 mg/cm^2 patches) were prepared using the 38 cm^2 petridish by solvent casting technique. Propylene glycol was incorporated as a plasticizer at a concentration of 10 % of dry weight of polymers. Backing membrane was casted by pouring and evaporating 6 % ethyl cellulose in acetone : isopropyl alcohol (65:35) and 10% w/w of dibutyl phthalate used as a plasticizer in room temperature for 12 h. Drug was transferred to the polymeric mixture containing different ratios of polymer and plasticizer and mixed thoroughly with magnetic stirrer. The matrix was prepared by pouring 25 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, before removing the patch was dried at 37 ^{0}C for 1h. The dry patches were cut into 1 cm^2, 2 and 4 cm^2 size, packed in aluminum foil and kept in desiccators until use. The formulation designs of atenolol buccal patches are represented in Table 1. [5, 6]

Table 1: Formulation design of atenolol buccal patches.

Formulations	Xanthan gum (mg)	HPMC K4M (mg)	NaCMC (mg)	Drug (mg/cm^2)	Propylene glycol (% w/w)	Tween 80 (%w/w)	Double distilled Water (ml)
F1	250	-	-	12.5	10	-	25
F2	250	-	-	12.5	10	1	25
F3	250	-	-	12.5	10	5	25
F4	125	125	-	12.5	10		25
F5	125	125	-	12.5	10	1	25
F6	125	125	-	12.5	10	5	25
F7	125	-	125	12.5	10		25
F8	125	-	125	12.5	10	1	25
F9	125	-	125	12.5	10	5	25

Characterization of atenolol buccal patches

Measurement of average weight and thickness

Three buccal patches from each batch, as a whole (38 cm^2) were weighed individually, and the average weights were calculated using digital balance. The thickness of these patches was measured at six different points using thickness gauze (Mitutoyo, Japan). For each formulation, three randomly selected patches were used. [7,8]

Determination of drug content

The drug contents of the buccal patches were determined by dissolving 1 cm^2 of patches in 100 ml phosphate buffer saline (pH 6.8) and shaken vigorously for 24 hours 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 = 0.9990. [4, 8]

Determination of folding endurance

The folding endurance was determined manually for the prepared buccal patches by repeatedly folding one patch at the same place till it broke or folded upto 300 times without breaking. The number of times the buccal patches folded at the same place without breaking or cracking gave the value of folding endurance. [8, 13]

Measurement of Surface pH

The surface pHs of the prepared atenolol buccal patches were determined to investigate the possibility of any side effect in the buccal cavity due to change in pH which may results in irritation to buccal mucosa. The surface pH was determined by placing each patch (1 cm^2) in a petridish and was allowed to swell in contact with 1 ml of distilled water for 2 h at room temperature and the pH was measured by bringing the electrode of the pH meter in contact with the surface of the patch and allowing it to equilibrate for 1 minute. The experiments were preformed in triplicate and a mean of three readings was recorded. [10]

Determination of moisture content

The atenolol 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: [10,13]

$$\text{Moisture content (\%)} = \frac{\text{Initial weight} - \text{Final weight}}{\text{Initial weight}} \times 100$$

Determination of percentage moisture absorption

The test was carried out to check the physical stability of the prepared buccal patches at high humid conditions. The present study focuses on the moisture absorption capacity of the buccal patches which was determined as follows. Three buccal patches of 1 cm^2 were weighed accurately and kept in a desiccator containing saturated solution of aluminium chloride, keeping 76% relative humidity inside the desiccator. After three days the patches were removed from desiccator, weighed and percentage moisture absorption was calculated using following formula; [12,13]

$$\text{Moisture absorption (\%)} = \frac{\text{Final weight - Initial weight}}{\text{Initial weight}} \times 100$$

In vitro release study

The in vitro release of atenolol buccal patches was carried out using Franz diffusion cell. The effective diffusion area was 1.74 cm^2. The receptor compartment (40 ml) was filled with phosphate buffer saline, pH 6.8, and its temperature was maintained at 37 ± 0.5°C. The patch was applied under occlusion on the cellophane membrane fitted between the donor and receptor compartments of the diffusion cell. A 50 rpm stirring speed was applied using a magnetic stirrer. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of atenolol released into the receptor medium was quantified by using UV–VIS spectrophotometer (UV-1700 Double beam spectrophotometer, SHIMADZU Corporation, Japan) at 274 nm against a blank. [2]

Preparation of goat buccal mucosa

The goat buccal mucosa excised from goat cheek pouch was obtained within 2 hours of its death from the slaughter house and immediately transported to the laboratory in phosphate buffer solution saline, pH 6.8. 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. [10]

***Ex vivo* permeability study**

The extent and rate of mucosal permeation of atenolol through the goat buccal mucosa were carried out using Franz diffusion cell. The effective diffusion area was 1.74 cm^2. The receptor compartment (40 ml) was filled with phosphate buffer saline, pH 6.8, and its temperature was maintained at 37 ± 0.5°C. The buccal mucosa was mounted between the donor and receptor compartment of the diffusion cell. Over which the buccal patch was placed. A 50 rpm stirring speed was applied using a magnetic stirrer to simulate buccal cavity environment. Five milliliters of the sample from receptor medium was withdrawn at regular intervals and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The amount of atenolol released into the receptor medium was quantified by using UV–VIS spectrophotometer (UV-1700 Double beam spectrophotometer, SHIMADZU Corporation, Japan) at 274 nm against a blank. [2,10]

Stability Studies

The atenolol buccal patch formulation having best drug content, drug release profiles both *in vitro* and *ex vivo* subjected to stability test. Formulation was stored in borosilicate glass bottles, flushed with nitrogen, and kept in stability chamber at 40 °C /75% RH for a period of six months. A known amount of sample from the formulations subjected to stability testing was analyzed at pre determined time intervals for the drug content, *in vitro r*elease and *ex vivo* permeation through the goat buccal mucosa. [10]

RESULTS AND DISCUSSION

The present research work was an attempt to develop and evaluate atenolol (an anti hypertensive drug) buccal patches containing drug in a mucoadhesive polymeric layer of xanthan gum, HPMC K4M, NaCMC and a drug free backing membrane composed of 6% ethyl cellulose using solvent casting technique.

Average weight and thickness

The atenolol containing buccal patches as a whole (38 $cm^{2)}$ were taken for measurement of average weight using a digital balance and found to be varied in the range

of 1.63±0.06 g (F1) to 1.76±0.04 g(F8).The thickness was measured using thickness gauze in the range, 0.51 ± 0.06 (F6) to 0.58± 0.05 (F8) (Table-2).

Drug content

The drug content uniformity of the prepared buccal patches was determined in 1 $cm^{2\ of}$ each buccal patch. The drug content of the Buccal patches found in the range of 98.32 ± 0.13 (F1) to 99.66 ± 0.09 (F6) indicating uniformity with respect to drug content (Table-2).

Folding Endurance

The folding endurance of the atenolol buccal patches was measured manually. Folding endurance was measured to be highest with F6 (92) and lowest with F7 (81) (Table-2).The folding endurance study signifies flexibility of the prepared buccal patches.

Surface pH

The surface pH of the atenolol buccal patches was determined to optimize both drug permeation and mucoadhesion. Since an acidic or alkaline pH may cause irritation to the buccal mucosa. In the present study attempt has been made to keep the surface pH as close to the buccal/salivary pH as possible by the proper selection of the polymers for developing the buccal patches. The surface pH of the buccal patches was found in the range of 6.26±0.01 (F7) to 7.0±0.02 (F1) (Table-2) (Close to buccal pH). Hence they may not produce any local irritation to buccal mucosa.

Table 2: Physico-chemical parameters

FC	Weight variation(g) (X± S.D.)	Thickness (mm) (X± S.D.)	Drug Content (%) (X± S.D.)	Folding endurance (X± S.D.)	Surface pH (X± S.D.)
F1	1.63±0.06	0.52 ± 0.03	98.32 ± 0.13	84	7.0 ±0.02
F2	1.64±0.03	0.54 ± 0.02	99.06 ± 0.11	85	6.86 ±0.01
F3	1.66±0.09	0.53 ± 0.05	98.85 ± 0.06	82	6.79±0.02
F4	1.68±0.08	0.53 ± 0.06	99.48 ± 0.09	86	6.55±0.03
F5	1.69±0.04	0.52 ± 0.05	99.36 ± 0.12	89	6.59±0.02
F6	1.65±0.05	0.51 ± 0.06	99.66 ± 0.09	92	6.69±0.01
F7	1.73±0.06	0.56 ± 0.06	98.91± 0.12	81	6.26±0.01
F8	1.76±0.04	0.58± 0.05	99.19± 0.10	83	6.41±0.01
F9	1.74±0.06	0.55 ± 0.03	99.16± 0.10	82	6.36±0.03

FC-Formulation code, n=3

Determination of percentage moisture content and percentage moisture absorption

The moisture content (%) and moisture uptake (%) of different atenolol buccal patches were carried out to check the physical stability of the patches at high humid conditions and patch integrity at dry conditions. The moisture content (%) of all the atenolol buccal patches were found to be within the range of 1.31±0.01 %(F6) to 1.71±0.03 % (F9) and moisture uptake (%) study results found in the range of 5.41 ±0.01 % (F6) to 7.12±0.02 % (F7) (Table-3).The study reveals that the moisture uptake of the patches was found to be increased with the more hydrophilic nature of the polymers. The low moisture content protects them well from microbial contamination and also provides stability from brittleness.

Drug-polymer compatibility study

The drug-polymer compatibility of the prepared buccal patches was analyzed by FTIR spectroscopy. The FTIR spectra of F-6 atenolol-containing buccal patch and the pure drug (atenolol) are presented in Fig. 1. The FTIR spectrum of pure atenolol showed various characteristic peaks of atenolol like at 3305 and 1416 cm^{1} due to -O-H, at 1337 cm^{1} due to -CH3, and at 1036 and 1242 cm^{1} due to -N-C, as expected. All these characteristic peaks of pure atenolol appeared in the spectra of the F-6 atenolol-containing buccal patch without or with very minute shifting, indicating that there was an absence of any chemical interaction between the drug (here atenolol) and the excipients used. The intensity of the peaks of pure atenolol was diminished due to the molecular dispersion of the atenolol in the polymer matrix of the buccal patch.

Table 3: Moisture content (%) and Moisture uptake (%) of different atenolol buccal patches

Formulations	Moisture content (75 % RH)	Moisture uptake (%) (76%RH)
F1	1.49±0.03	6.86±0.04
F2	1.44±0.01	6.49±0.05
F3	1.46±0.06	6.63±0.01
F4	1.33±0.08	5.56±0.06
F5	1.36±0.02	5.43±0.08
F6	1.31±0.01	5.41±0.01
F7	1.69±0.05	7.12±0.02
F8	1.66±0.01	6.93±0.01
F9	1.71±0.03	6.68±0.03

All values are expressed as mean ± S.D., n=3

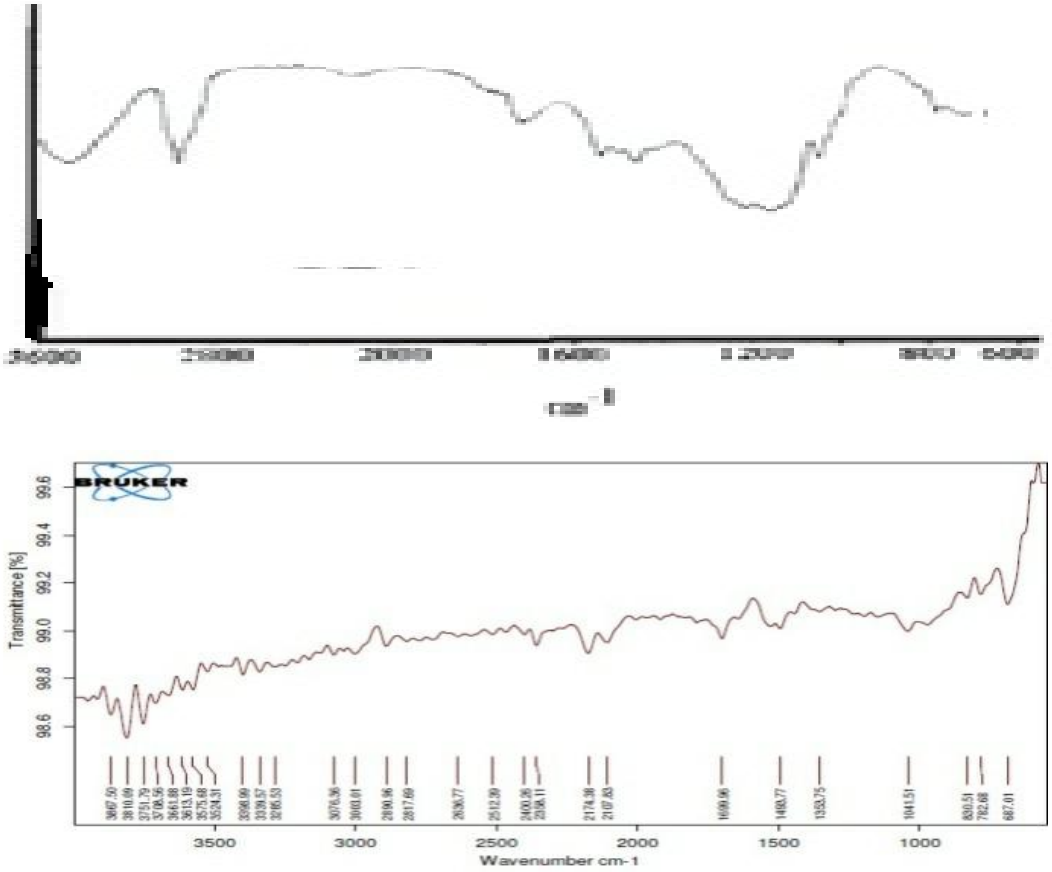

Figure 1: FTIR study of pure drug (Atenolol) and Formulation (F6)

Table 4: *In vitro* drug release study of different Atenolol buccal patch formulations.

Time(h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
	(%CDR)	(%CDR)	(%CDR)	(%CDR)	(%CDR)	(%CDR)	(%CDR)	(%CDR)	(%CDR)
0	0	0	0	0	0	0	0	0	0
0.5	6.6	8.1	8.2	8.7	9.04	9.1	6.7	6.8	7.1
1	15.8	17.8	18.8	18.8	20.4	20.9	14.5	16.2	16.5
2	23.1	25.0	26.8	25.4	27.6	28.07	20.2	23.3	25.3
3	31.2	32.7	34.0	31.8	34.6	35.6	27.3	29.7	33.02
4	37.9	39.7	42.7	37.5	39.8	42.8	33.3	34.2	37.4
5	45.2	48.8	50.1	43.6	44.7	49.2	38.7	40.5	42.5
6	51.4	55.1	57.2	49.2	51.1	54.6	43.02	45.1	47.5
8	56.7	61.2	64.2	54.4	58.06	60.9	48.5	51.3	55.7
12	68.2	71.9	73.5	67.1	70.3	75.3	58.07	62.1	65.3
24	84.5	86.3	89.8	89.6	92.1	96.01	86.76	88.3	92.05

%CDR- % Cumulative Drug Release

***In vitro* release studies**

The *in vitro* release data and profile of atenolol buccal patches are shown in Table 4 and Fig.2. Among the various formulations highest *in vitro* drug release was observed in formulation F6 (96.01 %) over a period of 24 hours while the lowest *in vitro* drug release with formulation F1 (84.5%) in 24 h. It was cleared from the table and graph that the drug release was governed by polymer content. Among nine formulations *in vitro* drug release is in the order of F6>F5>F9>F3>F4>F8>F7>F2>F1.The drug release in case of xanthan gum formulations was rapid up to 6 hours after that the formulations follows sustained release profile. As the concentration of xanthan gum decreases and incorporation of HPMC and NaCMC results in more sustainable drug release profile. The addition of tween-

80 as permeation enhancer increases the drug release profile significantly.

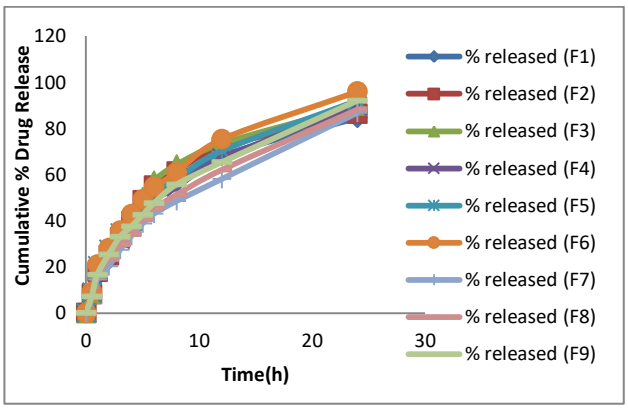

Figure 2: *In vitro* drug release comparative study of Atenolol buccal patch formulations

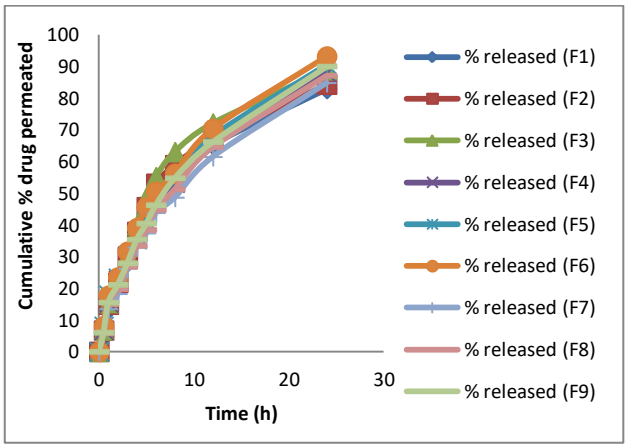

Figure 3: Ex *vivo* drug permeation comparative study of Atenolol buccal patch formulations.

Table 5: *Ex vivo* drug permeation study of different Atenolol buccal patch formulations.

Time(h)	F1	F2	F3	F4	F5	F6	F7	F8	F9
	(% CDP)	(%CDP)	(%CDP)	(%CDP)	(%CDP)	(%CDP)	(% CDP)	(%CDP)	(%CDP)
0	0	0	0	0	0	0	0	0	0
0.5	4.8	6.6	6.7	6.7	8.08	8.1	5.737548	5.8	6.0
1	13.5	14.8	15.3	15.3	17.9	17.7	13.48659	15.05	15.5
2	20.7	21.8	22.5	22.5	23.2	23.4	18.24713	19.7	21.1
3	28.2	29.8	30.3	30.3	29.6	31.5	26.24521	26.8	27.9
4	35.5	37.8	39.9	36.5	35.3	39.03	32.92146	33.4	35.4
5	42.8	45.6	48.7	42.8	41.2	45.5	37.37548	38.4	40.4
6	49.2	53.03	55.1	47.9	47.6	50.4	43.81226	44.7	46.2
8	54.09	58.9	63.02	53.1	54.6	56.1	48.63985	51.2	54.7
12	65.2	67.2	72.04	66.8	68.04	70.3	61.4751	64.5	66.2
24	82.9	84.3	88.8	87.9	90.6	93.1	84.81801	87.1	90.0

%CDP- %Cumulative Drug Permeated

***Ex vivo* permeation**

The ex vivo permeation study of atenolol from various buccal patches is shown in Table 5 and Fig.3. From the nine formulations it was observed that the maximum ex vivo drug permeation was 93.1 % over a period of 24 hours in case of formulation F6, while the minimum ex vivo drug permeation was found to be 82.9 % in case of formulation F1 in 24 h. The *ex vivo* permeation of atenolol from the buccal patches are in the order of F6>F5>F9>F3>F4>F8>F7>F2>F1. The drug permeation was slow and steady. The results of ex vivo permeation study reveals that drug easily permeate through the excised goat buccal mucosa during a period of 24 h and could possibly permeate through the human buccal membrane.

Stability Studies

Table 6: Stability study of formulation F6 for six months.

Time	Drug content (%)	%Drug release	Cumulative %drug permeation
Initial	99.65 ± 0.13	96.0± 4.8	93.0± 5.1
1 Month	98.19± 0.13	94.4± 5.2	92.2± 5.3
3 Month	98.03± 0.13	92.8± 4.9	90.6± 4.8
6 Month	97.31± 0.10	92.2± 4.5	89.5± 4.3

All values are expressed as mean ± S.D., n=3

Among all the atenolol buccal patch formulations, the optimized formulation F6 (atenolol-12.5 mg/cm ^{2}, xanthan gum-125 mg, HPMC-125 mg, propylene glycol-10% w/w, tween 80-5% w/w) having highest drug content, best drug release profile both *in vitro* and *ex vivo*, was subjected to stability test. The formulation F6 was stored in borosilicate glass bottles, flushed with nitrogen, and kept in stability chamber at 40°C / 75% RH for a period of six months. A known amount of sample from the formulations subjected to stability testing was analyzed at pre determined time intervals for the drug content, *in vitro r*elease and *ex vivo* permeation through the goat buccal mucosa. The result of the stability study indicates no significant change in drug content, *in vitro* drug release and *ex vivo* drug permeation.

Surface morphology

Figure 4: SEM study of formulation F 6

The SEM photographs of the optimized atenolol containing buccal patch formulation, F 6 (Fig.4.) indicates a nearly smooth surface and good lamination of the mucoadhesive polymers like xanthan gum, HPMC on the ethyl cellulose backing layer. It shows uniform dispersion of polymeric solution with the drug molecule and confirms perfect binding between the drug containing mucoadhesive layer and the adhesive layer of backing membrane.

CONCLUSION

From the results of the present research work it can be concluded that the atenolol containing mucoadhesive buccal patches made up of mucoadhesive polymers like xanthan gum, HPMC K4M and sodium CMC were found to be satisfactory in different evaluation parameters. The formulations indicate well lamination with the drug free backing layer (6% ethyl cellulose).The buccal patch formulation, F6 (atenolol-12.5 mg/cm^2, xanthan gum-125 mg, HPMC-125 mg, propylene glycol-10% w/w, tween 80 -5%w/w) was found to be best optimized formulation as it possessed good physicochemical properties, excellent drug content and best drug release and permeation profile. The optimized formulation was being confirmed as it was found to be stable in various storage conditions as per ICH guidelines. The investigation indicated a new buccal patch formulation for controlled release of atenolol formulated using mucoadhesive polymers. Thus it could be concluded that the new buccal patches of atenolol are very promising in effective control of hypertension for prolonged period of time by bypassing the extensive hepatic fast pass metabolism.

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