Research Article

Development and Evaluation of Atenolol Containing Mucoadhesive Buccal Patches

Surya Narayan Ratha Adhikari*, Satyabrata Panda
Department of Pharmaceutics, Seemanta Institute of Pharmaceutical Sciences, Mayurbhanj, Odisha, India.
***Corresponding author's E-mail:** snarayan.rath@gmail.com

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ABSTRACT

Among various routes available for drug administration the buccal route is an appealing substitute for drug delivery because of rapid drug absorption, enhance bioavailability of drugs that are more prone to degrade by extensive hepatic first pass metabolism and increase patient compliance. The main aim and objectives of the present investigation is development and evaluation of Atenolol containing mucoadhesive buccal patches with varying ratios of hydrophilic polymers like HPMC K4M, fenugreek seed mucilage (FSM) and tamarind seed polysaccharide (TSP) fabricated by solvent casting technique. Glycerine in 10 % w/w has been used as a plasticizer. Atenolol is β1- selective receptor antagonists widely employed in treating hypertension with t1/2 6-7 hours and suffer from hepatic first pass effect resulting reduced bioavailability of 40%. The prepared buccal patches were evaluated for various physicomechanical parameters like average weight, thickness, folding endurance, drug content, surface pH, moisture content, moisture absorption, % swelling and ex vivo mucoadhesion studies. The evaluation data demonstrated satisfactory physicomechanical properties. Ex vivo drug permeation study was conducted with goat buccal mucosa in Franz diffusion cell. All the buccal patch formulations of Atenolol exhibited sustained manner drug permeation for 24 hrs ex vivo. The ex vivo study results revealed that drug permeation is dependent on concentration and involves non-Fickian diffusion. The FT-IR study confirms absence of interaction between drug and polymers. The best buccal patch formulation F-2 (Atenolol- 25 mg/cm2, HPMC K4M- 100 mg, fenugreek seed mucilage-700 mg, glycerine-10 % w/w) was found to possess good surface morphology characteristics.

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

INTRODUCTION

The phenomenon of attachment between two materials (Natural/Synthetic) one of which is a biological surface by interfacial forces for extended period of time is depicted as bioadhesion. Although the oral route is the most convenient and appreciated route of drug administration by clinicians and patients, however the difficulties associated with the oral route such as presystemic metabolism, drug degradation in the gastrointestinal environment, poor bioavailability of certain group of drugs necessitate the development of some other non invasive route like buccal, transdermal, rectal, inhalation route of drug administration. The drug administration through the mucosal surface present on the inner surface of the cheek is known as buccal drug delivery system. [1, 2, 3]

The buccal route is preferred over other noninvasive routes such as transdermal, rectal, inhalation on the basis of following reasons: The transdermal route can also bypass the first pass metabolism like buccal route but suffering from a less drug penetration through the skin because the skin permeability is about 4 to 4000 times less than that of the buccal mucosal permeation. The rectal route of administered drugs such as suppositories suffers from 50 % of a rectal dose can be assumed to bypass liver due to the extensive anastomoses between the superior and middle hemorrhoid vein. In inhalation route although the hepatic first pass metabolism is prevented but the lungs also serve as a site for presystemic metabolism by excretion.[4]

Buccal patches are described as semi solid buccal preparations with laminates which comprise an impermeable backing layer that controls the direction of drug release and a drug-containing reservoir layer that releases the drug in a controlled manner having bioadhesive surface for mucosal attachment, administered to the inner lining of the cheek. Buccal patches are preferred because of several advantages over other buccal dosage forms such as buccal tablets, buccal gels and ointments. Buccal patches provide more flexibility and comfort than buccal tablets. The patches provide drug release for extended period of time in a controlled manner in comparison to oral gels and ointments which are having a less residence time in the buccal cavity as they are washed away and removed easily by the saliva. Therefore oral gels and ointments can't be suitable for drug release for prolonged period of time and thus lacks patient acceptability.[5, 6, 7]

The main aim and objectives of the present investigation was to develop and evaluate various mucoadhesive buccal patch formulations of Atenolol as drug candidate with mucoadhesive polymers like HPMC K4M, fenugreek seed mucilage (FSM), tamarind seed polysaccharide (TSP), so that the prepared formulations provide unidirectional drug release with sustained manner for prolonged periods and satisfactory physicomechanical properties to treat hypertension effectively.

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An ideal buccal patch formulation must possess following three properties:

(A) Maintaining its position in the buccal cavity for a few hours: the requirement was fulfilled in our investigation by the use of appropriate mucoadhesive polymers that establishes a strong adhesive contact to mucosal surface. (B) A controlled manner drug release profile: this is achieved by using mucoadhesive polymers that are able to control drug release for prolonged period of time. (C) Drug release must be unidirectional towards the buccal mucosa: the requirement can be accomplished by preparing a system having uniform adhesiveness and an impermeable backing membrane.[8, 9, 10]

Atenolol is a β1 selective receptor blocker employed widely in the treatment of hypertension, heart failure, angina pectoris and myocardial infarction. Atenolol is sparingly soluble in water, oral dose per day- 25 mg to 100 mg, having short half-life of 6 to 7 h and bioavailability only 40 %. The low dose, extensive first pass metabolism, short half-life and less oral bioavailability of Atenolol enables it a suitable candidate for administration by the buccal route.[11]

MATERIALS AND METHODS

Materials

Atenolol was a gift item from M/S. P.D.I.L, India. HPMC K4 M, and ethyl cellulose were purchased from Matrix Laboratories, India. Fenugreek (*Trigonella foenum-graecum L.*) seed mucilage was extracted from the raw fenugreek seeds. Tamarind seed polysaccharide was obtained from Tamarind (*Tamarindus indica)* seeds. Glycerine was purchased from Loba Chemie Pvt. Ltd., India. Ethyl cellulose was obtained from Matrix Laboratories, India. Dibutyl phthalate was purchased from Ranbaxy Laboratories, India. All other reagents used were of analytical grade.

Extraction of fenugreek seed mucilage (FSM)

Fenugreek seed mucilage was extracted by soaking 250 g washed fenugreek seed in 2000 ml of double distilled water for overnight at room temperature. The seeds were then boiled with double distilled water on a water bath with stirring to form a slurry. The slurry was then separated from the seeds by straining and kept in a refrigerator for overnight to settle down the un-dissolved material. The upper clear solution was then decanted off and centrifused at 1000 rpm for 30 minutes. The supernatant was then separated and concentrated at 50-55 °C on a water bath to reduce the volume to one third. The resulting solution was cooled to room temperature and poured into equal volume of acetone by stirring. The precipitate was washed three to four times with acetone and dried in the oven at 40 °C for 24 h. The dried mucilage was then powered and stored in desiccator until use.[12, 13]

Extraction of tamarind seed polysaccharide (TSP)

Tamarind seeds are soaked in hot water to peel out the outer cover. The seeds are then gently crushed and 200 g of powdered seed was soaked in double distilled water for 24 h to prepare slurry. The slurry was poured into 800 ml boiling distilled water for 20 minutes on a water bath to obtain a clear solution and the clear solution and was stored overnight. The thin clear solution was then centrifuged at 6000 rpm for 20 minutes to separate all the foreign matter. Then the supernatant was separated and poured into double volume of 95% ethanol with continuous stirring. The precipitate was dried in the oven at 40 °C for 12 h. The dried tamarind seed polysaccharide was powdered and stored in desiccator until use.[14, 15]

Preparation of buccal patches of Atenolol

Table 1: Formulation design of Atenolol buccal patches

Formulation Code	Atenolol (mg/cm²)	HPMC K4M (mg)	FSM (mg)	TSP (mg)	Glycerine (% w/w)	Double dist.water
F-1	25	700	100	-	10	30
F-2	25	100	700	-	10	30
F-3	25	400	400	-	10	30
F-4	25	700	-	100	10	30
F-5	25	100	-	700	10	30
F-6	25	400	-	400	10	30

HPMC- Hydroxy propyl methyl cellulose, FSM- Fenugreek seed mucilage, TSP- Tamarind

Seed polysaccharide.

Several buccal patch formulations of Atenolol were fabricated by solvent casting technique using a blend of mucoadhesive polymers such as hydroxy propyl methyl cellulose (HPMC K4M), fenugreek seed mucilage (FSM) and tamarind seed polysaccharide (TSP). Glycerine 10 % was incorporated as plasticizer. The backing membrane was developed by pouring 15 ml of 6 % ethyl cellulose in acetone: isopropyl alcohol (65:35) using 10% w/w of dibutyl phthalate as a plasticizer in a 54 cm^2 petridish and evaporated in room temperature for 12 h. The mucoadhesive polymeric mixture in varying concentration was prepared by transferring the required quantity of polymeric combinations into a beaker containing 30 ml of

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double distilled water by continuous stirring with a gentle heat for fenugreek seeed mucilage containing buccal patches. Drug (~25 mg/cm ^{2} patches) was transferred to the polymeric mixture with continuous stirring. To the polymeric drug solution glycerine was incorporated in 10 % w/w and mixed thoroughly with magnetic stirrer. The matrix was prepared by pouring 30 ml of the homogeneous solution in a 54 cm^2 petridish containing backing membrane 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 and 2 cm^2 sizes, packed in aluminum foil and stored in desiccator until use. The formulation designs of Atenolol buccal patches are represented in **Table 1**. [16]

Characterization of Atenolol buccal patches

Drug-polymer compatibility study

The compatibility study between drug (Atenolol) and various mucoadhesive polymers was carried out in FT-IR spectrophotometer employing KBR pellet. All the spectra were recorded in the range of 500 cm^{-1} to 3500 cm^{-1}.[16]

Determination of average weight and thickness

The buccal patch formulations as a whole (54 cm^2), were individually weighed employing a digital balance and the average weights were calculated. Thickness gauze was used for measurement of thickness of the three randomly selected patches for each formulation at six different points. [17]

Measurement of folding endurance

The folding endurance of the prepared buccal patch formulations can be measured manually by folding repeatedly one patch at the same place till it broke or folded up to 300 times without breaking. The folding endurance value is the number of times the buccal patches folded at the same place without breaking or cracking.[18]

Determination of drug content

For determination of drug content 1 cm^2 of Atenolol buccal patch formulations were dissolved in 100 ml of phosphate buffer saline (pH 6.8) and agitated at room temperature for 24 hours. After 24 hours the solutions were filtered through Whatman® filter paper (No. 42) and the optical density was measured by UV–VIS spectrophotometer (UV-1700 Double beam spectrophotometer, SHIMADZU Corporation, Japan) at 274 nm against a blank. The drug content was determined from the calibration curve, which was formulated between 1 to 5 µg/ml concentration ranges The regression equation for the calibration curve of Atenolol was Y = 0.048 X + 0.002, R^2 = 0.9990. [19]

Measurement of surface pH

The surface pH of the prepared buccal patch formulations of Atenolol were determined to conduct an investigation about the possibility of any side effect in the buccal cavity results from change in pH which may cause irritation to the surface of buccal mucosa. The surface pH was measured by placing each patch (1 cm^2) in a petridish containing 1 ml of distilled water and was allowed to swell for 2 h at room temperature and the pH was quantified by bringing the electrode of the pH meter in contact with the surface of the swellen patch and was allowed to equilibrate for 1 minute. The experiments were preformed in triplicate and a mean of three readings was reported. [20]

Measurement of moisture content

For determination of moisture content, the prepared buccal patches were accurately weighed and stored in a desiccator comprising anhydrous calcium chloride. The buccal patches were removed from the desiccator after 3 days and reweighed. The percentage moisture content was determined by calculating moisture loss (%) applying the formula: [21]

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

Determination of percentage moisture absorption

To examine the physical stability of the different buccal patch formulations of Atenolol the percentage moisture absorption test was conducted. For determining the moisture absorption capacity of the prepared buccal patch formulations, three 1 cm^2 buccal patches of each formulation were cut out, weighed accurately and placed in a desiccator comprising saturated solution of aluminium chloride, maintaining 76% relative humidity inside the desiccator. The buccal patches were taken out from the desiccator after 3 days, reweighed and percentage moisture absorption was calculated by applying the formula:[22]

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

Measurement of bioadhesive strength

Mucoadhesion is known as a state in which two materials one of which is a biological one are held together for extended period of time by interfacial forces. Mucoadhesive strength is the weight in gram required to separate the buccal patch from the buccal mucosa. A modified physical balance was employed for measurement of mucoadhesive strength. The two pans of physical balance were removed. The right pan was displaced with a lighter base and the left side having a Teflon ring held with a copper wire. A Teflon cylinder

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was hanged with a copper wire on the opposite side of the ring. The height of the total framework was arranged to accommodate a glass beaker in between. The two sides were then balanced so that the right hand side was exactly 5 grams heavier than the left. The excised goat buccal mucosal tissue was washed with saline phosphate buffer, pH 6.8 and was tied tightly with the mucosal side upward over the protrusion in the Teflon block. The block was then lowered in to the glass container containing phosphate buffer saline pH 6.8, so that the buffer solution just get in contact with the mucosal surface and maintains it moist. The buccal patch formulation of 2 cm2 area was moistened with 1 ml of phosphate buffer saline pH 6.8 for initial hydration and swelling. The hydrated buccal patch formulation was brought into contact with the mucosal membrane by uplifting the cylinder. In this position the balance was maintained for 3 minutes and then weights were increased slowly on the right pan until the patch was separated from the mucosal surface. A weight of 5g was deducted from the total weight which was the required weight for detachment of patch from the mucosal surface noted as mucoadhesive strength of the buccal patch. At the end of each experiment the mucosal membrane was gently and thoroughly washed with phosphate buffer saline, pH 6.8 and left for 5 minutes before the next measurement. A broken mucosal tissue should not be used for conducting the experiment and for each formulation fresh mucosal membrane must be used. For each formulation the experiment was repeated 3 times and the mean value was reported. [23, 24, 25]

Swelling index study

The swelling index of different buccal patch formulations were measured by the consequence of increase in weight results from swelling. For investigation of swelling index the drug loaded patches (n=3) of 1×1 cm were accurately weighed and kept in a petridish comprising 50 ml of phosphate buffer saline pH 6.8**.** At an interval of 1h up to 6 h the swollen patches were carefully withdrawn from the petridish, excess water was cleared from the patch by filter paper, reweighed and % swelling index was obtained by the following formula:[26, 27]

$$(\%)\ \text{Swelling index} = \frac{\text{Wet weight} - \text{Dry weight}}{\text{Dry weight}} \times 100$$

***Ex vivo* drug permeation study**

Franz diffusion cell having an effective diffusion area of 1.74 cm^2 was used for determination of extent and rate of mucosal permeation of Atenolol from the buccal patch formulations across the goat buccal mucosa. Phosphate buffer saline, pH 6.8 was filled in the receptor compartment (40 ml) and the temperature was maintained at 37 ± 0.5°C. The buccal mucosal tissue was mounted between the donor and receptor medium of the diffusion cell, over which the buccal patch was placed so that the drug releasing part of the buccal patch formulation facing towards the mucosal surface and the drug impermeable backing layer facing towards the donor compartment. A stirring speed of 50 rpm was employed using a magnetic stirrer for simulating buccal cavity environment. At regular intervals, five millilitres of the sample was withdrawn from the receptor compartment and replaced immediately with an equal volume of phosphate buffer saline, pH 6.8. The quantity of drug (Atenolol) permeated into the receptor medium was estimated by using UV–VIS spectrophotometer (UV-1700 Double beam spectrophotometer, SHIMADZU Corporation, Japan) at 274 nm against a blank.[28]

Scanning Electron Microscopy (SEM) study

The SEM study generally performed for demonstrating surface texture and to check the morphology of the fractured or sectioned surface. It is employed for producing three dimensional surface relief images obtained from secondary electrons. The surface examination of formulation containing drug and polymer can present essential information regarding the micro texture of appliance.[29]

RESULTS AND DISCUSSION

The present research study was an attempt to develop and evaluate Atenolol (an anti hypertensive drug) containing buccal patches having mucoadhesive polymeric layer of HPMC K4M, fenugreek seed mucilage, tamarind seed polysaccharide and a drug free backing membrane prepared from 6% ethyl cellulose employing solvent casting technique.

Average weight and Thickness

The average weight of different Atenolol buccal patch formulations as a whole (54 cm^2) was observed in the range of 1.69 ±0.06 g (F-1) to 1.93±0.03g(F-5) and the thickness were determined in the range, 0.59 ±0.04 mm (F-1) to 0.68 ± 0.02 mm (F-5)**(Table-2).**

Folding Endurance

The folding endurance value was measured to be highest with formulation, F-2 (99) and lowest with formulation F-3 (86)**(Table-2).** The folding endurance study signifies flexibility of the buccal patches.

Drug content

The drug content uniformity of the prepared buccal patch formulations were determined in the range of 99.28 ±0.18% (F-4) to 99.63 ±0.09 % (F-2)**(Table-2)** indicating uniformity with respect to drug content.

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Surface pH

The determination of surface pH of the prepared buccal patch formulations is important to improve both drug permeation and mucoadhesion, as an acidic or alkaline pH may results in irritation to the buccal mucosa. In the present investigation attempt was made to keep the surface pH as close to the buccal/salivary pH as possible by selecting appropriate polymers for formulation of the buccal patches. The surface pH of the buccal patch formulations were reported in the range of 6.42 ±0.03 (F-1) to 6.86 ±0.03 (F-6). The surface pH study illustrates absence of any buccal irritation as the prepared buccal patches exhibit pH range close to buccal pH **(Table-2).**

Table 2: Average weight, thickness, folding endurance, drug content and surface pH of buccal patches of Atenolol

FC	Average Weight (gm)(X±S.D.),n=3	Thickness(mm) (X± S.D.), n=3	Folding endurance	Drug content (%),(X±S.D.), n=3	Surface pH (X± S.D.)
F-1	1.69 ±0.06	0.59 ±0.04	91	99.49 ±0.19	6.42 ±0.03
F-2	1.76 ±0.08	0.61 ±0.06	99	99.63 ±0.09	6.59 ±0.04
F-3	1.74 ±0.05	0.60 ±0.03	86	99.58 ±0.11	6.56 ±0.02
F-4	1.81 ±0.07	0.66 ±0.05	97	99.28 ±0.18	6.69 ±0.01
F-5	1.93±0.03	0.68 ± 0.02	89	99.42 ± 0.19	6.52 ±0.01
F-6	1.84±0.06	0.63 ± 0.02	93	99.36 ± 0.13	6.86 ±0.03

Determination of percentage moisture content and percentage moisture absorption

The different buccal patch formulations of Atenolol were investigated for moisture content (%) and moisture absorption (%) to examine the physical stability of the buccal patches at high humid conditions and patch integrity at dry conditions. The percentage moisture content of buccal patch formulations of Atenolol was observed to be within the range of 1.29 ±0.06 % (F-3) to 1.56±0.03% (F-5). The moisture absorption (%) study results for Atenolol buccal patch formulations were obtained in the range 5.55±0.03 (F-1) to 6.44±0.06% (F-6) **(Table-3)**. The low moisture content of the buccal patch formulations protects them well from microbial contamination and also provides stability from brittleness.

Swelling Index Study

A good swelling property is expected for good mucoadhesive application by a polymer. The rate and extent of water absorption by a polymer is an important determinant in relation to its relative mucoadhesive strength. The absorption of water results in relaxation of originally stretched, entangled polymer chain that results in exposure of all the mucoadhesive polymers to mucoadhesive site for bonding to occur. The faster the process the faster is the polymer to adhere to its substrate. The swelling study results reveal that the percentage swelling of the buccal patch formulations were found in the order of F2>F-6>F-5>F-3>F-4>F-1. Among the various Atenolol buccal patch formulations highest swelling index of 256±0.88 % was observed with formulation F-2 and lowest swelling index of 203±0.96 % was recorded with formulation F-1**(Table-3).** The swelling index study demonstrates swelling of buccal patches significantly very with the polymer composition.

***Ex vivo* Mucoadhesion study**

The *ex vivo* mucoadhesion study findings has demonstrated that among the several Atenolol buccal patch formulations the maximum mucoadhesive strength of 32.82 ±0.63 g was observed with formulation F-2 while minimum mucoadhesive strength of 23.13 ±0.46 g with formulation F-1 and the mucoadhesive strength of different buccal patch formulations were found in the order of F-2>F-5>F-6>F-3>F-4>F-1. The highest force of adhesion was observed with formulation F-2 (32 ± 0.06 N) and lowest force of adhesion with formulation F-1 (23 ± 0.04 N) **(Table-3).** The Mucoadhesion study results revealed strong bonding between the mucoadhesive polymers and mucosal tissue.

Table 3: Moisture content, moisture uptake and swelling index, ex vivo mucoadhesion study of buccal patches of Atenolol

Formulation Code	Moisture content (%)	Moisture absorption (76%RH)	Swelling Index (%) 6h	Mucoadhesive Strength(g)	Force of adhesion(N)
F-1	1.43 ±0.09	5.55±0.03	203±1.19	23.13 ±0.46	23 ± 0.04
F-2	1.32 ±0.08	6.03±0.02	256±0.88	32.82 ±0.63	32 ± 0.06
F-3	1.29 ±0.06	6.18±0.06	243±0.96	29.41 ±0.32	29 ± 0.05
F-4	1.51 ±0.12	5.98±0.05	231±0.46	24.84 ±0.29	24 ± 0.06
F-5	1.56±0.03	6.26±0.04	249±1.33	31.94 ±0.57	31 ± 0.04
F-6	1.54±0.05	6.44±0.06	251±1.02	30.08 ±0.51	30 ± 0.06

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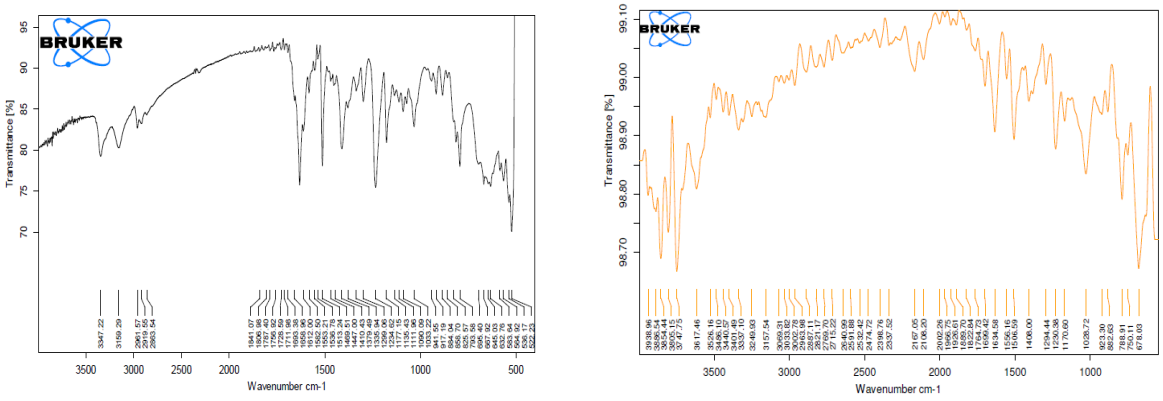
Drug-polymer compatibility study:



Pure Drug **Formulation F-2**

Figure 1: FTIR study of pure drug (Atenolol) and Formulation (F-2)

Table 4: FT-IR spectral analysis of pure drug (Atenolol) and Formulation (F-2)

Functional groups	Type of compound	Atenolol (Frequency cm^{-1})	Formulation, F-2 (Frequency cm^{-1})
C-H (stretching)	Alkane	2961.57	2963.98
O-H (stretching)	Alcohol	3347.22	3337.10
O-H (stretching)	Carboxylic acid	2863.54	2821.17
N-H (stretching)	Amine	3159.29	3157.54
C=C	Alkenes	1513.24	1506.59
C=O	ketones	1693.38	1699.42

The FT-IR spectra of pure drug, Atenolol illustrated characteristic peaks at 2961.57 cm^{-1}: the C-H (stretching) for alkane, 3347.22 cm^{-1}: the O-H (Stretching) for alcohol, 2817.69 cm^{-1} : the O-H (stretching) for Carboxylic acid, 3159.29 cm^{-1} : the N-H for Amines, 1513.24 cm^{-1} : the C=C for Alkenes, 1693.38cm^{-1} : the C=O for ketones, The FT-IR spectra of optimized Atenolol buccal patch formulation F-2 illustrated characteristic peaks at 2963.98 cm^{-1}: the C-H (stretching) for alkane, 3337.10 cm^{-1}: the O-H (Stretching) for alcohol, 2821.17 cm^{-1} : the O-H (stretching) for Carboxylic acid, 3157.54 cm^{-1} : the N-H for Amines, 1506.59 cm^{-1} : the C=C for Alkenes, 1699.42cm^{-1} : the C=O for ketones**(Table 4., Fig. 1.)**. All the characteristic peaks of pure drug Atenolol were found to be present in the optimized Atenolol buccal patch formulation F-2 with minute shifting, this demonstrates absence of any chemical interaction between the drug (Atenolol) and various hydrophilic polymers (HPMC K4M, fenugreek seed mucilage) employed in the investigation.

Table 5: *Ex vivo* drug permeation study of different buccal patches of Atenolol

Time (h)	Cumulative % Drug Permeated					
	F-1	F-2	F-3	F-4	F-5	F-6
0	0	0	0	0	0	0
0.5	3.61	4.84	5.14	5.59	5.81	5.02
1	5.14	8.12	9.35	8.26	9.58	8.89
2	8.32	12.33	14.01	12.18	15.21	13.21
3	10.85	15.69	18.33	16.09	19.35	17.96
4	13.65	19.38	22.29	19.57	24.13	22.47
5	17.08	23.12	26.48	24.11	28.29	26.95
6	19.58	28.35	31.5	28.39	34.15	32.13
8	24.55	35.86	38.61	41.01	45.87	41.48
12	49.38	57.59	59.51	61.32	64.66	61.33
24	83.69	92.98	90.38	87.43	91.59	90.75

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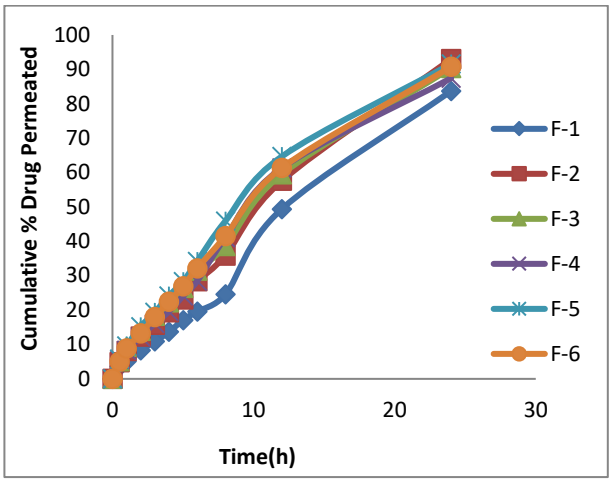

Figure 2: *Ex vivo* drug permeation comparative study of Atenolol buccal patches

The ex vivo drug permeation study of different Atenolol buccal patch formulations exhibited maximum permeation with formulation F-2 (92.98%) through goat buccal mucosa in 24 h and minimum with formulation F-1 (83.69 %) as evident from Table 4 and Fig.2. The drug permeation profile of all the formulations was observed in the order of F-2>F-5>F-6>F-3>F-4>F-1**(Table 5., Fig. 2.).** The study demonstrated slow and steady drug permeation profile. The results of ex vivo permeation study of Atenolol from buccal patch formulations reveals that the drugs (Atenolol) easily permeated through the excised goat buccal mucosa during a period of 24 h and could possibly permeate through the human buccal membrane.

Table 6: *Ex vivo drug* permeation kinetics study of different buccal patch formulations of Atenolol

Formulation Code	Zero order	First order	Higuchi	Korsmeyer- Peppas	"n"value
	r^2 values	r^2 values	r^2 values	r^2 values	
F-1	0.987	0.958	0.880	0.968	0.816
F-2	0.974	0.950	0.929	0.988	0.765
F-3	0.975	0.973	0.954	0.995	0.738
F-4	0.964	0.986	0.941	0.981	0.743
F-5	0.955	0.984	0.963	0.994	0.732
F-6	0.969	0.979	0.956	0.995	0.760

Surface Morphology Study

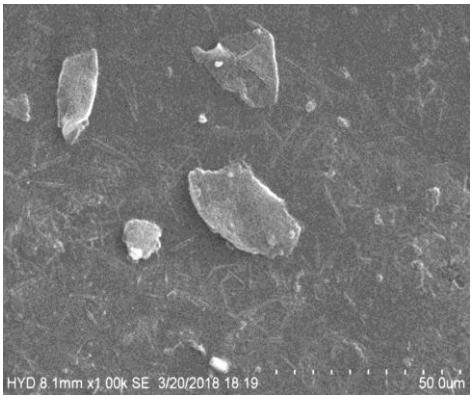

Figure 3: SEM study of Atenolol buccal patch formulation F-2.

The buccal patch formulation F-2 (Atenolol-25 mg/cm^2, HPMC K4M- 100 mg, fenugreek seed mucilage-700 mg, glycerine-10% w/w) was the best formulation among several buccal patch formulations of Atenolol on the basis of best drug content, *ex vivo* drug permeation profiles, highest swelling property and mucoadhesive strength. The SEM photographs of the best Atenolol buccal patch formulation, F-2 (**Fig. 3.**), revealed a nearly smooth surface and good lamination of the mucoadhesive polymers like HPMC K4M and fenugreek seed mucilage on the ethyl cellulose backing membrane. It indicates Atenolol is uniformly dispersed in the polymeric matrix of buccal patches and confirms perfect binding between the drug containing mucoadhesive layer and the adhesive layer of backing membrane.

CONCLUSION

Among the various mucoadhesive buccal patch formulations of Atenolol, formulation F-2 (Atenolol-25 mg/cm^2, HPMC K4M-100 mg, fenugreek seed mucilage-700 mg, glycerine 10 % w/w) was found to be most satisfactory as indicating very promising results in different evaluation parameters like drug content, thickness, weight variation, folding endurance, *ex vivo* drug permeation, surface pH, *ex vivo* mucoadhesive strength, moisture content, moisture absorption, swelling index, *ex vivo* drug permeation study, FT-IR study and SEM observations. The above investigation concluded the feasibility for developing new mucoadhesive bi laminated buccal patch formulations of Atenolol with various mucoadhesive hydrophilic polymers are safe, stable and can be very promising in sustaining drug release through the buccal mucosa and therefore, very effective in control and prophylaxis of hypertension for extended period of time.

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