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DEVELOPMENT EVALUATION AND CHARACTERIZATION OF LOSARTAN POTASSIUM BUCCAL PATCHES USING HYDROPHILIC POLYMERS

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ABSTRACT: Among different routes of drug delivery buccal route is an attractive alternate for drug administration which provides improved patient compliance and increase bioavailability of drugs undergoing extensive hepatic first pass metabolism. The present research work focussed on development, evaluation and characterization of buccal patches of losartan potassium using mucoadhesive hydrophilic polymers such as fenugreek seed mucilage (FSM), tamarind seed polysaccharide (TSP), sodium carboxy methyl cellulose (NaCMC) and propylene glycol as plasticizer. Losartan potassium is an angiotensin II type - 1(AT1) receptor antagonist used in treating hypertension. The plasma $t_{1/2}$ of the drug is 1.5 to 2.5 h as it undergoes extensive hepatic first pass metabolism which reduces the bioavailability of the drug up to 33%. The mucoadhesive buccal patches were prepared by solvent casting technique and were evaluated for various physico mechanical parameters like weight variation, thickness, folding endurance, drug content, surface pH, moisture content, moisture absorption, % swelling and mucoadhesion studies. *In-vitro* drug release study was carried out using commercial semi permeable membrane. *Ex-vivo* drug permeation study was performed using goat buccal mucosa in Franz diffusion cell. All the buccal patch formulations indicate sustained drug release profile for 12 h, both *in-vitro* and *ex-vivo*. The FT-IR study confirms no evidence of interaction between drug and polymers. The stability study of the optimized formulation F-4 ((losartan potassium-6.25 mg/cm^2, fenugreek seed mucilage-325 mg, tamarind seed polysaccharide-325 mg, propylene glycol-0.2 ml) was found to be stable with good surface morphology characteristics.

INTRODUCTION: The phenomenon of attachment of two materials, one of which is a biological (mucosal membrane) and the other is a mucoadhesive polymer for extended period of time is called as mucoadhesion.

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The buccal cavity is a most convenient and easily accessible site for local and systemic administration of therapeutic agents.

The drug delivery *via* buccal route provides direct access to systemic circulation through the internal jugular vein. Thus drug bypasses the extensive hepatic first pass metabolism and degradation in the harsh acidic environment of gastro intestinal tract that results in an increase in bioavailability. The well vascularised, lesser thickness, high permeability and low enzymatic activity of the buccal mucosa enables it a suitable site for rapid

absorption of drugs into the systemic circulation (underneath the buccal mucosa) [1].

The drugs having short biological half lives, low bioavailability needs a sustained effect, poor permeability, sensitivity to enzymatic degradation may be successfully delivered by the mucoadhesive drug delivery system. Research studies in recent years aims on increase use of mucoadhesive or bioadhesive polymers to control local and systemic delivery of drugs that are prone to degradation by presystemic metabolism and subsequent low bioavailability. Since, decades lots of research attempts have been made to design mucoadhesive formulations including tablets, patches, disks, gels, ointments. Buccal patches are preferred because of several advantages over other buccal dosage forms. 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 [2, 3].

An ideal buccal dosage form must possess 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 overcome by preparing a system having uniform adhesiveness and an impermeable backing membrane [3].

Losartan potassium is an angiotensin II type - 1 (AT1) receptor antagonist used in treating hypertension. The total oral dose of the drug per day ranging from 25 mg to 100 mg. However, the major drawback of oral administration of losartan potassium is that it undergoes extensive hepatic first pass metabolism by cytochrome P450 enzyme which reduces the bioavailability of the drug up to 33%. Losartan potassium is freely soluble in water having plasma $t_{1/2}$ 1.5 to 2.5 h. Therefore, in order to overcome the pre systemic metabolism, improving the half life and subsequent bioavailability Losartan potassium is a suitable candidate for administration in the form of mucoadhesive buccal patch [4].

The main aim and objectives of the present research work was to design, characterize and evaluate pharmaceutically equivalent mucoadhesive buccal patches for unidirectional release of Losartan Potassium through the buccal mucosa for extended period of time that circumvents the first pass metabolism and improving bioavailability of the drug and can be used in treating hypertension effectively.

MATERIALS AND METHODS:

Materials: Losartan Potassium was a gift item from Hetero Drugs Limited, India. NaCMC and ethyl cellulose were obtained from Matrix Laboratories, India. Fenugreek (*Trigonella foenum-graecum* L.) seed mucilage was extracted from the raw fenugreek seeds. Tamarind seed poly-saccharide was isolated from Tamarind (*Tamarindus indica*) seeds. 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.

Extraction of Fenugreek Seed Mucilage: About 250 g of fenugreek seed was washed thoroughly with double distilled water and then soaked in 2000 ml of double distilled water for overnight at room temperature. The seeds were then boiled with sufficient amount of double distilled water in stirring condition on a water bath till a slurry was formed. 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 min. 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 [5 - 7].

Isolation of Tamarind Seed Polysaccharide: Tamarind seeds are soaked in hot water to peel out the outer cover. The seeds are then gently crushed and 20 g of powdered seed was soaked in double distilled water for 24 h to prepare a slurry. The slurry was poured into 800 ml boiling distilled water for 20 min on a waterbath 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 min 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 [8, 9].

TABLE 1: FORMULATION DESIGN OF LOSARTAN POTASSIUM BUCCAL PATCHES

Formulation code	FSM (mg)	TSP (mg)	NaCMC (mg)	Drug (mg/cm^2)	Propylene glycol (ml)	Distilled water (ml)
F1	650	-	-	6.25	0.2	25
F2	-	650	-	6.25	0.2	25
F3	-	-	650	6.25	0.2	25
F4	325	325	-	6.25	0.2	25
F5	325	-	325	6.25	0.2	25
F6	-	325	325	6.25	0.2	25

FSM- fenugreek seed mucilage, TSP- tamarind seed polysaccharide, NaCMC- Sodium carboxy methyl cellulose

Preparation of Backing Membrane: The backing membrane was prepared by casting 6% ethyl cellulose in acetone: isopropyl alcohol (65:35) mixture using 10% w/w of dibutyl phthalate as a plasticizer in a 38 cm^2 petridish and dried in room temperature for 12 h. [10]

Preparation of Mucoadhesive Buccal Patches of Losartan Potassium: The mucoadhesive buccal patches of losartan potassium were prepared by solvent casting technique. The buccal patches composed of different ratios of fenugreek seed mucilage (FSM), tamarind seed polysaccharide (TSP), Sodium carboxy methyl cellulose (NaCMC) and propylene glycol as plasticizer. Formulation F-1 was prepared by dissolving the required amount of FSM in 25 ml of double distilled water applying gentle heat (37 °C) on a hot plate with continuous stirring for 2 h so that the mucilage was completely soluble in water. The solution was cooled to room temperature and required quantity of losartan potassium (~6.25 mg/cm^2 patches) was incorporated with continuous stirring for 1 h.

Propylene glycol was incorporated as a plasticizer at a concentration of 0.2 ml and stirred well for 2 h. The polymeric drug solution was set aside for 2 h to get a bubble free solution and casted on backing membrane in a 38 cm^2 petridish and dried at 40 °C in the incubator for 24 h. The formulation F2, F3 and F6 were prepared by the above method without heating the polymeric solution. In Formulation F-4 and F-5 at first the fenugreek seed mucilage solution was prepared with gentle heat, then the solution was cooled and required amount of polymers like tamarind seed polysaccharide and NaCMC was incorporated. Drug and plasticizer was transferred to the polymeric mixture, poured on to a backing membrane in the 38 cm^2 petridish and dried at 40 °C for 24 h in the incubator. After 24 h the patch was removed from the petridish, before removing the patch was dried at 37 ºC for 1h. The dry patches were cut into 1, 2 and 4 cm^2 circular shape (a 4 cm^2 patch contains 25 mg of drug) packed in aluminum foil and kept in desiccator until use. The formulation designs of losartan potassium buccal patches are represented in **Table 1**. [10]

Characterization of Losartan Potassium Buccal Patches:

Drug-Polymer Compatibility Study: The compatibility study between drug and polymer was carried out in FT-IR spectrophotometer using KBR pellet. All the spectra were reported in the range of 500 cm^{-1} to 3500 cm^{-1}. [10]

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). Three randomly selected patches were used for each formulation [11].

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 210 nm against a blank. The drug content was estimated from the calibration curve, which was constructed between 2 and 10 µg/ml concentration ranges. The method was validated for linearity, accuracy, and precision. The regression equation for the calibration curve was $Y = 0.081 X + 0.002$, $R^2 = 0.9990$. [10, 12]

Determination of Folding Endurance: The folding endurance of the buccal patches was determined manually by folding repeatedly one patch at the same place till it broke or folded up to 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 [13].

Measurement of Surface pH: The surface pH of the losartan potassium buccal patches was 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 min. The experiments were preformed in triplicate and a mean of three readings was reported [14].

Determination of Moisture Content: The buccal patches were weighed accurately and kept in a desiccator containing anhydrous calcium chloride. After 3 days, the patches were taken out from the desiccator and weighed. The moisture content (%) was determined by calculating moisture loss (%) using the formula: [15]

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

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 aims on the moisture absorption capacity of the buccal patches which was determined as follows. The buccal patches of 1 cm^2 (n=3) were weighed accurately and kept in a desiccator containing saturated solution of aluminium chloride, keeping 76% relative humidity inside the desiccators for a period of three days. After three days the patches were removed from desiccator, weighed and percentage moisture absorption was calculated using following formula: [15, 16]

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

Swelling Index Study: Swelling study of the prepared buccal patches were measured by function of weight increase due to swelling. For swelling index study (1 × 1 cm) of drug loaded patch was weighed accurately and placed in a petridish containing 50 ml of phosphate buffer saline pH 6.8. The patches were taken out carefully from the petridish at an interval of 1 h up to 6 h, the excess water was removed from the patch by filter paper. The swellen patch was reweighed and % swelling was determined by the following formula: [20, 21]

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

The experiment was carried out in triplicate and their average values were reported.

***Ex-vivo* Mucoadhesive Study:** Mucoadhesion is 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 may be defined as the weight in gram required to detach the buccal patch from the buccal mucosa. The mucoadhesive strength was measured using a modified physical balance. The two pans of physical balance were removed. The right pan was replaced with a lighter base and on the left side a Teflon ring was held with a copper wire. A Teflon cylinder was hanged with a copper wire on the opposite side of the ring. The height of the total set up was adjusted to accommodate a glass beaker in between. The two sides were then balanced so that the right hand side was exactly 5 grams heavier

then the left. The excised goat cheek pouch 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 just reaches the surface of the mucosal membrane and keeps it moist. The mucoadhesive patch of 2 cm^2 area was moistened with 1 ml of phosphate buffer saline pH 6.8 for initial hydration and swelling. The cylinder was raised upward and the hydrated patch was brought into contact with the mucosal surface. The balance was kept in this position for 3 min and then slowly weights were increased on the right pan until the patch was separated from the mucosal surface. A 5g was minus from the total weight which was the required weight for detachment of patch from the mucosal surface known as mucoadhesive strength of the buccal patch. After each experiment the mucosal tissue was gently and thoroughly washed with phosphate buffer saline pH 6.8 and left for 5 min before the next measurement. Care must be taken not to use a broken mucosa and fresh mucosal membrane should be used for each formulation. The experiment was repeated 3 times with each formulation and the mean value was reported [22, 23, 24].

***In-vitro* Drug Release Study:** The *in-vitro* release of losartan potassium from 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 in such a way that the drug releasing patch surface facing towards the receptor compartment and backing layer facing towards the donor compartment. A 50 rpm stirring speed was applied using a magnetic stirrer. Five milliliters of the sample from receptor compartment 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 210 nm against a blank [17].

Preparation of Goat Buccal Mucosa: The goat buccal mucosa excised from goat cheek pouch was obtained within 2 h of its death from the slaughter's house and immediately transported to the laboratory in phosphate buffer solution saline, pH 6.8. The buccal mucosa was washed several times with double distilled water, separated from the full thickness of the tissue immersed 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]

***Ex-vivo* Permeability Study:** The extent and rate of mucosal permeation of losartan potassium 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 so that the drug releasing portion of the patch facing towards the mucosal surface and the drug impermeable backing membrane facing towards the donor compartment. 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 210 nm against a blank [19, 20].

Stability Studies: The buccal patch formulation having best drug content, drug release profiles both *in-vitro* and *ex-vivo*, swelling index and muco-adhesive strength 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 [3, 25].

RESULTS AND DISCUSSION: The present investigation was an attempt to develop, evaluate and characterize losartan potassium (an anti hypertensive drug) buccal patches containing drug in a mucoadhesive polymeric layer of fenugreek seed mucilage, tamarind seed polysaccharide, NaCMC and a drug free backing membrane composed of 6% ethyl cellulose using solvent casting technique.

Average Weight and Thickness: The buccal patches of losartan potassium 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 1.79 ± 0.03 g (F1) to 1.89 ± 0.06 g (F6). The thickness was measured using thickness gauze and was in the range of 0.54 ± 0.03 (F4) to 0.63 ± 0.05 (F6) **Table 2**.

Drug Content: The drug content uniformity of the buccal patches was determined in 1 cm^2 of each buccal patch. The drug content of the patches found in the range of 98.36 ± 0.08 (F3) to 99.26 ± 0.11 (F4) indicating uniformity with respect to drug content **Table 2**.

Folding Endurance: The folding endurance of the buccal patches was measured manually. Folding endurance was measured to be maximum with F4 (118) and minimum with F1 (95) **Table 2**. The folding endurance study signifies flexibility of the prepared buccal patches of losartan potassium.

Surface pH: The surface pH of the prepared buccal patches was determined to optimize both drug permeation and mucoadhesion, as 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 formulating the buccal patches.

The surface pH of the buccal patches were found in the range of 6.29 ± 0.03 (F-1) to 6.78 ± 0.03 (F-6) **Table 2** (Close to buccal pH). Hence, they may not produce any local irritation to buccal mucosa. The surface pH study indicates no buccal irritation as the prepared buccal patches showing pH range close to buccal pH.

TABLE 2: PHYSICO-CHEMICAL PARAMETERS OF LOSARTAN POTASSIUM BUCCAL PATCHES

FC	Weight Variation (g) (X ± S.D.)	Thickness (mm) (X ± S.D.)	Drug Content (%) (X±S.D.)	Folding Endurance	Surface pH (X ± S.D.)
F1	1.79 ± 0.03	0.55 ± 0.03	99.02 ± 0.12	96	6.29 ± 0.03
F2	1.82 ± 0.05	0.56 ± 0.05	98.96 ± 0.13	101	6.69 ± 0.02
F3	1.83 ± 0.06	0.59 ± 0.02	98.36 ± 0.08	95	6.61 ± 0.02
F4	1.81 ± 0.09	0.54 ± 0.03	99.26 ± 0.11	118	6.49 ± 0.01
F5	1.84 ± 0.04	0.60 ± 0.06	99.09 ± 0.06	109	6.73 ± 0.02
F6	1.89 ± 0.06	0.63 ± 0.05	98.66 ± 0.08	111	6.78 ± 0.03

FC-Formulation Code, n=3

Determination of Percentage Moisture Content and Percentage Moisture Absorption: The buccal patches of losartan potassium were tested for moisture content (%) and moisture uptake (%) to check the physical stability of the patches at high humid conditions and patch integrity at dry conditions. The moisture content (%) of all the buccal patches were found to be within the range of 1.36 ± 0.02% (F1) to 1.89 ± 0.04% (F5) and moisture uptake (%) study results were found in the range of 5.33 ± 0.03% (F1) to 6.81 ± 0.08% (F6) **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.

Swelling Index Study: A good swelling property is expected for good mucoadhesive application by a polymer. When mucoadhesive polymers come in contact with aqueous medium they absorb water and swell to form a gel. The polymer swelling results in a mechanical entanglement due that exposure of the mucoadhesive site for hydrogen bonding and/or electrostatic interaction between the polymer and the mucosal surface. 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 are in the order of F4 > F5 > F6 > F1 > F3 > F2. Among the various formulations highest swelling was observed with formulation F4 (344 ± 0.39%) and least being formulation F2 (308 ± 0.68) **Table 3**. Fenugreek seed mucilage and tamarind seed polysaccharide in 1:1 ratio exhibit greater swelling.

***Ex-vivo* Mucoadhesion Study:** The *ex-vivo* mucoadhesion study results indicated that the maximum mucoadhesive strength was observed with formulation F-4 (33.33 ± 0.61 g) and minimum being with formulation F-3 (19.59 ± 0.95 g) the mucoadhesive strength of the losartan potassium buccal patch formulations follow the order of F4 > F5 > F1 > F6 > F2 > F3. The highest force of adhesion was observed with formulation F-4 (0.33 ± 0.03 N) and lowest force of adhesion with F-3 (0.19 ± 0.06N) **Table 3**. The mucoadhesion study results revealed that a combination of fenugreek seed mucilage and tamarind seed polysaccharide in 1:1 ratio showed highest mucoadhesive strength and force of adhesion which indicates strong bonding between the mucoadhesive polymers and mucosal tissue and at the same time sodium CMC alone showed lowest mucoadhesive strength and force of adhesion.

TABLE 3: MOISTURE CONTENT (%), MOISTURE UPTAKE (%), SWELLING INDEX (%), *EX-VIVO* MUCOADHESION STUDY OF DIFFERENT LOSARTAN POTASSIUM BUCCAL PATCHES

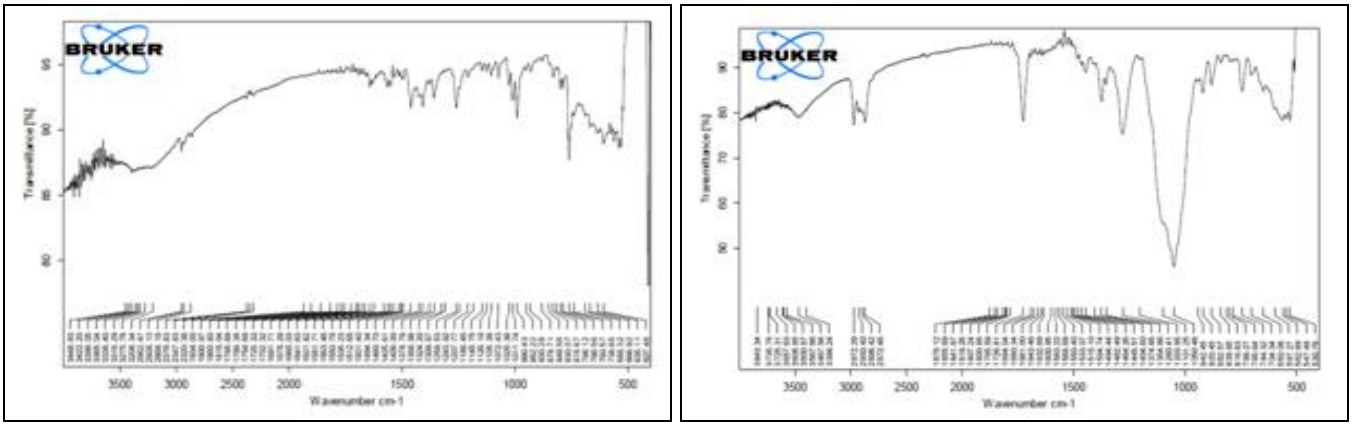
Formulation code	Moisture content (%)	Moisture uptake (%) (76% RH)	Swelling index (%) 6h	Mucoadhesive strength (g)	Force of adhesion (N)
F1	1.36 ± 0.02	5.33 ± 0.03	321 ± 0.93	27.36 ± 0.92	0.27 ± 0.05
F2	1.48 ± 0.01	6.19 ± 0.04	308 ± 0.68	24.44 ± 0.31	0.24 ± 0.02
F3	1.79 ± 0.05	6.68 ± 0.01	319 ± 1.12	19.59 ± 0.95	0.19 ± 0.06
F4	1.38 ± 0.06	5.55 ± 0.05	344 ± 0.39	33.33 ± 0.61	0.33 ± 0.03
F5	1.89 ± 0.04	6.49 ± 0.06	332 ± 1.62	28.45 ± 0.85	0.28 ± 0.04
F6	1.82 ± 0.02	6.81 ± 0.08	328 ± 1.19	25.69 ± 0.91	0.25 ± 0.02

Drug-Polymer Compatibility Study:

TABLE 4: FT-IR SPECTRAL ANALYSIS OF PURE DRUG (LOSARTAN POTASSIUM) AND FORMULATION (F-4)

Functional groups	Losartan Potassium (Frequency cm^{-1})	Formulation F-4 (LP+FSM+TSP) (Frequency cm^{-1})
OH	3398.05	3398.24
C-H Stretching	2928.13	2930.40
C=O	1725.33	1726.81
C=N	1641.63	1643.46
C=C	1581.71	1583.22
Al-CH-bend	1408.00	1404.60
Ar-CH (In plane Bending)	1105.38	1101.25
Ar-CH (Out plane Bending)	930.28	920.45

LP-Losartan Potassium, FSM-Fenugreek seed mucilage, TSP-Tamarind seed polysaccharide



Pure drug **Formulation F-4**

FIG. 1: FT-IR STUDY OF PURE DRUG (LOSARTAN POTASSIUM) AND FORMULATION (F-4)

The drug polymer compatibility of the pure drug (Losartan Potassium) and optimized buccal patch formulation F-4 (losartan potassium-6.25 mg/cm^2, fenugreek seed mucilage-325 mg, tamarind seed polysaccharide–325 mg, propylene glycol-0.2 ml) was analyzed by FT-IR spectroscopy and the FT-IR spectra are presented in **Table 4** and **Fig. 1**. The FT-IR spectrum of pure Losartan Potassium showed various characteristic peaks at 3398.05 cm^{-1} due to –OH-, at 2928.13 cm^{-1} due to C-H Stretching, at 1725.33 cm^{-1} due to C=O, at 1641.63 cm^{-1} due to C=N, at 1581.71 cm^{-1} due to C=C, at 1408.00 cm^{-1} due to Al-CH-bend, at 1105.38 cm^{-1} due to Ar-CH (In plane Bending) and at 930.28 cm^{-1} due to Ar-CH (Out plane bending). All these chararacteristic peaks of pure losartan potassium appear in the spectrum of the formulation F-4 losartan potassium containing buccal patch without or with very minute shifting, indicating that there was an absence of any chemical interaction between the drug (losartan potassium) and the polymers used.

***In-vitro* Drug Release Studies:** The *in-vitro* release data and profile of losartan potassium buccal patches are shown in **Table 5** and **Fig. 2**. The various buccal patch formulations showed sustained drug release up to 12 h. Among the several formulations highest *in-vitro* drug release was observed in formulation F-4 (94.69%) over a period of 12 h while the lowest *in-vitro* drug release with formulation F-3 (83.29%) in 12 h. It was cleared from the table and graph that the drug release was governed by polymer content. Among six formulations the *in-vitro* drug release was in the order of F4 > F5 > F1 > F6 > F2 > F3. The drug release pattern was rapid initially till the patches swelled which was followed by sustained drug release profile. A decrease in release rate of drug with time was observed due to swelling of polymers resulting in the formation of a thick gel barrier, thus drug diffusion slower with time. The release profile governs higher drug release pattern in a combination of polymers than the polymers alone.

TABLE 5: *IN-VITRO* DRUG RELEASE PROFILE OF DIFFERENT BUCCAL PATCH FORMULATIONS OF LOSARTAN POTASSIUM

Time (h)	F1 (% CDR)	F2 (% CDR)	F3 (% CDR)	F4 (% CDR)	F5 (% CDR)	F6 (% CDR)
0	0	0	0	0	0	0
0.5	6.29	7.34	5.83	6.95	6.49	6.62
1	13.91	16.86	14.5	15.15	15.41	17.19
2	21.71	26.18	23.95	23.55	22.3	26.57
3	29.58	36.55	32.16	34.02	30.7	37.74
4	36.18	44.92	41.09	40.41	43.56	46.93
5	41.87	52.09	48.26	46.75	49.44	52.83
6	47.11	59.96	56.96	54.61	53.48	60.54
8	64.08	71.06	65.05	68.9	67.63	71.1
10	78.16	81.6	74.65	84.9	79.36	82.12
12	91.36	88.08	83.29	94.69	92.24	89.16

% CDR- % Cumulative Drug Release

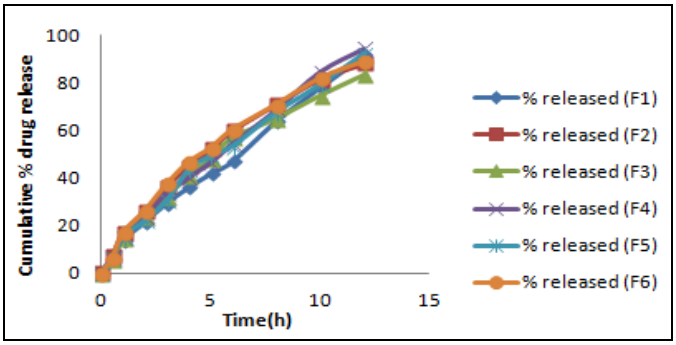


FIG. 2: *IN-VITRO* DRUG RELEASE COMPARATIVE STUDY OF LOSARTAN POTASSIUM BUCCAL PATCH FORMULATIONS

***Ex-vivo* Permeation:** The *ex-vivo* permeation study of losartan potassium from various buccal patches through goat buccal mucosa is shown in **Table 6** and **Fig. 3**. From all the formulations it was revealed that the maximum *ex-vivo* drug permeation was 93.45% over a period of 12 h in case of formulation F4, while the minimum *ex-vivo* drug permeation was found to be 81.23% indicated by formulation F3 in 12 h. The *ex-vivo* permeation of losartan potassium buccal patches follows the similar pattern as that of *in vitro* drug release and are in the order of F4 > F5 > F1 > F6 > F2 > F3. The study indicates slow and steady drug permeation profile. The results of *ex-vivo* permeation study reveals that losartan potassium easily permeate through the excised goat buccal mucosa during a period of 12 h and could possibly permeate through the human buccal membrane.

TABLE 6: *EX-VIVO* DRUG PERMEATION STUDY OF DIFFERENT BUCCAL PATCH FORMULATIONS OF LOSARTAN POTASSIUM

Time (h)	F1 (% CDR)	F2 (% CDR)	F3 (% CDR)	F4 (% CDR)	F5 (% CDR)	F6 (% CDR)
0	0	0	0	0	0	0
0.5	5.35	6.29	5.31	6.75	5.9	6.29
1	12.7	15.64	12.92	14.56	14.37	15.68
2	19.23	23.85	21.06	22.63	21.52	23.55
3	27.08	33.19	28.14	32.53	29.79	34.67
4	36.26	42.91	33.13	39.46	35.27	43.87
5	41.58	50.56	39.5	44.82	41.74	50.28
6	46.85	57.94	44.16	52.57	48.21	59.37
8	63.16	69.73	53.64	67.88	62.36	69.82
10	83.47	79.58	67.39	83.62	77.53	80.68
12	89.63	86.35	81.23	93.45	90.09	87.66

% CDP-% Cumulative Drug Permeated

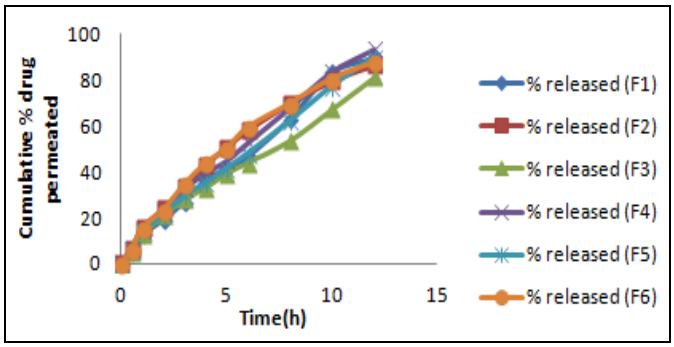


FIG. 3: *EX-VIVO* DRUG PERMEATION COMPARATIVE STUDY OF LOSARTAN POTASSIUM BUCCAL PATCH FORMULATIONS

Stability Studies: The buccal patch formulation F-4 (losartan potassium- 6.25 mg/cm^2, fenugreek seed mucilage-325 mg, tamarind seed polysaccharide-325mg, propylene glycol- 0.2ml) was the optimized formulation among several buccal patch formulations of losartan potassium on the basis of best drug content, drug release profiles both *in-vitro* and *ex-vivo*, highest swelling property and mucoadhesive strength subjected to stability test. The optimized Formulation F-4 was stored in glass bottles, flushed with nitrogen, and kept in stability chamber at 40 ºC / 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 results of the stability study indicates no significant change in drug content, *in-vitro* drug release and *ex-vivo* drug permeation.

TABLE 6: STABILITY STUDY OF FORMULATION F-4 FOR SIX MONTHS

Time	Drug content (%)	% Drug release	Cumulative % drug permeation
Initial	99.25 ± 0.10	94.69 ± 4.1	93.45 ± 4.13
1 month	98.56 ± 0.11	93.04 ± 3.5	92.11 ± 4.8
3 month	97.39 ± 0.09	92.16 ± 4.4	90.23 ± 3.8
6 month	96.51 ± 0.12	90.92 ± 4.6	88.13 ± 4.3

Surface Morphology Study:

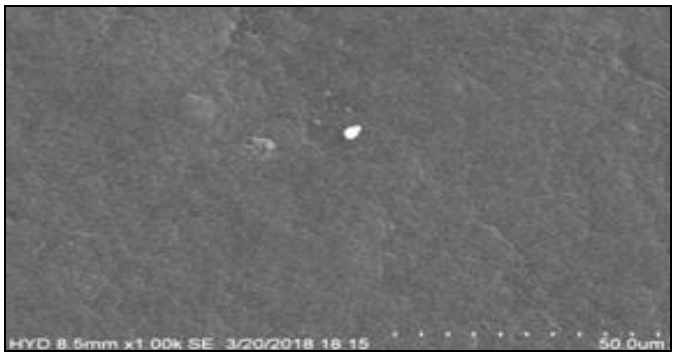


FIG. 4: SEM STUDY OF FORMULATION F-4

The SEM photographs of the optimized losartan potassium containing buccal patch formulation F-4 **Fig. 4** revealed a nearly smooth surface and good lamination of the mucoadhesive polymers like fenugreek seed mucilage, tamarind seed polysaccharide on the ethyl cellulose backing membrane. It shows losartan potassium being 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: The above investigation was an attempt to develop new buccal patch formulations containing losartan potassium. Among the various polymeric combinations the buccal patch formulation F-4 (losartan potassium-6.25 mg/cm^2,

fenugreek seed mucilage-325 mg, tamarind seed polysaccharide-325 mg, propylene glycol-0.2 ml) was found to be most suitable as it possessed good physico mechanical properties: excellent drug content, drug release and permeation profile, swelling and mucoadhesion properties. The formulation indicated well lamination with the drug free backing layer (6% ethyl cellulose). Further, there is absence of any interaction between the drug and mucoadhesive polymers confirmed by FT-IR study. The optimized formulation F-4 was being confirmed as it was found to be stable in various storage conditions as per ICH guidelines. Thus, it can be concluded that such new mucoadhesive buccal patch formulation of losartan potassium using mucoadhesive hydrophilic polymers that provides sustained drug release profile for extended period of time will be effective in bypassing extensive hepatic first pass metabolism, thus improving bioavailability and can be very promising in the control and management of hypertension.

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CONFLICT OF INTEREST: Nil

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