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Formulation and Evaluation of Buccoadhesive Films of Losartan Potassium

Umesh. D. Shivhare *, Parag. D. Bodkhe, Kishor P.Bhusari, Vijay B. Mathur

Sharad Pawar College of Pharmacy, Wanadongri, Hingna Road,
Nagpur-441 110, Maharashtra, INDIA

ABSTRACT

Buccoadhesive buccal delivery systems for losartan potassium in the form of buccal films were developed and characterized for improving bioavailability. The films were formulated by solvent casting method using different bioadhesive polymers like HPMC, Eudragit RS100, Eudragit RL100 and Ethylcellulose with glycerol as plasticizer. The films were characterized on the basis of their physical characteristics, bioadhesive performance and other parameters. In vitro studies revealed that release rate of losartan potassium was higher from films containing ratio of HPMC and Eudragit RL100 in proportion of 2:2. Drug diffusion from buccal films showed Peppas model kinetics and release mechanism was non-fickian. All the films exhibited sufficient in vitro bioadhesion strength. Promising formulation was further studied for temperature dependant stability studies. The results indicated that, therapeutic level of losartan potassium can be achieved using this buccoadhesive formulation.

Keywords: Buccal film, losartan potassium, bioavailability, bioadhesive strength

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INTRODUCTION

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike. However, peroral administration of drugs has disadvantages such as hepatic first pass metabolism and enzymatic degradation within the GI tract, that prohibit oral administration of certain classes of drugs especially peptides and proteins. Consequently, other absorptive mucosae are considered as potential sites for drug administration. Transmucosal routes of drug delivery offer distinct advantages over peroral administration for systemic drug delivery. These advantages include possible bypass of first pass effect, avoidance of presystemic elimination within the GI tract, and, depending on the particular drug, a better enzymatic flora

for drug absorption [1]. Mucoadhesive drug delivery systems are delivery systems, which utilize property of bioadhesion of certain polymers, which become adhesive upon hydration and hence can be used for targeting a drug to a particular region of the body for extended period of time [2]. Losartan is an angiotensin II receptor antagonist drug used mainly to treat high blood pressure (hypertension). The main drawback of conventional losartan potassium formulation is that it undergoes hepatic first pass metabolism. Thus the plasma $t_{1/2}$ is 1.5-2 h thereby decreasing its bioavailability up to 32%. Hence an alternative delivery system for improving the half life and bioavailability is needed.

The present work describes such delivery system, which will improve the biological half life and bioavailability of losartan potassium. Buccoadhesive films of losartan potassium using solvent casting technique were prepared and evaluated for different parameters.

MATERIALS AND METHODS

Losartan potassium was obtained as a gift sample from Zim laboratories, Nagpur. Eudragit RS100 and Eudragit RL100 were obtained from Rohm Pharma, Germany. HPMC and Ethylcellulose were obtained from Loba Pvt. Ltd. Mumbai. All other chemicals and reagents used were analytical grades.

Preformulation study is one of the important prerequisite in development of any drug delivery system. Hence the compatibility study of drug and polymers were carried out using DSC analysis.

Preparation of buccal films of losartan potassium:
The buccal films of losartan potassium were prepared by solvent casting method with HPMC alone and in combination with different copolymers namely Eudragit RL100, Eudragit RS100 and Ethyl cellulose with glycerol as plasticizer. Small films of 2 cm diameter, 0.2-0.3 mm thick and containing 25 mg drug were punched out from the cast films using a specially fabricated punch. The formula for various formulations attempted has been given in Table1.

The HPMC was soaked in ethanol for 24 h and then solution of chloroform and dichloromethane in the ratio 3:1 were added to the HPMC solution. To this required quantity of drug was added which was previously dissolved in methanol. Finally two drops (0.06 ml) of glycerol was added as plasticizer. This solution was mixed for about 30 min by using a magnetic stirrer. The polymeric solution was poured in to a glass ring, which was previously placed over mercury substrate in a petridish. The rate of evaporation of solvent was controlled at room temperature by inverting funnel over the petridish. After 12 h, the dried patches were collected and stored in desiccator. The other formulations were prepared by dissolving the Eudragit RL100, Eudragit RS 100, and Ethyl cellulose in acetone in three separate beakers. All these solutions were added to the alcoholic HPMC solution. Then the above procedure was adopted for the preparation of the film containing losartan potassium.

Table 1: Composition of Various Prepared Buccal Films

Formulation code	F1	F2	F3	F4	F5	F6	F7
Losartan Potassium (mg)	225	225	225	225	225	225	225
HPMC E15 (mg)	600	450	300	450	300	450	300
Eudragit RS100 (mg)	-	150	300	-	-	-	-
Eudragit RL 100 (mg)	-	-	-	150	300	-	-
Ethyl cellulose (mg)	-	-	-	-	-	150	300
Glycerol (ml)	0.06	0.06	0.06	0.06	0.06	0.06	0.06

Drug incorporated in each film: 25 mg and polymer incorporated in each film: 66.66 mg

Evaluation of prepared buccal films:

Mass uniformity and Thickness:

For the mass uniformity, three films from every formulation were taken and weighed individually on electronic balance. The average weight was calculated. Three films of each formulation of different batches were selected randomly and the thickness of the film was measured at different places using screw gauge. The average film thickness was computed [3].

Folding endurance test:

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

Surface pH:

The surface pH of the film was determined in order to investigate the possibility of any side effects, *in vivo* due to film pH. The method adopted by Bottenberg *et al* was used to determine the surface pH of films. A combined glass electrode was used for this purpose. Each film was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 h at room temperature, and the pH was noted by bringing the electrode into contact with the surface of the film and allowing it to equilibrate for 1 minute. The experiment was performed in triplicate, and average values were reported [5].

Drug Content Uniformity:

Three films of each formulation were taken in separate 100 ml volumetric flask; 100 ml of pH 6.8 phosphate buffer was added and continuously stirred for 24 h. The solutions were filtered, diluted suitably and analyzed on a UV spectrophotometer. The average of drug contents of three films was taken as final reading [6].

Swelling:

The three films were tested for each formulation. After determination of the original film diameter, the sample was allowed to swell on the surface of an agar plate kept in an incubator

(hot air incubator) maintained at 37 °C. Measurement of the diameter of the swollen film was done at 1 h intervals up to 5 h. Radial swelling was calculated from the following equation [7].

S_D (%) = [(D_t – D_o)/D_o] × 100…… (1)

Where,
S_D (%) - The percent swelling obtained by the diameter method.
D_t - The diameter of the swollen film after time t.
D_o - The original patch diameter at time zero.

***In –vitro* bio-adhesion test:**
The goat cheek pouch was carefully excised without removing connective and adipose tissue and washed with saline. The tissue was stored in saline; later the membrane was placed over the surface of glass slide mounted on lower Teflon block and secured. The block was then lowered into a glass container, which was then filled with phosphate buffer of pH 6.8 and kept at 37±1°, such that the buffer just reaches the surface of mucosal membrane and kept it moist. One formulation at a time was taken and stuck to the lower surface of upper Teflon block with a standard cyanoacrylate adhesive. The beaker containing mucosal tissue containing the lower block was adjusted over the base of the balance so that the mucosal tissue exactly below the upper block. A preload weight of 5 g was placed above the expanded cap, left for 5 min, after which the patch binds with the mucin. The weights were then removed slowly and gradually after binding the patch with mucin the weights were added slowly on the right side pan till the patch separates from the mucosal surface/membrane. The weights required for complete detachment was measured and expressed as bioadhesive strength in g. Procedure was repeated for three more patches of each formulation of different batches. Average was computed and recorded [8].

The force of adhesion (F) calculated from the bioadhesive strength.
Force of adhesion (F) = [W x g] / 1000…… (2)
Where,
F = Force of adhesion in N
W = Bioadhesive strength in g
g = Acceleration due to gravity

***In vitro* Residence Time:**
The *in vitro* residence time was determined using USP disintegration apparatus. The disintegration medium was 800 ml of pH 6.8 phosphate buffer maintained at 37±2^o. The segments of goat cheek mucosa, each of 3 cm length, were glued to the surface of a glass slab, which was then vertically attached to the apparatus. Three mucoadhesive films of each formulation were hydrated on one surface using phosphate buffer pH 6.8 and the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down. The film was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time required for complete erosion or detachment of the film from the mucosal surface was recorded (mean of triplicate determination) as given in Table 3 [9].

In Vitro Buccal Permeation Study:

The *in vitro* buccal permeation study of losartan potassium through the goat buccal mucosa was performed using a Keshary-Chien type glass diffusion cell at 37° ± 0.2°. Goat buccal mucosa was obtained from a local slaughterhouse and used within 2 h of slaughter. Freshly obtained goat buccal mucosa was mounted between the donor and receptor compartments. The film was placed on the mucosa and the compartments were clamped together. The donor compartment was filled with 1 ml of phosphate buffer (pH 6.8). The receptor compartment (20-ml capacity) was filled with phosphate buffer (pH 7.4), and the hydrodynamics in the receptor compartment were maintained by stirring with a magnetic bead at 50 rpm. At predetermined time intervals, a 1-ml sample was withdrawn and analyzed. The experiments were performed in triplicate, and average values were reported [10].

In-Vitro Drug Release:

The US Pharmacopeia XXIII rotating paddle method was used to study drug release from the buccal patches; 200 ml of phosphate buffer (pH 6.8) was used as the dissolution medium, at 37°.0 ± 0.5, and a rotation speed of 50 rpm was used. One side of the buccal patch was attached to the glass disk with instant adhesive (cyanoacrylate adhesive). The disk was put in the bottom of the dissolution vessel. Samples (5 ml) were withdrawn at defined intervals and replaced with fresh medium. The samples were filtered through Whatman filter paper and analyzed. The experiment was performed in triplicate, and average values were reported [10].

Stability studies:

The Optimized formulation F5 was subjected to accelerated stability testing. The ageing studies were conducted at 37° and 45° to investigate the effect of temperature on the drug content in formulation. Films were packed in glass Petri dishes lined with aluminum foil and kept in an incubator maintained at 37±0.5° and 45 ±0.5° for one month. Changes in the appearance, drug content of the stored bioadhesive patches were investigated after 7, 14, 21 and 28 days [8].

RESULTS AND DISCUSSION

To assess any interaction between the drug and the polymer DSC studies were performed on a DSC-61000 (Seiko Instruments, Japan) as shown in fig. 1 and fig. 2. The DSC analysis of the physical mixture of the drug and the polymers revealed a negligible change in the melting point of losartan potassium in the presence of the polymer mixtures under study. Thus, DSC results suggest that the drug and polymers are compatible.

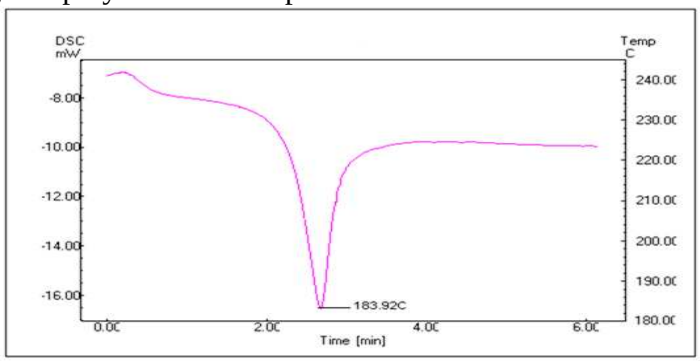

Fig. 1: Thermograph of losartan potassium

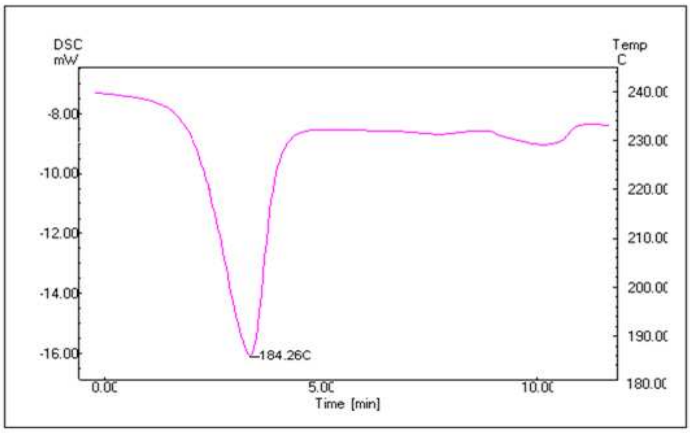

Fig. 2: Thermograph of physical mixture of losartan potassium, HPMC and Eudragit RL 100

The average weight of film from each group of formulation was reported in (Table 2) by using three films for standard deviation. The weight of buccal films ranges from 90.60±0.025 mg to 92.88±0.086 mg. Results indicated that formulation F5 (HPMC and Eudragit RL 100) having highest mass while formulation F6 (HPMC and Ethyl cellulose) having the least among the different formulations.

The thickness (Table 2) of the films varied from 0.19±0.005 mm to 0.23±0.012 mm. Formulation F5 (HPMC and Eudragit RL 100) having the highest thickness 0.23±0.012 mm because of F5 having highest mass among all formulations.

The folding endurance (Table 2) of the films was measured manually and they were folded between 205 to 305 times without breaking or cracking. It shows that the films having good strength and mechanical property for all formulation. The higher folding endurance was observed in formulation containing Ethylcellulose as copolymer. The high folding endurance was observed in formulation F7 in which HPMC was used in combination with Ethylcellulose in 2:2 ratios, which indicates that an increase in polymer concentration increased the folding endurance.

The surface pH (Table 2) of all the films exhibited almost uniformity in their values and they were found in between 6.21±0.020 to 6.49±0.015 indicating its compatibility with buccal pH.
The drug content (Table 2) was estimated in all the formulations using standard method. The drug content of all the films was found to be uniform with low s.d. values, which indicates that the drug was distributed uniformly in all the films.

Any polymer with good swelling property is expected to be a good candidate for bioadhesive application. When bioadhesive comes in contact with aqueous medium they swell and form a gel. The rate and extent of water uptake by a polymer has been reported to be an important factor in determination of its relative bioadhesive strength, uptake of water results in relaxation of originally stretched, entangled or twisted polymer chain resulting in exposure of all polymer bioadhesive sites for bonding to occur. The faster this phenomenon occurs more rapidly will be the polymers adhering to its substrate. The results showed that the swelling index (Table 2) of

formulation F5 containing HPMC and Eudragit RL 100 was more than the film containing HPMC alone and films with other copolymers. It showed that the Eudragit RL 100 having more water uptake property than the other polymers. It was observed that there was proportionate increase in swelling of film as the increased in concentration of polymer.

Table 2: Physical Evaluation of Formulation F1-F7.

Formulation	Mass uniformity (mg ± SD)	Thickness (mm ± SD)	Folding endurance (± SD)	Surface pH	Drug Content (mg)	% Swelling (After 5 h)
F1	91.75±0.32	0.20±0.05	215±4.58	6.21±0.20	24.79±0.28	20
F2	92.38±0.37	0.20±0.07	205±3.21	6.26±0.11	24.56±0.25	25
F3	91.92±0.55	0.21±0.01	234±5.56	6.31±0.15	24.66±0.12	35
F4	92.10±0.15	0.22±0.05	228±4.75	6.21±0.11	24.68±0.30	35
F5	91.88±0.86	0.22±0.02	239±4.58	6.24±0.36	24.77±0.25	40
F6	91.60±0.25	0.21±0.05	286±3.51	6.25±0.12	24.80±0.21	15
F7	91.92±0.87	0.21±0.07	305±4.55	6.39±0.15	24.75±0.30	25

Table 3: *in –vitro* bioadhesive strength and *in vitro* residence time of buccal films of losartan potassium.

Formulation	Bioadhesive strength. (g ± S.D.)		Force of adhesion (N± S.D.)		Residence Time (h ±S.D.)
	5 min	10 min	5 min	10 min	
F1	30.40±0.10	38.21±0.18	0.28±0.05	0.35±0.02	3.20±0.12
F2	32.53±0.15	39.30±0.10	0.30±0.06	0.36±0.06	3.12±0.24
F3	42.80±0.050	60.19±0.24	0.39±0.05	0.55±0.02	3.25±0.34
F4	33.46±0.042	41.58±0.057	0.31±0.07	0.38±0.04	3.42±0.53
F5	43.08±0.076	64.23±0.23	0.40±0.05	0.59±0.03	4.05±0.27
F6	28.51±0.066	36.09±0.59	0.26±0.05	0.33±0.06	3.20±0.45
F7	34.74±0.040	54.07±0.25	0.31±0.01	0.49±0.45	3.45±0.19

The results for bioadhesion indicated that the bioadhesive strength (Table 3) of formulation F5 containing HPMC and Eudragit RL 100 was more than the other formulations. Here we conclude that, the HPMC base having good bioadhesion properties in combination with Eudragit RL 100.

As the concentration of Eudragit RL 100 increases the bioadhesive strength was found to increase, may be due to combination of hydrophilic and hydrophobic nature which gains the bond strength with mucosal surface. It can be seen that increasing the contact time for adhesion, increased the bioadhesive force.

The values of the *in vitro* residence time were reported in the (Table 3). Time required for the complete erosion or detachment of buccal films from the mucosa was found satisfactory. The highest duration (4.05 h) was recorded for formulation F5 containing Eudragit RL 100. Films of formulation F1 containing only HPMC; eroded completely in 3.20 h. This indicated that the water soluble hydrophilic additives dissolved rapidly introducing porosity. The void volume is expected to occupy by the external solvent diffusing into the film and thereby accelerating the dissolution of the film.

Drug permeation from *in vitro* diffusion studies of formulation F1-F7 was shown in (fig 3). All the formulation F1- F7 follows Peppas model. The slope of the straight line obtained after plotting the mean cumulative amount diffused per film vs. time was taken as the *in vitro* release for losartan potassium. Formulation F5 has showed maximum release (93.32%) in 6 h and follows Peppas model with highest correlation coefficient value (0.9990) and mechanism of release was non-fickian mediated with lowest diffusion coefficient.

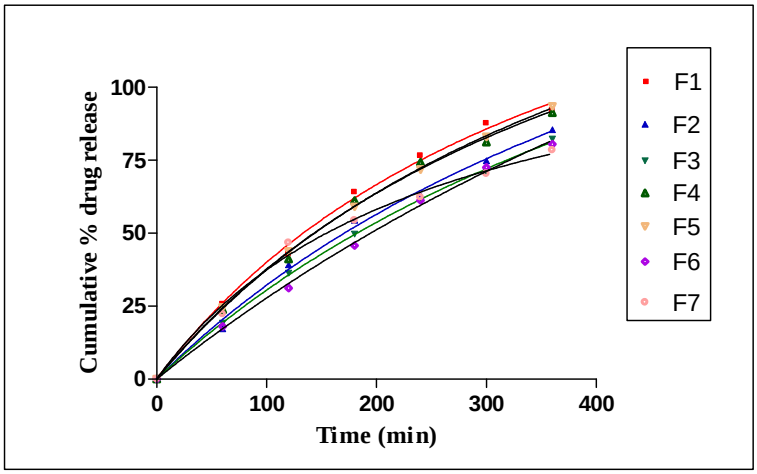

Fig. 3: *In-vitro* diffusion study of losartan potassium from buccal films of formulation F1-F7

In vitro dissolution studies were shown in (fig 4). The study of drug release kinetics showed that all the formulations F1-F7 were governed by Peppas model and mechanism of drug release was non-fickian mediated. Regression analysis of the *in vitro* permeation curves was carried out. The slope of the curve obtained after plotting the mean cumulative amount released per patch vs. time was taken as the *in vitro* release for losartan potassium. All the formulations showed release up to 6 h. Formulation F5 showed maximum release (96.548%) while formulation F7 showed lowest release (82.408%). Formulation F5 has highest K value and follows Peppas model rate release and mechanism of drug release was non-fickian mediated with lowest diffusion coefficient.

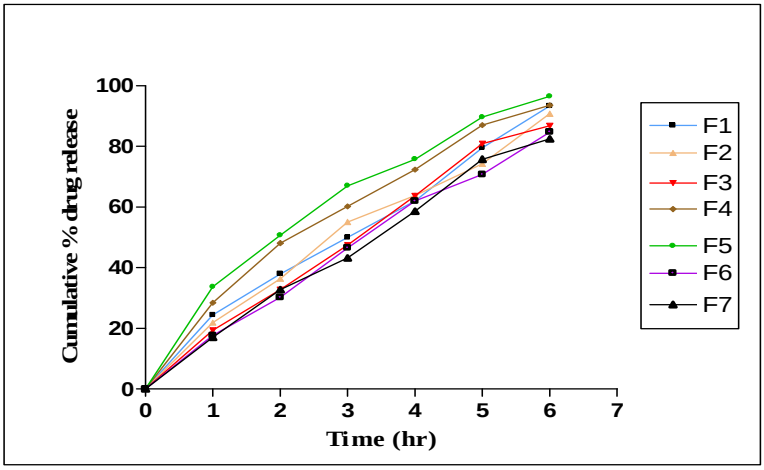

Fig. 4: *In-vitro* drug release for formulation F1-F7.

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

CONCLUSION

Among the various polymeric combinations, the combination **F5** was found to be most suitable. The formulation **F5** comprising polymers HPMC and Eudragit RL 100 in 2:2 ratios fulfill the requirement of good buccal film. It showed highest swelling as well as highest bioadhesive strength. It shows *in vitro* residence time up to 4 h. It follows *In vitro* drug release up to 96.54 % for 6 h and *In vitro* drug permeation up to 6 h.

Thus from the present study it can be concluded that, buccoadhesive drug delivery system for losartan potassium with HPMC and Eudragit RL 100 meet the ideal requirement for buccal devices which can be good way to bypass the extensive hepatic first pass metabolism and increase bioavailability.

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