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ORIGINAL RESEARCH ARTICLE

Buccoadhesive Tablets of Losartan Potassium: Design and Characterization

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ABSTRACT

Adhesive buccal tablets of losartan potassium were prepared with an objective to increase the bioavailability by avoiding first pass metabolism and also to prolong the drug release. Carbopol 934P was used as a primary mucoadhesive polymer and either sodium CMC, HPMC K4M or sodium alginate as secondary polymer, in different ratios. The buccal tablets were subjected for evaluation of various physicochemical properties such as weight variation, tablet thickness, content uniformity, surface pH, bioadhesive strength and swelling index. *In vitro* drug release studies were carried out using flow thru cell. Chicken pouch was used as model mucosa membrane in *in vitro* permeation study. Stability studies were carried out at refrigerator (2-8°C), room temperature (25-30°C) and accelerated temperature (45-50°C) for two months. The results of weight variation, thickness, content uniformity, surface pH and bioadhesive strength of all batches were satisfactory and comply with theoretically expected values. *In vitro* release studies demonstrate a highest percentage of drug release from the group III formulations (sodium alginate as a secondary polymer). However formulation of this group showed fast fragmentation and higher matrix erosion. Formulation of group I (sodium carboxymethyl cellulose as secondary polymer) and group II (HPMC K4M as secondary polymer) showed an adequate release and mucoadhesion. *In vitro* drug release follows zero order kinetics for all the formulations. *In vitro* permeation studies further confirm the prolonged release as well as transport of drug molecule across a biological membrane. Stability studies indicate no significant changes with respect to surface pH, bioadhesive strength and drug content at the end of two months.

Key Words: : Buccal tablet, Losartan Potassium, Mucoadhesion, Bioadhesive Polymer.

INTRODUCTION

High blood pressure is known as ‘silent killer’. Hypertension is the leading cause of mortality in the world after malnutrition and tobacco used and is responsible for an estimated 5% of all deaths. Losartan is a competitive antagonist of angiotensin II (AII), devoid of partial agonistic activity and 10,000 times more selective for AT_1 than AT_2 receptor; does not block any other receptor or ion channel. It blocks all over action of AII. Losartan potassium is widely used in management of hypertension. One of the main adverse effects is dose related hypotension.

Losartan is readily absorbed from the gastrointestinal tract following oral administration. However oral bioavailability is only about 33% due to the first pass metabolism. The terminal elimination half life of losartan is 1.5 to 2.5 hours. Due to high first pass metabolism a critical dose adjustment is required in patient with hepatic impairment. [1, 2]

Drugs administered by buccal route offers several advantages such as rapid absorption through oral mucosa and high blood level due to high vascularisation of the region; thereby avoiding first pass effect. Other advantages of this route are ease of administration and therefore better patient compliance. The residence time of a dosage form in buccal cavity can be prolonged by the use of mucoadhesive polymer(s). Several bioadhesive tablet system have been developed in recent years with a goal to improve he bioavailability of administer drug. Adhesive buccal tablets can be applied to different sites in

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the oral cavity i.e., the palate, mucosa of the cheek and between the upper lip and gum. The tablet softens and adheres to the substrate and is retained in position until dissolution and /or release is complete. After a short time the presence of tablet is reported to be no longer noticeable to the patient. The position of successive tablets can be alternated on either side of the mouth. Some systems have been developed and are already available in the market, such as NICORETTE (nicotine), SUSCARD (glyceryl trinitrate) and STRAINT (testosterone), while others are still in the development stage. [3,4] Thus formulation of losartan potassium into bioadhesive tablet will overcome bioavailability problems due to first pass effect and use of controlled drug delivery will optimize therapeutic effect.

MATERIALS AND METHODS

Losartan potassium, Carbopol 934 P, HPMC K4M was obtained as gift samples from Micro Lab Ltd., Hosur. Sodium carboxymethyl cellulose and sodium alginate obtained from Sulab, Baroda. Magnesium stearate obtained from Genuine Chemical Co., Mumbai. All other reagents and chemicals used were of analytical grade.

Preparation of buccal tablets:

Matrix type buccal tablets were prepared by direct compression method. The buccal tablets were prepared by using Carbopol 934 P (CP 934 P) as primary mucoadhesive polymer because of its excellent mucoadhesive properties. HPMC K4M, NaCMC and sodium alginate were used as secondary polymers. CP 934 P and secondary polymers in the ratio of 1:1, 1:1.5, 1:2 and 1:3 were incorporated in different buccal tablets. The composition of different formulations is represented in **Table 1**. The components of each formulation sufficient were mixed and passed through the mesh (100μ) and triturated well in a glass mortar to ensure homogeneous mixing. 200 mg each was compressed using 8 mm diameter die and punches on tablet compression machine (Kambert, D-Tooling Machine).

TABLE 1: COMPOSITION OF PREPARED BUCCOADHESINE TABLETS.

Formulation code	Ingredients (weight in mg) per tablet.					
	Losartan potassium	Carbopol 934	NaCMC	HPMC	Sodium alginate	Magnesium stearate
FA1	20	89	89	-	-	2
FA2	20	71.200	106.800	-	-	2
FA3	20	59.333	118.667	-	-	2
FA4	20	44.50	133.500	-	-	2
FB1	20	89	-	89	-	2
FB2	20	71.20	-	106.800	-	2
FB3	20	59.333	-	118.667	-	2
FB4	20	44.500	-	133.500	-	2
FC1	20	89	-	-	89	2
FC2	20	71.200	-	-	106.800	2
FC3	20	59.333	-	-	118.667	2
FC4	20	44.500	-	-	133.500	2

Uniformity of weight test:

Twenty tablets were weighed individually and the average weight was determined. The % deviation was calculated and checked for weight variation. [5]

Tablet thickness:

The thickness of the tablets of 10 tablets of each formulation measured using screw gauge. [6]

Content uniformity:

Representative tablets (three) of each formulation were crushed using a mortar and a pestle. Aliquots of the crushed tablets equivalent to 20mg of losartan potassium were weighed and required amount of distilled water was added to extract the drug. This suspension was shaken for 6 hour and volume was made up to 100 ml with distilled water, filtered through Whatman filter paper, 2 ml of filtrate were diluted to 50 ml with distilled water. The samples were analyzed in Jasco V-530 spectrophotometer at 205.8 nm. [7]

Surface pH of the buccal tablets:

The surface pH of the tablets was determined in order to investigate the possibility of any side effects due to change in pH *in vivo*, since an acidic or alkaline pH may cause irritation to the buccal mucosa. The tablets were allowed to swell by keeping them in contact with 1.0 ml of distilled water (pH 6.33±0.01) for 2 hours and pH was noted by bringing the electrode in contact

with the surface of the formulations and allowing it to equilibrate for 1.0 minute. [6]

Measurement of bioadhesive strength:

Several techniques have been reported in literature for measurement of bioadhesive strength. In the present work, we have studied the bioadhesion using a modified physical balance, fabricated in the laboratory based on published literature. [8]

Swelling studies:

The tablets of each formulation were weighed individually (designated as W_1) and placed separately in petridishes containing simulated salivary fluid. At regular intervals (0.5, 1, 2, 3, 4, 5, 6, 7 and 8 hr), the tablets were removed from the petridishes and excess water was removed carefully by using filter paper. The swollen tablets were reweighed (W_2); the swelling index of each formulation was calculated using the formula, [9]

$$\text{Swelling Index (S.I)} = \frac{W_2 - W_1}{W_1}$$

***In vitro* release studies:** [6]

In the present work, a flow thru apparatus was designed for carrying out *in vitro* release studies and determination of duration of bio adhesion / erosion of buccal tablet. The flow thru cell was made up of glass and had a length of 10.5 cm and diameter of 2.1 cm. It was closed at one end and open at other. A small inlet of 0.5 cm diameter was attached to lower end of cell. In the centre of the lower base there was a cavity of 1.6 cm length and 1.5 cm depth for the placement of porcine mucous membrane. Buccal tablet was placed on the top of the mucous membrane, such that drug release occurs from only one side of the tablet. Total capacity of flow thru cell is 30 ml.

A buccal tablet was fixed on the top of the porcine mucous membrane, placed within the cavity of the flow thru cell. Flow thru cell was placed in water bath and temperature was maintained at 37±0.5ºC. Such, that drug release occurs from only one side of the tablet. Simulated salivary fluid (pH 6.75), 30 ml was added into the flow thru cell. Simulated salivary fluid from a reservoir was allowed to flow into the lower inlet at a flow rate of 0.65 ml/min using flow regulator. This corresponded to the mean resting salivary flow rate. The outlet was connected to a collecting beaker, to collect the fluid passing through the flow thru cell. The collecting beaker was pre-calibrated which ensure the flow rate of simulated salivary fluid. Samples of (5 ml) were withdrawn at different time intervals from the collecting beaker and replaced with fresh simulated salivary fluid; till the tablet eroded completely or dislodged whichever was earlier. The cumulative percent drug released was determined by measuring absorbance in UV visible spectrophotometer at 208 nm.

***In vitro* permeation studies:** [8, 10]

It is essential to investigate the permeation of the drug molecule through the appropriate buccal mucosa to ascertain the systemic availability of the drug molecule from the developed buccal adhesive system. This study was carried out by using modified version of a diffusion cell. It consists of a glass tube open at both end. Chicken buccal mucosa was chosen as the model membrane, tied with mucosal side facing upward at one end of the diffusion cell. The end containing mucosal membrane was dipped carefully in a beaker containing 200 ml of isotonic phosphate buffer (pH 7.4). This beaker was placed on magnetic stirrer with heating plate. The beaker content was maintained at 37±0.5°C and stirred with a magnetic bead. The tablet was stuck on the chicken buccal membrane which was previously moistened with a few drops of simulated salivary fluid. 10 ml of simulated salivary fluid was placed within the cylindrical tube. Samples of (2 ml) were withdrawn from the beaker at a predetermined time interval and filtered and then analyzed.

Stability studies

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. In the present work stability studies were carried out at refrigerator (2-8°C), room temperature (25-30°C) and accelerated temperature (45-50°C) for 2 months. The formulations were evaluated for surface pH, bioadhesive strength and drug content.

RESULTS AND DISCUSSION

The results of weight variation and content uniformity shows all the formulations complies with that prescribed in the Indian Pharmacopoeia. Surface pH of all the formulations of three groups is in an acceptable pH range of 5.5 to 7.0 (salivary pH). Hence they may not produce any local irritation to the mucosa. However on the basis of other parameters ie bioadhesive strength, swelling index, *in vitro* dissolution study and *in vitro* permeation study; group-II formulation (HPMC

K4M as secondary polymer) emerge as optimized formulation. The results of bioadhesive strength and surface pH of optimized tablets are shown in **Table 2** and the bar graph of the same is represented in **Fig. 1**. The bioadhesive strength of the tablets was found to be a function of concentration of polymers, an increase in amount of CP 934P shows increase in bioadhesive strength. Bioadhesive strength exhibited by the optimize tablets can be considered satisfactory for maintaining them in the oral cavity for 8 hrs.

Table 2: Surface pH and Bioadhesive Strength of Optimized Buccal Tablets

Parameters	FB1	FB2	FB3	FB4
Surface ph	6.22	6.34	6.31	6.38
Bioadhesive strength (gm)	29.833	28.233	25.733	25.4

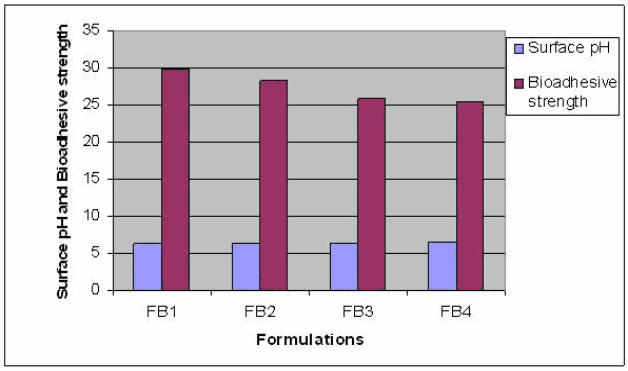

Fig 1: Surface pH & Bioadhesive Strength of Optimized Buccal Tablets.

The swelling index of optimize buccal tablets for a period of 8 hrs is shown in **Fig. 2.** Tablets containing carbopol 934P and HPMC K4M at the ratio of 1:1, 1:1.5, 1:2, 1:3 showed a swelling rate in the order 1:1>1:1.5>1:2>1:3. The hygroscopic nature of the polymers is one of the important properties that affect swelling. Among all the formulation the optimized group (**group II**) showed minimum swelling and matrix erosion at the end of 8 hrs.

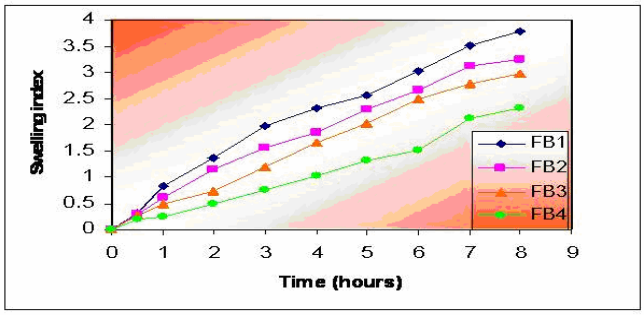

Fig 2: Swelling Index of Buccal Tablets.

In vitro release studies:

In vitro release profile of losartan potassium from optimized buccoadhesive tablets are shown in **Fig 3.** The *in vitro* release study showed a satisfactory sustained release of losartan potassium from optimized tablets. It is evident that a higher release of losartan potassium occurred from the tablets contain higher proportion of carbopol 934. The *in vitro* release data was analyzed to find out the release kinetics. Correlation co-efficient (r^2) for both zero order and first order for optimized formulation are shown in table 4. Results indicate that the drug release from the optimized buccal tablets follows zero order kinetics. This could be explained on the basis of the following hypothesis. Initially in dry state losartan is distributed uniformly throughout the polymer matrix. After coming in contact with dissolution and as gelation takes place the release of losartan occurs from the surface of the swollen matrix. The movement of losartan to the surface is governed by the viscosity of the external hydrogel phase. Also carbopol in its non-neutralized form does not gel completely, as it still remain in coiled form. As the proportion of carbopol increases, viscosity also decreases in the same order. Thus a higher release with larger proportion of carbapol may be observed. **Table 3& 4**.

Table 3: Maximum Percentage of Drug Released & Permeated For the Optimized Formulation.

Formulation	Maximum percentage of drug release at the end of 8 hrs	Maximum percentage of drug permeated at the end of 8 hrs
FB1	67.0374	57.1955
FB2	65.2759	52.2415
FB3	61.0447	44.3524
FB4	55.8567	41.0250

Table 4: Correlation Co-Efficient (R^2) Values for Optimized Formulation.

Formulation Code	Zero order	First order
FB1	0.9808	0.6556
FB2	0.9828	0.7010
FB3	0.9860	0.6649
FB4	0.9883	0.6926

In vitro permeation studies:

A comparable result was obtained between *in vitro* drug release and *in vitro* drug permeation study. *In vitro* permeation studies data confirm the prolonged release as well as transport of drug molecule across a biological membrane. Maximum percentage of drug release and permeated at the end of 8 hrs is shown in **Table 2.** *In vitro* drug permeation profiles for optimized buccal tablets are shown in **Fig. 3.**

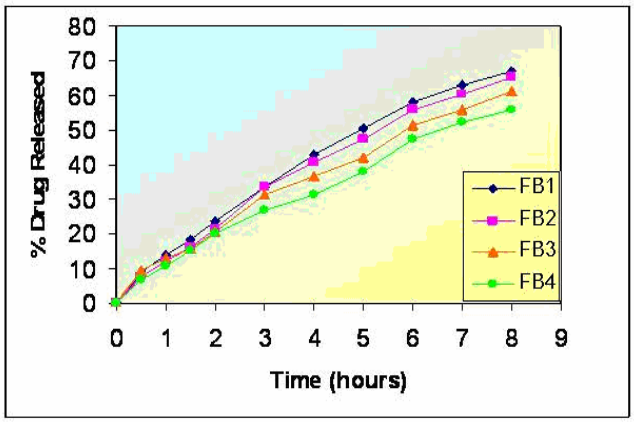

Fig 3: *In Vitro* Drug Release Profile of Formulation FB1-FB4

Stability studies:

The results of stability studies of buccal tablets indicate no significant change with respect to drug content, surface pH and bioadhesive strength at the end of two months when stored in refrigerator (2-8°C), room temperature (25-30°C) and accelerated temperature (45-50°C).

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