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Original Article

Bioadhesive Polymer Buccal Tablets for Losartan Potassium Controlled Delivery: Formulation, *In-vitro* and *Ex-vivo* Evaluation

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ABSTRACT

The intention of this research was to develop buccal drug delivery system of Losartan Potassium to enhance the oral bioavailability and prolong the drug release. Carbopol 940P with HPMC (K4M, K15M, K100M), Guar gum, Sodium cmc, Sodium alginate were used as polymers. Tablets were fabricated by direct compression technique and were evaluated for weight variation, thickness, Hardness, Friability, Surface pH, *in vitro* retention time, mucoadhesive strength, *in-vitro* drug release & *ex-vivo* permeation studies. The results of post compressional parameters were within acceptable limits. Amidst all the formulations F9 was tracked down to be the most compatible. The tablets evaluated for various parameters and results are appeased. *In-vitro* drug release in phosphate buffer (pH 6.8) was found to be 60.25% at the end of 8th hour. The release of Losartan Potassium from the tablet followed Zero order, Higuchi's model and mechanism diffusion rate limited. Fourier transform infrared results proclaimed that there are no interactions amid Losartan potassium and the polymers used.

Keywords: Buccoadhesive tablets, Losartan potassium, Carbopol 940P, HPMC (K4M, K15M, and K100M), Sodium CMC, Sodium alginate, Guar gum.

INTRODUCTION

Losartan Potassium is an Angiotensin II receptor antagonist (Anti hypertensive). It undergoes extensive first pass metabolism in liver as a result it has low bioavailability. Hence it is selected as a suitable candidate for Bioadhesive buccal

drug delivery[1]. Bioadhesive buccal drug delivery is one of alternative to the oral route of drug administration, the drug via the buccal route can circumvent problems such as drug degradation in the gastrointestinal environment, inconvenience of parenteral administration[2,3]. In this study buccal tablets were prepared by using Carbopol 940 P as primary mucoadhesive polymer because of its mucoadhesive properties and different grades of HPMC, Sodium CMC, Sodium alginate, Guar gum were used as secondary polymers[4].

MATERIALS AND METHODS

Materials

Losartan Potassium was obtained as a gift sample from Hetero laboratories, Hyderabad, India. HPMC K4M, HPMC K15M, HPMC K100M, Carbopol 940P, Sodium CMC was obtained as a gift sample from SD Fine Chemicals, Mumbai, India. Sodium alginate, Guar gum was obtained as a gift sample from Dr. Reddy's laboratories, Hyderabad, India, Sodium hydroxide, Magnesium Stearate, Talc was obtained as a gift sample from Universal laboratories Pvt. Ltd. and Potassium dihydrogen phosphate, was obtained as a gift sample from Merck Pvt. Ltd. Goa.

Preparation of tablets

Buccoadhesive tablets containing Losartan Potassium were prepared by direct compression method using Carbopol 940P as primary mucoadhesive polymer because of its mucoadhesive properties. HPMC K4M, HPMC K15M, HPMC K100M, Sodium CMC, Sodium alginate, and Guar gum were used as secondary polymers. The entire ingredients except talc, magnesium stearate were blended uniformly. After sufficient mixing of drug as well as other components, talc and magnesium stearate were added and further mixed for additional 2-3 minutes, the tablets were compressed with 6 mm punches on tablet compression machine[7]. Formulation of Buccoadhesive Tablets of Losartan Potassium is shown in Table no.1.

Evaluation of physical properties of buccal tablets

The prepared tablets were evaluated for weight variation, hardness, thickness, friability, drug content, *in-vitro* drug release studies, measurement of bioadhesion strength, *in-vitro* retention time, surface pH of the buccal tablets, and *ex-vivo* permeation of the buccal tablets.

Hardness

Pfizer hardness tester was used for the determination of the hardness. For each formulation the hardness of 6 tablets was evaluated[7]. The values are shown in table no.2.

Weight variation test

In weight variation test twenty tablets were selected randomly and average weight was calculated. Then individual tablets were weighed and the weight was compared with an average weight[7,8]. The values are shown in table no.2.

Thickness

Thickness of ten tablets from each batch was determined using vernier calipers[7,8]. The values are shown in table no.2.

Friability

The Friability of the 6 tablets was determined using Roche friabilator (Electro lab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100

revolutions. Tablets were dedusted using a soft muslin cloth and reweighed[8]. The friability (F) is given by the formula:

$$F = (1- W_0 / W) \times 100$$

Where, W_0 is the weight of the tablets before the test and W is the weight of the tablet after the test. The values are shown in table no.2.

Drug content

Ten tablets were weighed individually, an accurately weighed portion of the drug powder equivalent to about 50 mg of Losartan Potassium was extracted in phosphate buffer pH 6.8 and the mixture was filtered through a Whatman filter paper (No.1). From this resulted solution 1 ml was taken, suitably diluted with phosphate buffer pH 6.8 and absorbance was measured against blank at 208 nm[9]. The values are shown in table no.2.

In vitro drug release studies

In vitro drug release studies for the prepared matrix tablets were conducted for a period of 24 hrs using a USP apparatus type II (Tab-Machines, Mumbai, India) at 37±0.5°C and at 50 rpm speed, the *in vitro* release study was performed in phosphate buffer pH 6.8 upto 8 hrs. At every interval 5 ml of sample was withdrawn from the dissolution medium and replaced with fresh medium to maintain the volume constant. After filtration and appropriate dilution, the sample solutions were analyzed at 208 nm for Losartan potassium by a UV-Visible spectrophotometer[10]. The amount of drug present in the samples was calculated.

Kinetic analysis of dissolution data

For finding out the mechanism of drug release from tablets, the dissolution data obtained from the above experiments were treated with the different release kinetic equations[1,2]. The values are shown in table no.3.

Zero order release equation:

$$Q = K_0 t \quad \text{..... (1)}$$

First order equation:

$$\ln Q = K_f t \quad \text{..... (2)}$$

Higuchi's square root of time equation:

$$Q = K_H t^{1/2} \quad \text{..... (3)}$$

Korsmeyer and Peppas equation:

$$F = (M_t/M) = K_m t^n \quad \text{..... (4)}$$

Measurement of bioadhesion strength

A modified balance method was used for determining the *ex vivo* buccoadhesive strength. Fresh sheep buccal mucosa was obtained from a local slaughter house was stored in pH 6.6 phosphate buffer at 4^0C upon collection. The experiment was performed within 3 hours of procurement of the mucosa. The buccal mucosa was fixed to the stainless steel piece with cyanoacrylate adhesive and placed in a beaker then pH 6.6 phosphate buffer[10] was added into the beaker up to the upper surface of the mucosa to maintain buccal mucosal viability during the experiment. Then the tablet was attached to the upper clamp of the apparatus and the beaker was raised slowly to establish contact between buccal mucosa and the tablet. A preload of 50 gm was placed on the clamp for 5 min to establish adhesive bond between the tablet and porcine buccal mucosa. After completion of preload time, preload was removed from the clamp and water was added in to the beaker from the burette at a constant rate. The weight of water required to detach tablet from buccal mucosa was noted as Bioadhesive strength and experiment was prepared with fresh mucosa in an identical manner[11]. The values are shown in table no.4.

In-vitro retention time

The tablet side was wetted with 50 µl simulated saliva and pressed over porcine buccal mucosa for 30 sec and secured on glass slab and was immersed in the dissolution apparatus containing 750 ml of pH 7.4 phosphate buffer, at 37^0 C. The paddle

was adjusted at a distance of 5 cm from the tablet and rotated at 25 rpm. The tablet behaviour was observed until complete detachment[12]. The values are shown in table no.4.

Surface pH of the buccal tablets

The tablets were allowed to swell by keeping them in contact with 1.0 ml of distilled water (p^H 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[12]. The values are shown in table no.4.

In-vitro permeation of buccal tablets

The porcine buccal membrane was mounted between the donor and receptor compartment of the standard Franz diffusion cell with an area of 30.02 cm^2 and the acceptor compartment volume of 21 ml. A semipermeable membrane (buccal mucosa) was clamped between the donor and acceptor compartments. The phosphate buffer in the acceptor compartment was continuously stirred at 600 rpm using a magnetic stirrer. The tablet was placed in to the donor compartment and was wetted with 1 ml of phosphate buffer. The amount of drug permeated through the membrane was determined by removing aliquots from the acceptor compartment and by replacing the same volume of buffer. The flux (J) through the membrane was calculated by using the equation[13,14]. The values are shown in table no.5.

$$J = d Q / A dt$$

Where, J is flux (mg h-1 cm^2); d Q /dt is the slope obtained from the steady-state portion of the curve and A is the area of diffusion (cm^2).

RESULTS AND DISCUSSION

Physical properties of losartan potassium buccal tablets

Physical properties like average weight, thickness, hardness and friability complied with the official limits of IP[1]. While 96.27-102.5% drug content range was seen for all the formulations. There was no evidence of local irritation to the buccal mucosa as the surface pH was found to be 6-7.

Ex-vivo bioadhesive strength and *in vitro* mucoadhesion time

The Buccal tablets containing carbopol 940P in combination with HPMC (K4M, K15M, K100M, Sodium cmc, Sodium Alginate and guar gum in 1:2 and 1:4 ratio have shown the bioadhesive strength as follows. F1, F2 (18.39 & 15.39), F3, F4 (16.89 & 13.85), F5, F6 (24.19-22.89), F7, F8 (19.5 & 14.10), F9, F10 (30.09 & 22.95), F11, F12 (23.30 & 19.19). (Table 4). It was observed that increase in the concentration of the secondary polymer led to increase in the bioadhesive strength. The exhibition of the highest to lowest bioadhesive strength is in this fashion Sodium alginate > HPMC K100M > Guar gum > Sodium cmc > HPMC K4M > HPMC K15M.

The time period of mucoadhesion of the tablet on sheep buccal mucosa was between 6-7 hrs. Highest retention time was exhibited by formulation F9. The highest to lowest mucoadhesion strength is shown in this pattern sodium alginate > HPMC K100M > Sodium cmc > HPMC K15M > Guar gum > HPMC K4M. In this evaluation test too it was observed that with an increase in the amount of the secondary polymer there was an increase in the retention time.

In-vitro drug release

In accordance to the proportion of the matrix producing polymers, the release of the Losartan Potassium from buccal tablets

varied. It was observed that an increment in the amount of secondary polymer has shown a declining effect on the release rate of the drug from the buccal tablets. The aspect behind this may be an increase in concentration of the polymer, led to increase in hydration, finally ending up with increased swelling of the polymer. Matrix permitted drug to diffuse outward at delayed rate because of the expanded diffusional path length.[15,16] The Losartan potassium buccal tablets containing carbopol 940P have shown the percent drug release in this fashion HPMC K4M > Sodium cmc > HPMC K15M > Sodium Alginate > K100M > Guar gum.

In order to anticipate and correlate the release style of Losartan potassium from various tablets, it is essential to fit into an appropriate mathematical model. The *in vitro* Losartan potassium release results from buccal tablets were examined kinetically using different mathematical models like zero order, first-order, higuchi and Korsmeyer-Peppas model equations. When the Losartan potassium release rates were correlated with correlation coefficients, it was found to pursue zero order release kinetics (R^2 0.816 to 0.975). When the release data were examined according to Korsmeyer Peppas equations formulations F1, F2, F3, F4 & F7 followed anomalous transport, where as rest of the formulations followed super case – II transport.

Formulation F9 was considered to be the optimized one based on the result of *ex-vivo* bioadhesive strength, mucoadhesion time and *in-vitro* drug release, hence it was chosen for carrying out the *in-vitro* permeation studies across Sheep buccal mucosa. The drug penetration was slow and uniform and 26.64% of Losartan Potassium could permeate through the buccal mucosa in 8 hrs with a flux of 0.0496 mg/hr/cm^2.

FTIR analysis confesses that the inherent absorbance bands of different functional groups of Losartan potassium were found in the proximity of standard absorbance range. Thus the FTIR analysis has shown that there was no interaction between the drug and polymer under study.

CONCLUSION

It can be concluded that Losartan Potassium can certainly be administered through the oral mucosa. The designed buccoadhesive patches can overcome the disadvantage of extensive first pass effect and low oral bioavailability of Losartan Potassium. This increased and predictable availability of Losartan Potassium from designed formulation may result in substantial dose reduction of the dosage form when the drug is administered through oral mucosa so that it will be economical to the patient. Further work is recommended to support its efficacy claims by pharmacokinetic and pharmacodynamic studies in human beings.

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Table 1. Formulation of buccoadhesive tablets of losartan potassium

F. code	Drug	Carbopol 940P	HPMC K4M	HPMC K15M	HPMC K100M	Sodium CMC	Sodium alginate	Guar gum	Mannitol
F1	25	50	25						16
F2	25	50	12.5						28.5
F3	25	50		25					16
F4	25	50		12.5					28.5
F5	25	50			25				16
F6	25	50			12.5				28.5
F7	25	50				25			16
F8	25	50				12.5			28.5
F9	25	50					25		16
F10	25	50					12.5		28.5
F11	25	50						25	16
F12	25	50						12.5	28.5

- All the formulations contain Talc (2 mg), Magnesium Stearate (2 mg).
- Total tablet weight in all the formulations is 120 mg.

Table 2. Physical evaluation of buccoadhesive tablets

F. code	Hardness (kg/cm^2) ± S.D	Thickness (mm) ± S.D	Weight variation (mg) ± S.D	Friability (%) ± S.D	Drug content (%) ± S.D
F1	5.50±0.44	2.38±0.73	120.5±0.80	0.37±0.01	96.34±2.18
F2	5.00±0.31	2.20±0.68	118.2±0.83	0.42±0.01	97.29±0.98
F3	4.08±0.37	2.48±0.88	122.1±0.93	0.48±0.03	97.35±0.43
F4	5.41±0.70	2.21±0.36	119.2±0.97	0.15±0.01	98.88±0.88
F5	4.33±0.50	2.26±0.46	117.2±0.83	0.27±0.02	96.7±1.22
F6	5.58±0.57	2.48±0.38	122.2±0.92	0.29±0.02	98.5±2.09
F7	5.75±0.77	2.25±0.37	120.0±1.22	0.33±0.03	99.54±2.15
F8	4.91±0.80	2.24±0.52	119.8±1.48	0.44±0.01	102.55±2.31
F9	5.08±0.86	2.15±0.56	121.4±1.04	0.21±0.01	98.8±1.56
F10	4.16±0.75	2.20±0.44	125.4±1.09	0.42±0.02	96.27±1.88
F11	4.25±0.67	2.21±0.55	118.7±0.65	0.46±0.03	97.5±1.56
F12	4.30±0.47	2.31±0.56	122.1±1.82	0.38±0.01	102.87±0.97

Table 3. Drug release kinetics of losartan potassium buccoadhesive formulations

F. code	Zero order		First order		Korsmeyer-peppas		Higuchi
	R^2	K_0	R^2	K_1	R^2	n	R^2
F1	0.97	9.67	0.89	0.16	0.97	1.25	0.81
F2	0.92	9.84	0.83	0.18	0.88	1.01	0.76
F3	0.81	8.37	0.75	0.13	0.76	1.02	0.60
F4	0.84	8.83	0.78	0.14	0.76	1.12	0.65
F5	0.82	5.41	0.77	0.07	0.75	0.66	0.66
F6	0.97	6.81	0.97	0.10	0.95	0.77	0.92
F7	0.96	10.64	0.96	0.19	0.98	1.24	0.87
F8	0.96	10.82	0.94	0.21	0.91	1.05	0.86
F9	0.95	7.81	0.86	0.12	0.93	1.09	0.77
F10	0.92	8.56	0.87	0.13	0.96	0.82	0.76
F11	0.90	5.29	0.85	0.07	0.90	0.86	0.77
F12	0.93	6.57	0.86	0.09	0.86	0.84	0.80

Table 4. Buccoadhesive strength, *in-vitro* retention time and surface ph of losartan potassium buccoadhesive formulations

F. code	Bioadhesive strength (gm)	*In-vitro* retention time (Hrs)	Surface pH
F1	18.39±0.14	6 hrs 25 min	7. 05±0.70
F2	15.39±0.26	6 hrs 8 min	6.91±0.010
F3	16.89±0.54	6 hrs 35 min	7.08±0.085
F4	13.85±0.70	6 hrs 17 min	6.21±0.015
F5	24.19±0.78	7 hrs 20 min	7.0±0.035
F6	22.89±0.59	7 hrs 15 min	6.85±0.015
F7	19.5±0.43	6 hrs 40 min	6.73±0.010
F8	14.10±0.45	6 hrs 15 min	6.91±0.040
F9	30.09±0.67	7 hrs 50 min	7.05±0.005
F10	22.95±0.54	7 hrs 15 min	6.75±0.010
F11	23.30±0.37	6 hrs 35 min	6.85±0.015
F12	19.19±0.45	6 hrs 10 min	6.92±0.030

Table 5. *In-vitro* drug permeation studies of losartan potassium buccoadhesive formulations

Time (hrs)	*Ex-vivo* Permeation (%)
0.5	0.55
1	1.68
2	2.82
3	3.81
4	4.26
5	5.43
6	11.76
7	18.54
8	26.64

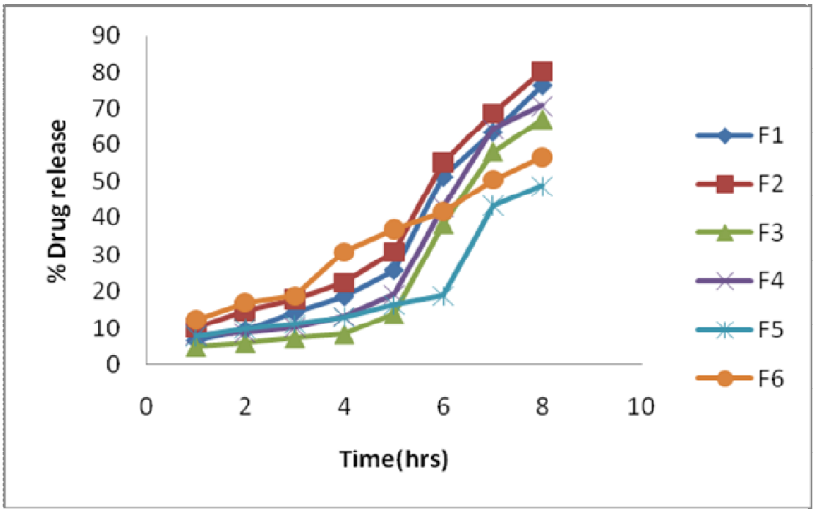

Figure 1. Release profiles of losartan potassium from buccoadhesive tablets containing combination of carbopol with HPMC K4 M/ HPMC K15 M / HPMC K100 M

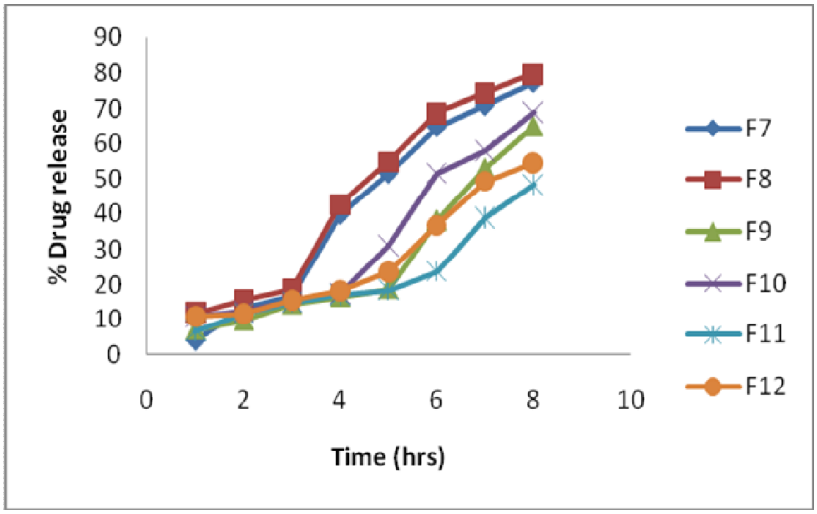

Figure 2. Release Profiles of Losartan Potassium from Buccoadhesive tablets containing combination of Carbopol with sodium CMC/Sodium Alginate/ Guar gum