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FORMULATION AND *IN VITRO* EVALUATION OF BUCCAL TABLETS OF LOSARTAN POTASSIUM

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Abstract:

The main objective of the present study was to formulate and evaluate the controlled release buccal tablets of losartan potassium by using carbopol, HPMC K4M, HPMC K15M and chitosan were selected as buccoadhesive polymers on the basis of their matrix-forming properties. The prepared tablets were evaluated for various parameters such as drug content, weight variation, hardness, thickness, friability, swelling studies, microenvironment pH, in vitro drug release studies, mucoadhesion strength and release rate kinetics. Based on the evaluation studies, the formulation BL6 has been considered as an optimised formulation, which showed a higher percentage of drug release, 98.47% and it follows zero-order kinetics with diffusion-controlled release.

Keywords: *Losartan potassium, Buccal delivery, Buccoadhesive polymers and Bioadhesion*

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1. INTRODUCTION:

The drugs administered by buccal route offer several advantages, such as rapid absorption through oral mucosa and high blood level due to high vascularisation of the region; thereby avoiding the first pass effect [1]. The residence time of a dosage form in the buccal cavity can be prolonged by the use of mucoadhesive polymers. The bioadhesive system has been developed to improve he bioavailability of the administered drug [2].

Losartan potassium is an angiotensin II receptor (AT_1) antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract following oral administration. However, oral bioavailability is only about 33% due to the first-pass metabolism. Due to high first-pass metabolism, a critical dose adjustment is required in a patient with hepatic impairment [3].

The present work is aimed at preparing buccal tablets of losartan potassium using various mucoadhesive polymers. The developed formulations will improve the bioavailability and avoid the first-pass effect.

2. MATERIALS AND METHODS:

2.1. Materials

Losartan potassium (LP) was a gift sample from Hetero Labs Ltd, Hyderabad. Carbopol 934 P was gifted from S.D. Fine Chemical Pvt Ltd, Mumbai. Chitosan, HPMC K4M, and HPMC K15M were procured from Sigma-Aldrich, USA. Lactose acquired from Salius Pharma Pvt Ltd. Magnesium stearate was gifted from Green Pharma, Hyderabad. All other reagents and chemicals used were of analytical grade.

2.2. Methods

2.2.1. Formulation of buccal tablets of losartan potassium:

The buccal tablets were formulated by a direct compression approach. The buccal tablets were prepared by using Carbopol 934 P (934 P) as the primary mucoadhesive polymer because of its excellent mucoadhesive properties. HPMC K4M, HPMC K15M and chitosan were used as secondary polymers. The buccal tablets were prepared using different polymers in combinations with varying ratios, as summarised in Table 1. The buccoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 min. Magnesium stearate was added as a lubricant, and lactose acts as a diluent in the blended material and mixed. The blended powder (200mg) was then compressed on an 8 mm flat-faced punch using a tablet compression (Cadmach) machine [4].

Table 1: Composition of buccal tablets of losartan potassium

Formulations	Ingredients of formulation						
	API	Carbopol 934 P	HPMC K4M	HPMC K15M	Chitosan	Lactose	Mg Stearate
BL1	50	40	60	--	--	45	5
BL2	50	50	50	--	--	45	5
BL3	50	60	40	--	--	45	5
BL4	50	40	--	60	--	45	5
BL5	50	50	--	50	--	45	5
BL6	50	60	--	40	--	45	5
BL7	50	40	--	--	60	45	5
BL8	50	50	--	--	50	45	5
BL9	50	60	--	--	40	45	5
The total weight of each tablet is 200mg.							

2.2.2. Evaluation of tablets

Weight Variation:

Formulated tablets were tested for weight uniformity; 20 tablets were weighed collectively and individually. From the collective weight, the average weight was calculated. Each tablet's weight was then compared with the average weight to ascertain whether it is within permissible limits or not [5].

Hardness:

Hardness of the tablet was determined using the Monsanto hardness tester. The lower plunger was placed in contact with the tablet, and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed, a pointer rides along a gauge in the barrel to indicate the force [6].

Friability:

The Roche friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus, which was given 100 revolutions. After which the tablets were reweighed. The percentage friability was calculated [7].

Drug content:

Five tablets of each formulation were weighed and powdered. The quantity of powder was equivalent to 100 mg. The equivalent weight of losartan potassium was transferred into a 100 ml volumetric flask by using methanol as the extracting solvent, and samples were analysed spectrophotometrically [8].

***In vitro* swelling studies:**

Buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37°C ±1°C. At regular 1-hour time intervals until 6 hours, the tablet was removed from the Petri dish, and excess surface water was removed carefully with filter paper [9]. The swollen tablet was then reweighed (W2), and the swelling index (SI) was calculated using the formula.

$$\% \text{ Swelling index (SI)} = [(W_2 - W_1)/W_1] \times 100$$

Surface pH of the buccoadhesive tablets:

The surface pH of the buccal tablets was determined to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may irritate the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The method was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute [10].

Bioadhesion time:

The ex vivo mucoadhesion time was performed (n = 3) after application of the buccal tablet on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was tied on the glass slide, and the mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8, and was kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 8 hours. The time for the tablet to detach from the sheep buccal mucosa was recorded as the bioadhesion time [11].

***In vitro* dissolution studies:**

Dissolution studies were carried out for all the formulation combinations in triplicate, employing the USP-II paddle method and 500ml of pH 6.8 phosphate buffer as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. The tablet was placed in the vessel, and the vessel was covered. The apparatus was operated for 8 hours in a pH 6.8 phosphate buffer at 50 rpm. At definite time intervals of 5 ml of the aliquot of the sample was withdrawn periodically, and the volume was replaced with an equivalent amount of the fresh dissolution medium. The samples were analysed spectrophotometrically at 235 nm using a UV-spectrophotometer [12].

Release Kinetics:

The dissolution data were fitted to release models such as zero-order, first-order, diffusion and exponential equations, which have been described in the literature. The order of drug release from matrix systems was described by using zero-order kinetics or first-order kinetics. The mechanism of drug release from matrix systems was studied by using the Higuchi equation, the erosion equation and the Peppas-Korsemeyer equation [13].

3. RESULTS AND DISCUSSION:

3.1. Evaluation studies of buccal tablets:

The developed buccal tablets are subjected to various parameters, and the results are represented in Table 2.

The average weight of the tablet was found to be between 196.18 mg and 206.51 mg; all the developed buccal tablets showed hardness in the range of 6.53 to 8.62 kg/cm, and increased with increasing amounts of polymer ratio. The friability (%) range between 0.24 and 0.65% and the

thickness of the tablets for all the formulations was found to be between 2.12 mm and 2.52 mm, with an average of 2.30 mm. The drug content in various formulations varied between 96.72% and 103.05%. The difference in the tablet strengths is reported not to affect the release of the drug from hydrophilic matrices [8].

3.2. Swelling index (SI) studies

The bioadhesion and drug release profile are dependent upon the swelling behaviour of the tablets. The swelling index was calculated with respect to time. The SI increased as the weight gain by the tablets increased proportionally with the rate of hydration, as shown in Table 3. Swelling index measurements could be done up to 8 hours, with the tablets containing chitosan, since it loses its shape at the end of 4 hours. Maximum swelling was seen with the formulations (BL6) containing HPMC K15M and Carbopol; the values increased with increasing amounts of carbopol and decreasing amounts of polymer [14].

Table 2: Evaluation parameters of buccal tablets of losartan potassium

Formulations	Post compression parameters (Mean±S.D)			
	Avg. Weight (n=20)	Hardness (Kg/cm^{2}); (n=3)	Friability (%) (n=6)	Drug content (%) (n=3)
BL1	201.35±3.74	7.16±0.58	0.46	96.72±2.58
BL2	205.71±4.62	6.75±0.72	0.39	98.48±3.72
BL3	196.18±3.59	6.53±0.47	0.61	100.17±2.46
BL4	203.94±3.23	8.62±0.39	0.34	97.39±1.62
BL5	204.72±.4.64	8.18±0.64	0.57	99.16±2.47
BL6	199.87±5.31	7.29±0.81	0.65	99.53±2.71
BL7	206.51±4.26	8.10±0.76	0.37	103.05±3.49
BL8	201.47±2.92	7.25±0.31	0.48	98.48±1.62
BL9	203.39±3.17	6.92±0.45	0.56	99.65±2.54

Table 3: Swelling index of buccal formulations

Formulations	% Swelling index (hrs)					
	0.5	1	2	4	6	8
BL1	32.67±1.24	81.24±1.46	161.75±3.14	186.34±3.04	214.37±1.33	188.67±2.24
BL2	41.42±1.84	84.14±2.48	167.49±1.66	182.43±1.41	218.68±1.98	204.4±1.58
BL3	44.38±1.41	84.56±1.72	171.24±3.14	214.67±2.25	242.67±2.55	226.7±4.51
BL4	50.24±1.16	83.48±1.21	185.67±2.78	218.37±1.23	248.47±1.14	230.5±2.69
BL5	52.63±2.88	88.96±2.11	182.46±3.32	236.11±3.45	251.64±3.14	238.47±2.27
BL6	53.24±1.63	92.64±1.23	189.49±1.48	231.64±1.34	261.48±1.66	243.5±3.48
BL7	32.14±1.58	61.76±2.87	131.64±3.88	152.37±1.02	161.23±1.18	150.2±1.95
BL8	26.49±2.69	54.31±3.28	111.55±2.26	146.29±1.06	174.24±3.39	154.8±3.42
BL9	36.48±2.88	63.74±1.88	139.63±1.37	158.72±2.95	184.38±2.48	163.8±3.46

3.3. Microenvironment pH:

The prepared formulations were subjected to microenvironment pH. Tablets of all formulations had shown surface pH values in the range of 5.2 to 6.8, which indicates no risk of mucosal damage or irritation. Tablets of formulation BL7 (pH 4.8) had shown lower surface pH, which is due to the presence of a higher amount of chitosan [10].

3.4. *In vitro* drug release of buccal tablets:

The formulations are prepared by using various polymers such as Carbopol, HPMC K4M, HPMCK15M and chitosan. Formulations BL1 to BL3, prepared by HPMC K4M, showed 86.71 to 96.58%, formulations BL4 to BL6 with HPMC K15M showed 89.83 to 98.47%, formulations BL7 to BL9 containing chitosan showed 79.32 to 94.76%. Based on the release studies, the formulation F6 showed a higher % of drug release, i.e. 98.47%. The results are presented in Fig. 1.

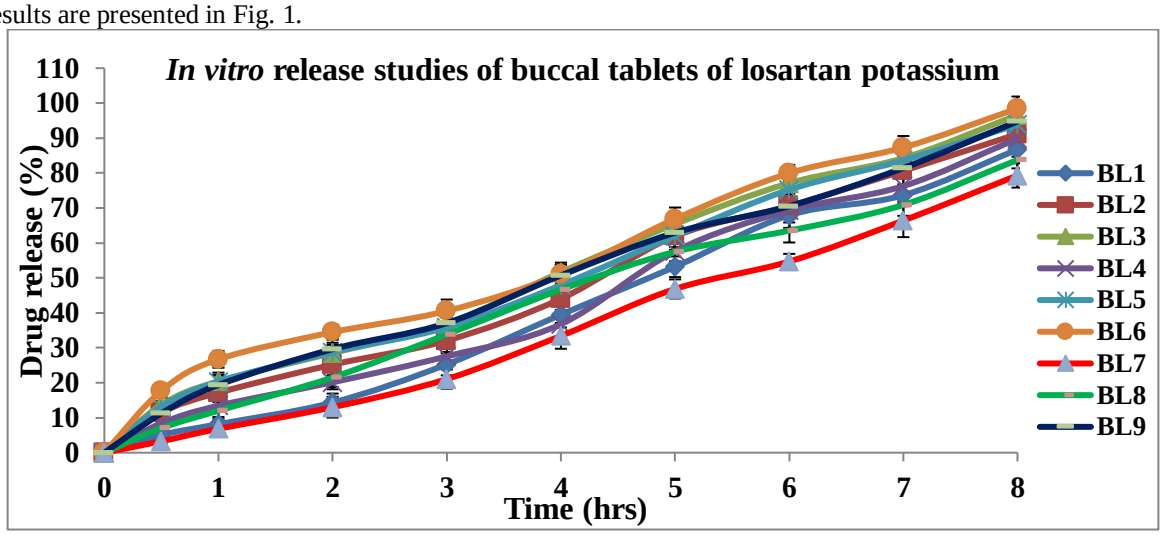

Fig 1: *In vitro* release of buccal tablets of losartan potassium

The release rate of losartan potassium decreased with increasing concentration of HPMC K4M and HPMC K15 M in BL3 and chitosan, respectively. These findings comply with the ability of HPMC to form a complex matrix network, which leads to a delay in the release of the drug from the device. The increasing HPMC concentration tends to slow down drug release due to the formation of a more viscous gel layer, while Carbopol can initially slow release but may also lead to faster release later in the process due to its swelling and erosion properties. A higher release of losartan potassium occurred from the tablets containing a higher proportion of Carbopol 934 P [15].

3.5. *In vitro* bioadhesion time:

The bioadhesive property of buccoadhesive tablets of losartan potassium containing varying proportions of polymers was determined with an insight to develop the tablets with adequate bioadhesiveness without any irritation and other problems. The highest bio-adhesion time, i.e. highest contact time of the mucoadhesive polymer, was observed with the formulation BL6 containing only Carbopol and HPMCK15M, followed by the BL3 formulation containing Carbopol and HPMC K4M, respectively [12]. Tablets of formulation BL9 containing high amounts of chitosan showed the least adhesion time than tablet of all other formulations, which might be due to low viscosity, and the results are presented in Fig. 2.

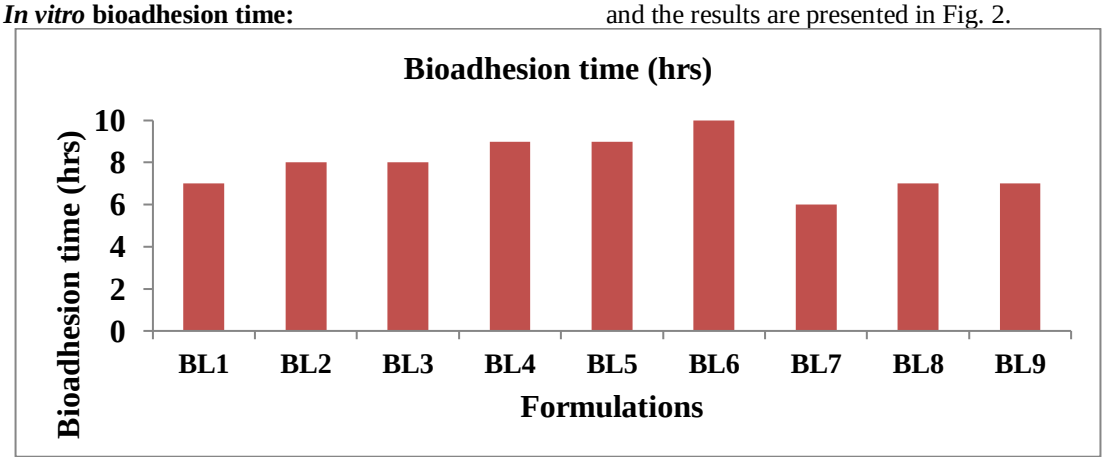

Fig 2: Bioahesion profile of formulations BL1 –BL9

3.6. Kinetics of release studies:

The kinetic models describing drug release from buccal tablets of losartan potassium. The correlation coefficient (r) value was used as a criterion to choose the best model to describe the drug release from the buccoadhesive tablets. The 'r' value in various models is in Table 3. The 'r' values obtained for fitting the drug release data to first order indicate that the drug release mechanism follows first-order kinetics. From Higuchi's equation, the high values of the correlation coefficient 'r' indicate that the drug release mechanism from these tablets was diffusion-controlled. From the above results, it is concluded that the drug release from the formulated buccoadhesive tablets (BL6) of losartan potassium followed first-order kinetics and was diffusion-controlled [(11)].

Table 3: Dissolution data obtained by kinetic models

Formulations	Zero order (R^2)	First order (R^2)	Higuchi (R^2)
BL1	0.783	0.899	0.972
BL2	0.607	0.883	0.966
BL3	0.704	0.923	0.958
BL4	0.804	0.909	0.984
BL5	0.418	0.918	0.983
BL6	0.851	0.964	0.996
BL7	0.722	0.835	0.849
BL8	0.536	0.835	0.908
BL9	0.488	0.836	0.927

4. CONCLUSION:

In conclusion, the present study aimed to develop a buccoadhesive drug delivery system for losartan potassium with a prolonged effect and to avoid first-pass metabolism. Based on the results, the formulation BL6 is considered as optimised formulation, as it showed release of 98.47% in 8 hours. In drug release kinetics follow a first-order manner, followed by Higuchi diffusion-controlled controlled attained in the study, indicating that the hydrophilic matrix tablets of Losartan potassium, prepared using Carbopol 934P and HPMC K15M, can successfully be employed as a buccoadhesive controlled released during delivery system.

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