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Development and *In vitro*Evaluation of Buccoadhesive Tablets of Losartan Potassium

G. Praveen[1*]

1. Department of Pharmaceutical Technology, KGRL College of pharmacy, Bhimavaram-534202, Andhra Pradesh, India.
[E-mail: praveen.pharma33@gmail.com]

The buccoadhesive tablets of Losartan Potassium were developed to prolong the drug release and to improve the bioavailability of the drug by avoidance of the hepatic first pass metabolism during the treatment of chronic hypertension. The formulations were tested for weight variation, hardness, friability, content uniformity, swelling index, bio- adhesive time and the drug release rate. The Carbopol 934P was used as the bio-adhesive polymer, HPMC K4M and HPMC K15 M was added as a matrix former. The ethyl cellulose was used as the backing layer. The optimised formulation containing Carbopol 934P and HPMC K4M (in the ratio of 1:1) showed the surface pH value in the range of 6 to 7 and 94.49% of drug was released in 10hours and showed the best bio- adhesive time up to 11 hours.

*Keyword:*Losartan Potassium, Carbopol 934P, HPMC ,Buccal Tablets

1. Introduction

The potential route of buccal mucosal route of drug administration was first recognized by Walton[1]. The buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery.The unique environment of the oral (buccal) cavity offers its potential as a site for drug delivery because of the rich blood supply and direct access to the systemic circulation. The buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect). The drugs with short biological half-lives, requiring a sustained effect, poor permeability, sensitivity to enzymatic degradation and poor solubility may be successfully delivered via bioadhesive buccal delivery systems. It is a safer method of drug administration, since drug absorption can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity[2].

Losartan potassium[3,4] is an angiotensin II receptor (type AT_1) antagonist. The Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. The Losartan is readily absorbed from the gastrointestinal tract following oral administration. It undergoes first pass metabolism to form a carboxylic acid metabolite E-3174 (EXP-3174). The terminal elimination half-life of Losartan is about 1.5 to 2.5 hours. Hence, it is

a suitable candidate for administration via the buccal route. The bioavailability of Losartan is about 32%. Following oral administration, 6 % of Losartan is excreted unchanged in the urine.

The aim of the present study was to design buccoadhesive bilayered tablets to release the drug unidirectionally in the buccal cavity for extended period of time in order to avoid the first-pass metabolism and to improve the bioavailability of the drug.

2. Materials and Methods

Losartan Potassium (Cipla, Goa), Carbopol 934P (SD Fine chemicals Ltd., Mumbai), HPMC K4M, HPMC K15M , sodium carboxy methyl cellulose (NaCMC),ethyl cellulose(SD Fine chemicals Ltd., Mumbai) and magnesium separate (Yarrow-chem. products, Dombivli) were used. All other chemicals, either reagent or analytical grade, were used as received.

Experimental:

2.1 Preparation of Buccoadhesive bilayered Tablets:

Thebuccoadhesive bilayered tablets were prepared using different polymers either alone or in combination with varying ratios as summarized in table 1.The bilayered tablets were prepared by direct compression procedure involving two consecutive steps. The buccoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and the polymers in a glass mortar for 15 min. The magnesium stearate (MS) was added as a lubricant in the blended material and mixed. The blended powder was then lightly compressed on 8 mm flat faced punch using single punch tablet compression machine (Cadmach), the upper punch was then removed and the backing layer material (ethyl cellulose)was added over it and finally compressed at a constant compression force that gave a Monsanto hardness of 8-10 kg/cm[2].

2.2 Evaluation of Buccoadhesive Bilayered Tablets:

The tablets were evaluated for weight variation, hardness, friability and drug content uniformity. The hardness was determined using the Monsanto hardness tester and the friability test was performed by using the Roche friabilator. The weight variation test and the test for content uniformity was conducted as per the specifications of the indian pharmacopoeia(2010).

2.3 *In Vitro* swelling studies of buccoadhesive tablets:

The swelling index of the buccoadhesive tablets was evaluated using a 1 % w/v agar gel plate. For each formulation 3 tablets were weighed and the average weight of the 3 tablets was calculated (W1). The tablets were placed with the core facing the gel surface in petri dishes which were placed in an incubator at 37 ± 0.1°C. The three tablets were removed at the time intervals of 0.5. 1, 2, 3, 4, 5 and 6 hour, the excess water on the tablet surface was carefully absorbed using the filter paper and the swollen tablets were weighed. The average weight (W2) was determined and then the swelling index was calculated by using the formula:

$$\text{Swelling index}(\%) = ((W2-W1)/W1) \times 100$$

Table 1: Composition Of Losartan Potassium Tablets

Formulation	Drug	Carbopol	HPMC K4M	HPMC K15M	Sodium CMC	Magnesium Stearate	Ethyl cellulose
F1	50 mg	150 mg	-------	-------	-------	5 mg	50 mg
F2	50 mg	75 mg	75 mg	-------	-------	5 mg	50 mg
F3	50 mg	50 mg	100 mg	-------	-------	5 mg	50 mg
F4	50 mg	100 mg	50 mg	-------	-------	5 mg	50 mg
F5	50 mg	75 mg	-------	75 mg	-------	5 mg	50 mg
F6	50 mg	50 mg	-------	100 mg	-------	5 mg	50 mg
F7	50 mg	100 mg	-------	50 mg	-------	5 mg	50 mg
F8	50 mg	-------	150 mg	-------	-------	5 mg	50 mg

F9	50 mg	-------	-------	150 mg	-------	5 mg	50 mg
F10	50 mg	-------	-------	75 mg	75 mg	5 mg	50 mg
F11	50 mg	-------	-------	50 mg	100 mg	5 mg	50 mg
F12	50 mg	-------	-------	100 mg	50 mg	5 mg	50 mg

Table 2: Release Kinetics of Formulations

Formulation Code	Zero Order(r)	First Order(r)	Higuchi (r)	Korsmeyer Peppas (r)	n value
F1	0.9037	0.9704	0.9809	0.9769	0.6521
F2	0.9541	0.9581	0.9679	0.9885	0.7570
F3	0.9888	0.9751	0.9695	0.9882	0.7875
F4	0.9689	0.8169	0.9834	0.9913	0.7002
F5	0.9277	0.99555	0.9797	0.9568	0.8241
F6	0.8330	0.9388	0.9512	0.9160	0.7584
F7	0.9308	0.9886	0.9876	0.9459	0.7150
F8	0.9642	0.9778	0.9394	0.9701	0.8245
F9	0.9397	0.9544	0.9497	0.9812	0.7535
F10	0.8756	0.9806	0.9801	0.9637	0.5901
F11	0.8475	0.9212	0.9067	0.9123	0.7450
F12	0.9141	0.9443	0.9191	0.9416	0.8257

2.4 Surface pH of buccoadhesive tablets:

The surface pH of the tablets was determined in order to investigate the possibility of any side effects, on the buccal mucosa. As acidic or alkaline pH is found to cause irritation to the buccal mucosa, hence attempt was made to keep the surface pH close to the neutral pH. The buccoadhesive tablets were left to swell for 2 h on the surface of an agar plate. The surface pH was measured by means of pH paper placed on the core surface of the swollen tablet[5,6].

2.5 Bioadhesive studies:

The bioadhesive time of the tablets was measured using the method described by Gupta *et al.*[7, 8]. The porcine buccal mucosa was used as the model membrane and the phosphate buffer pH 6.8 was used as the moistening fluid. The biodhesion studies were performed in triplicate and the average bioadhesive time was determined. The bioadhesive time means the time required for the tablet to detach from the buccal mucosal membrane.

2.6 *In Vitro* drug release studies:

The dissolution rates of the buccal tablets were studied using the USP rotating basket method at 37±0.5° C and 50 rpm. The tablet containing 50 mg of Losartan Potassium was added to 900 ml of phosphate buffer (pH 6.8). The samples were withdrawn at the specific time intervals and replaced with the fresh dissolution medium. The amount of Losartan Potassium released was determined spectrophotometrically at 235 nm. The release rate study was conducted in triplicate (n= 3)for 12 h.

2.7 Evaluation of release kinetics:

To investigate the mechanism of drug release from the buccoadhesive tablets, the release data was analysed using zero order, first order and the Higuchi equation.Further to characterize the release mechanism of Losartan Potassium from the buccoadhesive tablets, the dissolution data were evaluated according to the relationship proposed by Korsmeyer *et al.*, as in following equation[9.10], $Mt/M_\infty = kt^n$, where, Mt/M_∞ is the fractional release of the drug, t denotes the release time, k- constant incorporating structural and geometrical characteristics of the device and *n*- diffusional exponent that characterized the type of release mechanism during the dissolution process. The values of *n* as estimated by linear regression of log (Mt/M_∞) versus log (t) and the coefficient of correlation(r^2) of all the 12 formulations are shown in table-2.

2.8 FT-IR studies:

The possibility of drug-excipient interactions were investigated by FT-IR studies.The FTIR graph of pure drug and the optimized formulation

were recorded using the potassium bromide pellets.

3. Results and Discussion:

The assayed drug content in the various formulations varied between 98.64% and 100.26% (mean 99.68%). The average weight of the tablet was found to be between 253.4 mg and 258.2 mg (mean 256.2 mg), the % friability range was between 0.21% and 0.68% (mean 0.43 %) and the thickness of the tablets for all the formulations was found to be between 2.12 mm and 2.52 mm (average of 2.30 mm). The buccoadhesive tablets containing Carbopol showed hardness in the range of 8.54 to 10.86 kg/cm ^{2} and it decreased with increasing amounts of HPMC. The hardness of the tablets containing NaCMC was much lower, ranging from 4.20 to 8.98 kg/cm ^{2} and increased with increasing amounts of HPMC or Carbopol. The difference in the tablet strengths are reported not to affect the release of the drug from the hydrophilic matrices.

Table 3: Swelling Index of Losartan Potassium Buccoadhesive Tablets

Formulation Code	% Swelling index* Time (hours)				
	0.5	1	2	4	6
F1	61.04±0.84	104.46±1.25	221.48±0.098	254.49±.68	284.26±1.48
F2	49.28±0.98	82.48±1.47	179.48±1.21	209.37±2.41	227.64±2.01
F3	38.42±0.95	74.84±0.52	147.43±1.66	168.27±1.41	198.49±1.21
F4	45.49±.09	92.64±1.23	189.49±1.48	231.64±1.34	261.48±1.66
F5	41.42±0.99	84.14±1.48	167.49±1.66	182.43±1.41	218.68±1.98
F6	36.48±0.88	63.74±0.88	139.63±1.37	158.72±0.95	164.38±0.48
F7	50.24±1.16	83.48±1.21	185.67±0.78	218.37±1.23	248.47±1.14
F8	32.14±0.58	61.76±.87	131.64±0.88	152.37±1.02	161.23±1.18
F9	26.49±0.69	54.31±0.28	111.55±2.26	146.29±1.06	154.24±0.39
F10	44.38±1.41	84.56±1.72	171.24±3.14	214.67±2.25	242.67±2.55
F11	52.63±0.88	88.96±2.11	182.46±3.32	236.11±3.45	274.40±3.14
F12	32.67±1.24	81.24±1.46	161.75±3.14	186.34±3.04	214.37±1.33

* Indicates mean±S.D. values(n=3)

The drug is released by diffusion through the gel layer and/or erosion of this layer and is therefore independent of the dry state of the tablet [13].

The bioadhesion and the drug release profiles are dependent upon the swelling behaviour of the tablets. The swelling index was calculated with respect to time. The swelling index increased as the weight gain by the tablets increased proportionally with the rate of hydration as shown in the table 3. The swelling index measurements could be done up to 6 hours with the tablets containing 95 mg of NaCMC, since it loses its shape at the end of 4 hours. The swelling indices of the tablets with Carbopol and HPMC increased with increasing amounts of Carbopol. The maximum swelling was seen with the formulations (F9, F10, F8, and F1) containing

NaCMC and/or Carbopol, the values increased with increasing amounts of NaCMC and/or Carbopol[11].

The tablets of all the formulations except F1 had shown a surface pH value in the range of 5 to 7 that indicates no risk of mucosal damage or irritation. The tablets of formulation F1 had shown lower surface pH which is due to the presence of higher amount of polyacrylic acid. These observations reflect that Carbopol alone cannot be incorporated in the design of buccoadhesive tablets.

The bioadhesive property of buccoadhesive tablets of Losartan potassium containing varying proportions of the polymers was determined with an insight to develop the tablets with adequate bioadhesiveness without any irritation and other problems. The bioadhesion characteristics were found to be affected by the nature and the proportions of the bioadhesive polymers used as shown in figure 1. The highest bio-adhesion time i.e. highest contact time of the buccoadhesive polymer was observed with the formulation F1 containing only Carbopol, this was followed by F2 and F6 formulations containing Carbopol: HPMC K4M and Carbopol: HPMC K15M, respectively. The reason for such findings might be ionization of Carbopol at salivary pH which leads to improved attachment of the device to the mucosal surface. The adhesion time decreased as another polymer is mixed with the Carbopol. The tablets of formulation F12 containing high amounts of NaCMC showed least adhesion time than the tablets of all other formulations, which might be due to low viscosity of the NaCMC. These observations indicate that the bioadhesive time of Carbopol is much more than the NaCMC.

In vitro drug release studies revealed that the release of Losartan potassium from the different formulations varies with the characteristics and the composition of the matrix forming polymers as shown in Figure 2, Figure 3 and Figure 4 .

Table 4: Bioadhesion Time of Losartan Potassium Tablets

Formulation	Time (hours)
F1	12
F2	11
F3	8
F4	7
F5	9
F6	12
F7	10
F8	10
F9	9
F10	8
F11	4
F12	7

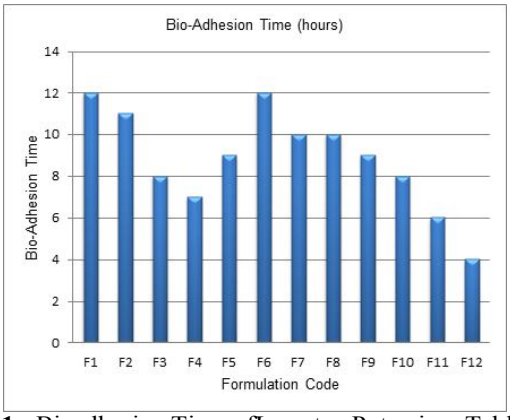

Fig1: Bioadhesion Time ofLosartan Potassium Tablets

The release rate of Losartan potassium decreased with the increasing concentration of HPMC K4M and HPMC K15 M in F3 ,F5 to F6 and F8 to F9, respectively. These findings are in compliance with the ability of HPMC to form complex matrix network which leads to delay in the release of the drug from the device. The Carbopol is more hydrophilic than HPMC; it can swell rapidly,

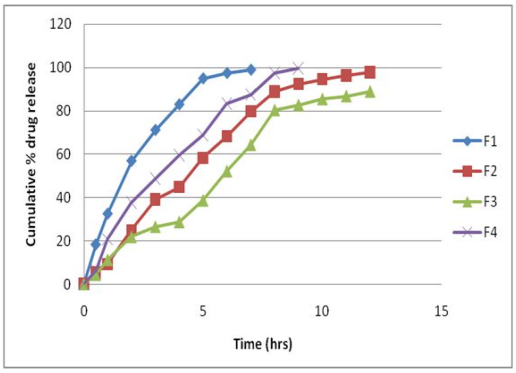

Fig 2: Dissolution profiles of F1, F2, F3, F4formulations of Losartan potassium buccal tablets

therefore decrease of Carbopol content delays the drug release in F3 and F5 to F6.

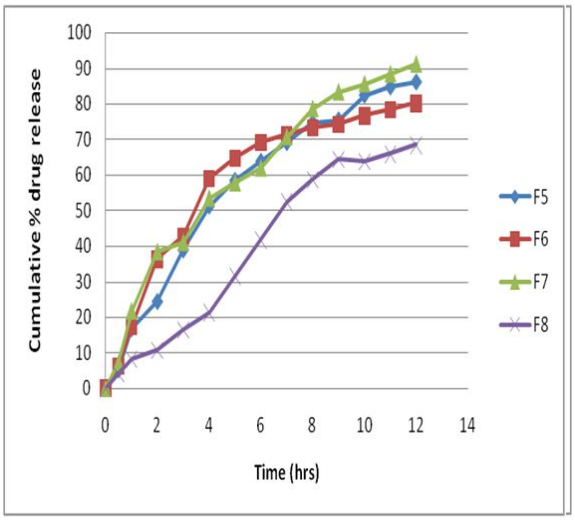

Fig 3: Dissolution profiles of F5, F6, F7, F8 formulations of Losartan potassium buccal tablets

The drug release rate was increased with the increasing amount of the hydrophilic polymer. The maximum cumulative percent release of Losartan potassium from the formulation F1 could be attributed due to ionization of Carbopol at the pH environment of the dissolution medium.The ionization of the Carbopol leads to the development of negative charges along the backbone of the polymer. The repulsion of like charges uncoils the polymer into an extended structure.

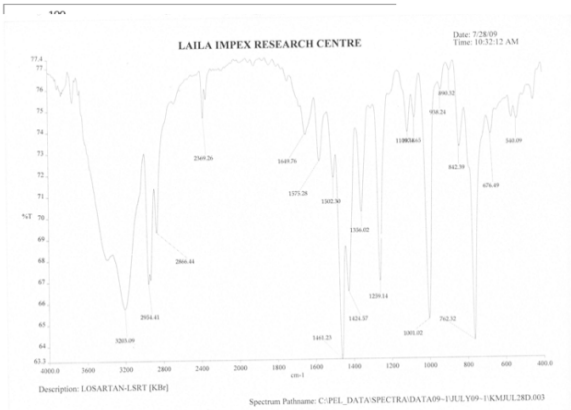

Fig 5:FTIR Spectra of Losartan Potassium Drug Sample

The counter ion diffusion inside the gel creates an additional osmotic pressure difference across the gel leading to the high water uptake. This water uptake leads to the considerable swelling of the polymer. The continued swelling of the polymer matrix causes the drug to diffuse out from the formulation at a faster rate. The formulations F10, F11 showed relatively high rate of release of Losartan potassium which is due to rapid swelling and erosion of NaCMC. Further, the increase in rate of drug release could be explained by the ability of the hydrophilic polymers to absorb water, thereby promoting the dissolution, and hence the release, of the highly water soluble drug. Moreover, the hydrophilic polymers would leach out and hence, create more pores and channels for the drug to diffuse out of the device. The formulation F12 which contains high amounts of NaCMC gets eroded during the dissolution study before the stipulated study period. Thus higher concentration of NaCMC cannot be incorporated into such formulations for sustaining the drug release.

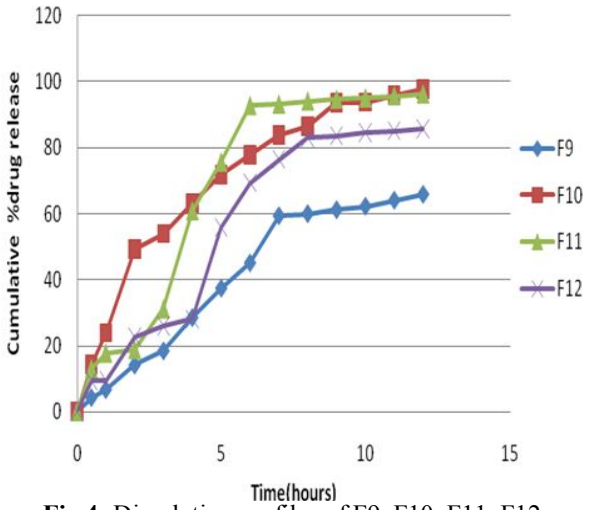

Fig 4: Dissolution profiles of F9, F10, F11, F12 formulations of Losartan potassium buccal tablets

The table 2 enlists the various dissolution parameters computed for all the controlled release buccoadhesive tablets. To examine further the release mechanism of Losartan potassium from

the buccoadhesive tablets, the results were analyzed according to the equation, $Mt/M_{\infty} = Kt^{n}$ proposed by Peppa's and Korsemeyer[12]. The obtained values of release rate exponent (n) lie between 0.5901 and 0.8257 in all the formulations for the release of Losartan potassium. In general, the released pattern was found to be non-Fickian tending to approach the first order kinetics.

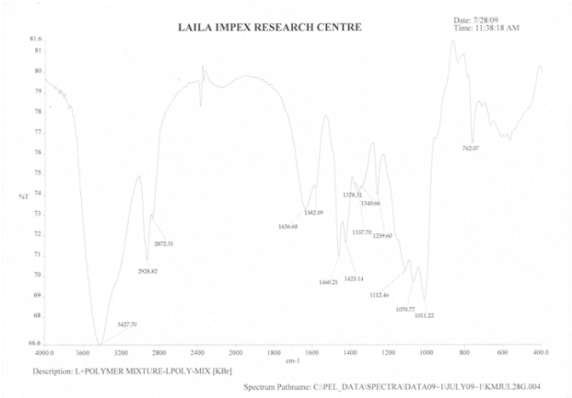

Fig 6: FTIR Spectra of the Optimized Formulation (F2)

Several kinetic models describe the drug release from the immediate and the modified released dosage forms. The model that best fits the release data was evaluated by the correlation coefficient (r). The correlation coefficient (r) value was used as criteria to choose the best model to describe the drug release from the buccoadhesive tablets. The 'r' value calculated for the various models is shown in the table 2. The higher values of correlation coefficient (r), indicated that the drug release mechanism follows first order kinetics. From the higuchi's equation, the high values of correlation coefficient obtained indicated that the drug release mechanism from these tablets was diffusion controlled. The values of **'n'** in Peppa's model indicated that the drug release follows non-Fickian diffusion.

From the above results, it is concluded that the drug release from the formulated buccoadhesive tablets of Losartan potassium followed first order kinetics and was diffusion controlled.

The FTIR spectroscopic studies were performed at the LAILA IMPLEX research centre ,Vijayawada. From the FTIR.Spectra, it is evident, that the drug peaks at 3203 cm^{-1}, 2954 cm^{-1}, 2866 cm^{-1}, 1649 cm^{-1}, 1575 cm^{-1}, 1356 cm^{-1}, 1424 cm^{-1}, 1259 cm^{-1}, 1001 cm^{-1}, and 762 cm^{-1} are evident in the drug-polymer mixture also, hence the drug-polymer (Losartan and Polymer mixture :Carbopol, HPMC K_4M and ethyl cellulose) interactions are absent in the optimized formulation F_2.

4. Conclusion

The bilayered buccoadhesive tablets of Losartan potassium were developed to a satisfactory level in terms of drug release, bioadhesive time, physicochemical properties and the surface pH. The FTIR studies indicated the lack of drug-excipient interaction in the optimized formulation F2.The formulation F2 composed of HPMC K4M and Carbopol 934P extended the drug release up to 10 hours and exhibited buccoadhesive time up to 11 hours. These bilayered buccoadhesive tablets can improve the bioavailability of the drug by avoiding the hepatic first pass metabolism.

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