RESEARCH ARTICLE JPAR 2019

Journal of Pharmaceutical Advanced Research

(An International Multidisciplinary Peer Review Open Access monthly Journal)

Available online at: www.jparonline.com

Formulation and Evaluation of Losartan Potassium as Bilayered Buccal Tablets

P. Sasi Harshitha*, Biswa Mohan Sahoo, N. Malini, Y. Tejo Kumar

Department of Pharmacy, Vikas Group of Institutions, Nunna-521212, Vijayawada, A.P., India.

Received: 29.12.2018 Revised: 10.01.2019 Accepted: 16.01.2019 Published: 31.01.2019

ABSTRACT: Background: Buccal drug delivery is considered as an alternative to oral dosing for compounds subjected to degradation in the gastrointestinal tract or to hepatic first pass metabolism. Losartan Potassium is having less bioavailability of about 25 to 33 %. In order to increase the bioavailability and also to avoid the hepatic metabolism, the buccal tablet has gained its access to a greater extent. **Aim:** The aim of the present study was to prepare bucco-adhesive bi-layered tablets to release the drug in buccal cavity for extended period of time to reduce the frequency of dosing. **Method:** Tablets of Losartan potassium were prepared by direct compression method using bioadhesive polymers like Carbopol 934P, HPMC K15 and HPMC K100 either alone or in combinations with backing layer of ethyl cellulose. The muco-adhesive buccal tablets of Losartan Potassium were evaluated for hardness test, friability test, uniformity of drug content, swelling index and in vitro drug release. **Results:** Among all the buccal tablet formulations, Formulation F5 containing HPMC K100 M in the concentration of 1:1.5 was found to be good with better drug release, as it released 93.62 % of drug in 9 h. The model that best fits the release data was evaluated by correlation coefficient (r). The high values of correlation coefficient 'r' indicate that the drug release mechanism from these tablets was diffusion controlled. **Conclusion:** It may be concluded that the release rate of drug from the buccal tablets can be governed by the polymer and concentration of the polymer employed in the preparation of tablets.

Corresponding author*
Ms. P. Sasi Harshitha
Department of Pharmacy,
Vikas Group of Institutions,
Nunna-521212, Vijayawada, A.P., India.
Tel: +91-9040442719
Mail ID-drbiswamohansahoo@gmail.com

Keywords: Losartan potassium, hypertension, buccal tablets, mucoadhesion, *in vitro* drug release.

INTRODUCTIONS:

Buccal drug delivery system plays key role for oral administration of drugs which are degraded in the gastrointestinal tract and also it is useful to avoid any hepatic first pass metabolism [1]. This type of drug delivery provides safer mode of drug utilization because absorption of drugs can be promptly terminated in cases of toxicity by removing the dosage form from the buccal cavity [2]. Generally, Losartan Potassium possesses 25 to 33 % of bioavailability. Thus, the buccal tablets of

Losratan potassium were prepared to increase the bioavailability of drugs and also to avoid the hepatic metabolism. In case of bi-layered tablets, drug can be incorporated in the adhesive layer, which comes in contact with the mucosal surface [3]. This drug containing mucoadhesive layer is then protected from the oral cavity environment by upper inert layer which faces into the oral cavity [4-7]. Losartan potassium is an Angiotensin-II receptor antagonist. Chemically, it is (S)-l-[*N*-[l-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-L-proline (Fig 1). The administration of conventional tablets of Losartan potassium has been reported to exhibit fluctuations in the plasma drug levels which results either in manifestation of side effects or reduction in drug concentration at the receptor site [8]. So, the bucco-adhesive bi-layered tablets of Losartan Potassium were prepared by using bioadhesive polymers such as Carbopol 934P, HPMC K15 and HPMC K100 [9,10].

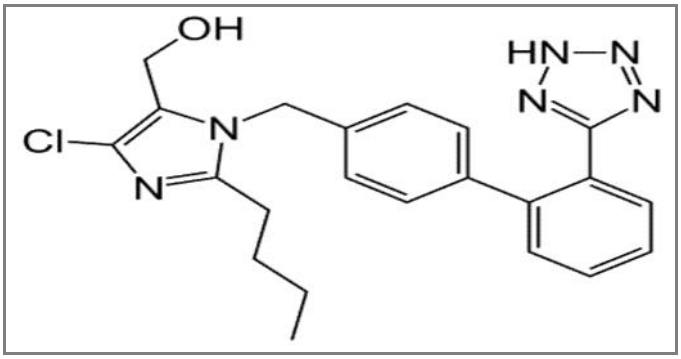

Fig 1. Structure of Losartan potassium.

MATERIALS AND METHODS:

Chemicals and reagents:

Losartan potassium was procured from Yarrow Chem. Lab, Mumbai and other materials from Merck Specialities Pvt. Ltd., Mumbai, India. All other chemicals and reagents used were analytical grade unless otherwise indicated.

Estimation of Losartan Potassium:

By using electronic digital balance (Sartourious), weighed amount of Losartan Potassium was dissolved in phosphate buffer pH 6.8 to obtain a 1000 µg/ml solution. This solution was subjected for scanning between 200 to 400 nm and absorption maximum was determined. The effect of dilution on absorption maxima was studied by diluting the above solution to10 µg/ml and scanned from 200 to 400 nm. From the spectra of drug, the λ_{max} of 216 nm was selected for the analysis for Losartan Potassium. The calibration curve was prepared in the concentration range of 2 to 12 µg/ml at 216 nm. By using the calibration curve, the concentration of the sample solution can be determined.

Standard calibration curve of Losartan Potassium in phosphate buffer pH 6.8 solution:

A stock solution containing 1mg/ml of pure drug was prepared by dissolving 100 mg of Losartan Potassium in sufficient phosphate buffer pH 6.8 to produce 100 ml solution in a volumetric flask. From the standard stock solution, 5 ml of the stock solution was further diluted to 50 ml with phosphate buffer pH 6.8 into a 50 ml volumetric flask and diluted up to the mark with phosphate buffer pH 6.8. Aliquots of 0.2, 0.4, 0.6, 0.8, 1 and 1.2 ml of stock solution were pipette out into 10 ml volumetric flasks. The volume was made up to the mark with phosphate buffer pH 6.8. These dilutions gave 2, 4, 6, 8, 10 and 12 µ/ml concentration of Losartan Potassium respectively. The absorbance was measured in the UV-Visible spectrophotometer (Shimadzu UV-visible spectrophotometer, UV-Pharmaspec 1700 series) at 216 nm using distilled water as blank and graph of concentration versus absorbance was plotted.

Drug-Excipient Compatibility Studies:

Fourier Transform Infrared (FTIR) spectroscopy:

The physical properties of the physical mixture were compared with those of pure drug. Samples was mixed thoroughly with 100 mg potassium bromide powder and compacted under vacuum at a pressure of about 12 psi for 3 min. The disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer (Perkin Elmer) and the IR spectrum was recorded from 3500 to 500 cm^{-1} [6].

Preparation of Mucoadhesive Tablets:

Direct compression method has been employed to prepare buccal tablets of Losartan Potassium using HPMC K15, HPMC K100, and Carbopol 934 as polymers. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (Table 1). All the ingredients except lubricants were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend (230 mg) of each formulation was pre-compressed on multi stationed tablet punching machine at a pressure of 0.5 ton for 30 s to form single layered flat-faced tablet of 9 mm diameter. Then, 50 mg of ethyl cellulose powder was added and final compression was done at a pressure of 3.5 tons for 30 s to get baitlayer tablet.

Table 1. Composition of bilayer buccal tablets of Losartan potassium.

Ing	F1	F2	F3	F4	F5	F6	F7	F8	F9
LP	25	25	25	25	25	25	25	25	25
K15	25	37	50	--	--	--	--	--	--
K100				25	37	50	--	--	--
C934	--	--	--	--	--	--	25	37	50
Talc	3	3	3	3	3	3	3	3	3
MS	3	3	3	3	3	3	3	3	3
MCC	qs	qs	qs	qs	qs	qs	qs	qs	qs
EC	50	50	50	50	50	50	50	50	50

All quantities are expressed in mg. Ing – Ingredients. LP – Losartan potassium, K15 – HPMC K15, K100 – HPMC K100, C-934 – Carbopol 934, MS – Magnesium stearate, MCC – Microcrystalline cellulose pH 102, EC – Ethyl cellulose and qs – Quantity sufficient to make the total tablet weight is 280 mg.

Evaluation of muco adhesive buccal tablets of Losartan Potassium [7-10]:

Hardness test:

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the hardness was determined. The study was done in triplicate and mean, standard deviation was calculated.

Thickness:

The thickness of three randomly selected tablets from each formulation was determined in mm using a Screw gauge.

Friability test:

The friability of tablet was determined by using Roche Friabilator as per IP procedure of friability. It is expressed in percentage (%). Twenty tablets were initially weighed (Wi) and transferred into friabilator. The friabilator was operated at 25 rpm for 4 min or run up to 100 revolutions. The tablets were weighed again (Wf).

The percentage friability was then calculated by using formula,

Friability (%) = [(Wi+Wf)/Wi] × 100. ..... (1)

Wi and Wf are initial and final weight and the percentage Friability of tablets less than 1% is considered acceptable.

Uniformity of weight:

The weight variation test was performed as per procedure of IP. The weight (mg) of each of 20 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The weight data from the tablets were analyzed for sample mean and percent deviation.

Uniformity of drug content:

Five tablets were powdered in a glass mortar and the powder equivalent to 50 mg of drug was placed in a 100 ml conical flask. The drug was extracted with 40 ml distilled water with vigorous shaking on a mechanical gyratory shaker (100 rpm) for 1 h. Then heated on water bath with occasional shaking for 30 min and filtered into 50 ml volumetric flask through cotton wool and filtrate was made up to the mark by passing more distilled water through filter, further appropriate dilution were made and absorbance was measured at 220 nm against blank (distilled water).

In-vitro Drug Release Studies:

The *in vitro* drug release from bucoadhesive tablet was studied by using USPXXXI Paddle type dissolution apparatus, using 900 ml of phosphate buffer pH 6.8, as dissolution media. The temperature of dissolution fluid was maintained at 37±1 °C. The dissolution was carried out at stirring speed of 100 rpm. An aliquot of 5 ml drug solution was pitted out at regular interval of 1 h, which was immediately replaced by 5 ml of fresh phosphate buffer pH 6.8 to maintain sink condition. The drug contained in various solutions was analyzed by using UV-Visible spectrophotometer at the λ_{max} of 216 nm. The drug concentration was determined by using regression equation of standard curve.

RESULTS AND DISCUSSION:

The main aim of this work was to develop bilayered buccal tablets to release the drug at buccal mucosal site in unidirectional pattern for extended period of time without wash out of drug by saliva. Carbopol 934, HPMC K15, HPMC K100 were selected as buccoadhesive polymers on the basis of their matrix forming properties and mucoadhesiveness, while ethyl cellulose, being hydrophobic, used as a backing material. The formulation design for various Losartan tablet formulation is given in Table 2. Ethyl cellulose has recently been reported to be an excellent backing material, given its low water permeability and moderate flexibility.

The FTIR data showed that no significant physical or chemical interactions being taking place inbetween losartan potassium and excipients, as evident from Fig 3

and 4. Buccoadhesive tablets containing Carbopol showed hardness in the range of 5.00 to 5.60 kg/cm ^{2} and it increased when used in combination with HPMC K100. The hardness of the tablets containing HPMC K15 was much lower, ranging from 4.30 to 4.8 kg/cm^2 and increased with increasing amounts of HPMC or Carbopol. The hardness, thickness and weight variation data of various tablet formulation is given in Table 3.

Table 2. Standard calibration graph of Losartan Potassium.

Sl. No	Conc. (µg/ml)	Absorbance
1	2	0.080
2	4	0.158
3	6	0.237
4	8	0.318
5	10	0.397
6	12	0.485

Table 3. The hardness, thickness and weight variation data of Losratan potassium bilayer buccal tablets.

FC	Hardness (kg/cm^2)	Thickness (mm)	WV (mg)
F1	4.8±0.02	2.80±0.00	279.6±0.99
F2	4.3±0.05	2.83±0.06	278.8±0.99
F3	4.3±0.05	2.87±0.06	279.8±0.38
F4	5.7±0.06	2.86±0.06	280.7±0.99
F5	5.4±0.03	2.87±0.06	279.8±0.38
F6	5.0±0.02	2.90±0.00	280.1±0.99
F7	5.6±0.07	2.97±0.06	279.6±0.17
F8	5.3±0.05	3.01±0.01	281.0±0.40
F9	5.1±0.02	2.95±0.00	280.0±0.20

All values are presented as mean ± standard deviation (n = 3). FC – Formulation code, WV – Weight variation.

Table 4. The friability, drug content and drug release data of bilayer buccal tablets.

FC	Friability (%)	Drug content (%)	CDR (%)
F1	0.79±0.01	100.09±0.56	101.52±0.58
F2	0.67±0.01	102.73±0.46	102.95±1.54
F3	0.57±0.01	98.75±0.88	88.24±0.11
F4	0.55±0.00	99.70±0.34	97.79±0.34
F5	0.51±0.01	97.95±0.38	93.62±1.95
F6	0.87±0.03	98.75±0.88	83.41±1.31
F7	0.46±0.01	103.36±0.83	98.89±3.45
F8	0.72±0.01	101.09±4.00	99.43±1.98
F9	0.56±0.02	99.75±0.38	99.32±1.98

All values are presented as mean ± standard deviation (n = 3). FC – Formulation code, CDR – Cumulative drug release.

The thickness of tablet formulations was uniform in ranges of 2.80±0.01 to 3.01±0.01 mm. The weight of all tablet formulations was uniform and within the range of 278.8±0.99 to 281.0±0.40 mg and the weight variation test was passed as per the USP. The friability, drug content and drug release data of various tablet formulation is given in Table 4. The friability test revealed that almost all the tablet formulation showed percentage loss less than the 1 %, thus all formulation passed for friability test as per USP.

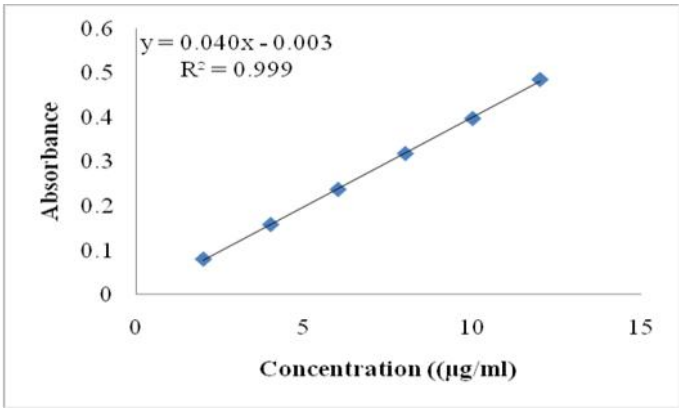

Fig 2. Calibration curve of Losartan Potassium.

The drug content of tablet formulations was found to be in ranges of 97.95±0.38 to 103.36±0.83 %, which revealed that all tablet formulations exhibited good drug content.

In vitro drug release studies revealed that the release of Losartan Potassium from different formulations varies with characteristics and composition of matrix forming polymers. The release rate of Losartan Potassium decreased with increasing concentrations of the polymers. The release rate of the tablets decreased from F1 to F3 when tablets are prepared with HPMC K15 in 1:1, 1:1.5 and 1:2 ratios respectively (Fig 5). The release rates were similarly studied with increasing concentrations of HPMC K100 and the release rate decreased with increasing concentrations from F4 to F6 respectively (Fig 6). Similarly release rates were studied with Carbopol 934 in increasing concentrations that are 1:1, 1:1.5, and 1:2 respectively and release rate was found to be decreased with all the three polymers when used in the ratio 1:2. Among

all the formulations Formulation, F5 containing HPMC K100 M in the concentration of 1:1.5 was found to be good with better drug release i.e., 93.62 % in 9 h. The difference in the tablet strengths are reported not to affect the release of the drug from hydrophilic matrices. 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. The correlation coefficient (r) value was used as criteria to choose the best model to describe the drug release from the buccoadhesive tablets. From higuchi's equation, the high values of correlation coefficient 'r' indicating that the drug release mechanism from these tablets was diffusion controlled.

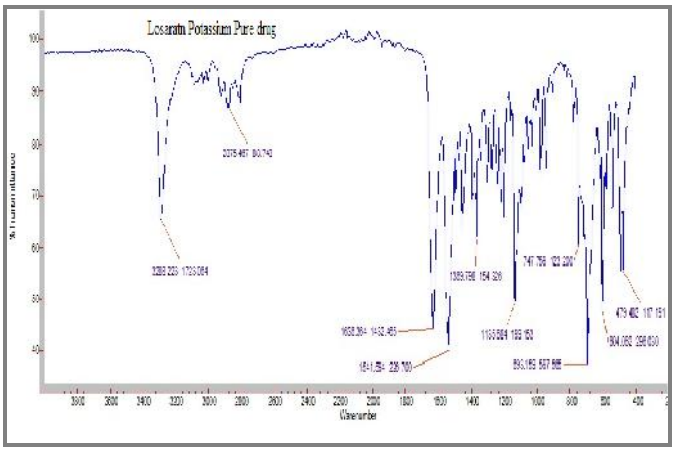

Fig 3. FT-IR spectrum of pure drug Losartan potassium.

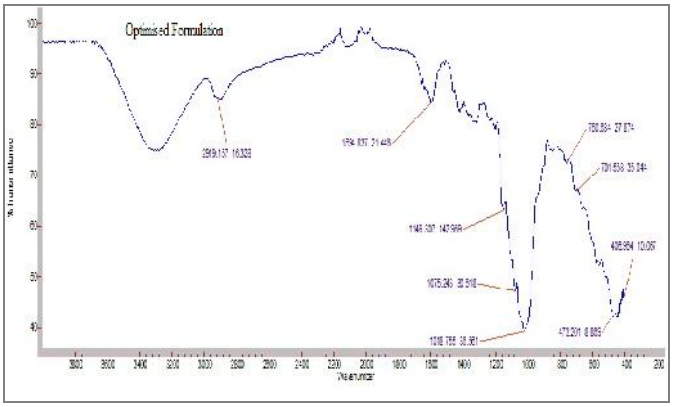

Fig 4. FT-IR spectrum of optimised formulation Losartan tablet formulation F5.

CONCLUSION:

Among all the formulations Formulation F5 containing HPMC K100 M in the concentration of 1:1.5 was found to be good with better drug release i.e., 93.62 % in 9 h. Several kinetic models describing drug release from immediate and modified released dosage forms. The model that best fits the release data was evaluated by 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' values obtained for fitting the drug release data to first order, indicating that the drug release mechanism follows first order kinetics. From higuchi's equation, the high values of correlation coefficient 'r' indicating that the drug release mechanism from these tablets was diffusion controlled. Slow, controlled and complete release of Losartan Potassium over a period of 11 h was obtained from matrix tablets formulated employing HPMC K 100 (F5) with 93.45 % drug release.

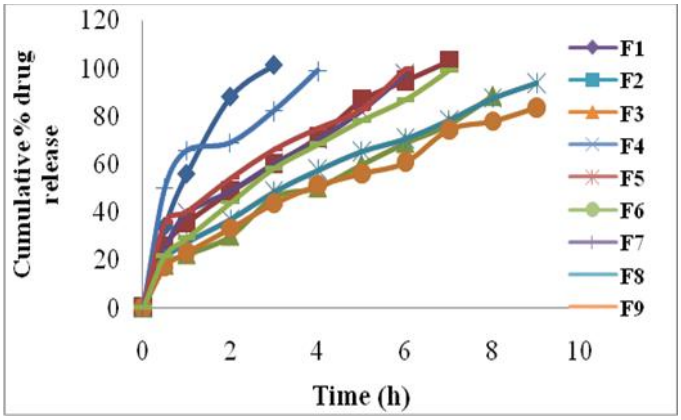

Fig 5. *In vitro* drug release data of various Losartan tablet formulations.

ACKNOWLEDGEMENT:

Authors are thankful to authority of Dept. of Pharmacy, Vikas Group of institutions, Nunna, Vijayawada rural, Andhra Pradesh, India and Inception Source Pvt. Ltd., Hyderabad, India for giving facility to carry out this research work.

REFERENCES:

1. Gupta A, Garg S, Khar RK. Mucoadhesive Buccal Drug Delivery System: A Review. Indian Drugs, 1992; 29(13): 586-593.
2. Singh B, Ahuja N. Response surface optimization of drug delivery system. Progress in Controlled and Novel Drug Delivery Systems. New Delhi, India: CBS Publishers and Distributors; 2004, pp. 200-240.
3. Harris D, Robinson JR. Drug Delivery via Mucous Membrane of the Oral Cavity. J Pharm Sci, 1992; 81: 1-10.
4. Wong FC, Yuen KH, Peh KK. Formulation and Evaluation of Controlled Release Eudragit Bucccal Patches. Int J Pharm, 1999; 178: 11-12.

5. Marriott C, Gregory NP. Mucus physiology. In: Lenaerts V, Gurny R, Editors. Bioadhesive Drug Delivery Systems. Boca Raton: CRC Press; 1990; pp. 1-24.
6. Langer RS, Peppas NA. New Drug Delivery Systems. BMES Bull, 1992; 16: 3-7.
7. Ponchel G, Irache J. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. Adv Drug Deliv Rev, 1998; 34: 191-219.
8. Hwang SJ, Park H, Park K. Gastric Retentive Drug-Delivery Systems. Crit Rev Ther Drug Carr Syst, 1998; 15(3): 243-284.
9. Whitehead L, Fell JT, Collett JH. Development of a Gastroretentive dosage form. Eur J Pharma Sci, 1996; 4 (1): 182-185.
10. Velmurugan S, Srinivasan P. Formulation and evaluation of Losartan Potassium muco adhesive buccal tablets. Asian J Pharm Clin Res, 2013; 6(3): 125-130.

Conflict of Interest: None

Source of Funding: Nil

Paper Citation: Harshitha PS, Sahoo BM, Malini N, Kumar YT. Formulation and Evaluation of Losartan Potassium as Bilayered Buccal Tablets. J Pharm Adv Res, 2019; 2(1): 458-463.