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Research

Formulation and in vitro evaluation of mucoadhesive buccal tablets of losartan potassium using natural polymer

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Abstract

The purpose of the present investigation is to formulate and invitro evaluation of mucoadhesive buccal tablets of Losartan potassium using natural polymer. Losartan potassium is an angiotensin II receptor (type AT1) antagonist. Losartan is an orally active agent that undergoes substantial first pass metabolism by cytochrome P450 enzyme. It is converted into carboxylic acid metabolites. The aim of the present study was to design mucoadhesive buccal tablets to release the drug unidirectionally in buccal cavity for extended period of time in order to avoid first pass metabolism for improvement in bioavailability to reduce the dosing frequency and to improve patient compliance. Tablets of Losartan potassium were prepared by direct compression method using natural polymers sodium alginate, xanthan gum and guar gum. Preformulation studies like FTIR were done and postformulation studies like mucoadhesive force, mucoadhesive strength and swelling index were done and compared with different natural polymer.

Keywords: Mucoadhesive Buccal Tablets, Losartan Potassium, Natural Polymers, First Pass Metabolism, *in vitro* evaluation

INTRODUCTION

Buccal delivery is defined as drug administration through the mucosal membranes lining the cheeks (buccal mucosa). In recent years, significant interest has been shown in the development of novel mucoadhesive dosage forms for mucosal delivery of drugs. Because after oral administration many drugs are subjected to presystemic clearance extensive in liver, which often leads to a lack of significant correlation between membrane permeability, absorption, and bioavailability. The term 'mucoadhesive' describes materials that bind to biological substrate, such as mucosal membranes. Adhesion of mucoadhesive drug delivery devices to mucosal membranes

lead to an increased drug concentration gradient at the absorption site and therefore improved bioavailability of systemically delivered drug.

Buccoadhesive drug delivery

The potential route of buccal mucosal route of drug administration was first recognized by Walton and others reported in detail on the kinetics of buccal mucosal absorption[9-11]. Mucoadhesion, 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 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). Buccal route of administration: The medicament is placed between the cheek and the gum. The barrier to drug absorption from this route is the epithelium of oral mucosa. Passive diffusion is the major mechanism for absorption of drugs. Drugs with short biological half-lives, requiring a sustained effect, poor permeability, sensitivity to enzymatic degradation and poor solubility may be successfully delivered via Mucoadhesive buccal delivery systems.

Advantages of Buccal route

- Rapid absorption and higher blood levels due to high vascularization of the region and therefore particularly useful for administration of antianginal drugs.
- No first-pass hepatic metabolism.
- No degradation of drugs such as that encountered in the GIT.
- Presence of saliva facilitates both drug dissolution and its subsequent permeation by keeping the oral mucosa moist.
- 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.

Disadvantages of buccal route

- Accidental swallowing of the formulation by the patient.
- Difficulty in speaking and drinking.

Limitations

- Only limited amount of drug can be used in these systems (25-50 mg).
- Drug must be non-irritant to the buccal mucosa.

Factors affecting systemic absorption of drugs through the buccal mucosa

There are several factors affecting the absorption of drugs through the buccal mucosa.

Delivery through Buccal Mucosa

Administration of a drug via the buccal mucosa to the systemic circulation is defined as buccal delivery. Despite, the buccal mucosa is significantly less permeable than the sublingual mucosa and usually not able to provide rapid drug absorption, it is relatively more permeable than the skin so it is more desirable site for sustained drug delivery.

MATERIALS AND METHODS

Materials

Table 1: Materials used for the formulation development

1	Losartan potassium	Dr.Reddy's Lab Ltd., Hyderabad	USP Grade
2	agnesium stearate	Scientific lab Erode, Tamilnadu	Pharmaceutical grade
3	Sodium alginate	Scientific lab Erode, Tamilnadu	Pharmaceutical grade
4	Xanthan gum	Taian ruitai cellulose co Ltd, Chennai	Pharmaceutical grade
5	Guar gum	Taian ruitai cellulose co Ltd, Chennai	Pharmaceutical grade

Equipments

Table 2: Equipments used for the process

S.No.	Name of Equipment	Manufactured by
1	8 Basket dissolution apparatus	Electro lab
2	Single Stage tablet punching machine	Cadmach
3	U.V Spectrophotometer	Elico SL 164
4	Analytical Balance	Adair Dutt Instruments Pvt Ltd., AD50B
5	Friability apparatus	Electro Lab
6	Hardness tester	Ketan
7	pH meter	Electro lab
8	Tapped density tester	Electro Lab

Experimental methods
Preformulation Studies

Bulk Density

It refers to a measurement to describe packing of particles. Bulk density is used to determine the amount of drug that occupies the volume in mg/ml.

$$\text{Bulk density} = \frac{\text{Weight of powder}}{\text{Bulk volume of powder}}$$

Procedure

Weighed quantity of API was transferred into 100 ml measuring cylinder without tapping during transfer. The volume occupied by DRUG was measured. Bulk density was measured by using formula.

$$P_i = m/v_i$$

Tapped Density
Procedure

Weighed quantity of API was taken into a graduated cylinder. Volume occupied by DRUG was noted down. Then the cylinder was subjected to 500, 750 & 1250 taps in tap density tester (Electro Lab USP II). According to USP, the blend was subjected for 500 taps. % Volume variation was calculated and subjected for additional 750 taps. % Variation is calculated.

$$\text{Tapped density} = \frac{\text{weight of powder}}{\text{Tapped volume of powder}}$$

Compressibility Index

Weighed API was transferred to 100ml-graduated cylinder and subjected to 500,750&1250 taps in tap density tester (Electro lab). The difference between two taps should be less than 2%. The % of compressibility index calculated using formula

$$\text{Carrs index} = \frac{\text{Tapped density} - \text{bulk density}}{\text{Tapped density}} \times 100$$

Limits

S.No	Compressibility index	Flow
1	5-12	Free flow
2	12-16	Good flow
3	18-21	Fair

4	23-25	Poor
5	33-38	Very poor
6	>40	Extremely poor

Hausner's Ratio

It is measurement of frictional resistance of the drug. The ideal range should be 1.2 –1.5.it is the determined by the ratio of tapped density and bulk density.

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Where
v_t = Tapped volume
v_i = Untapped volume

Limits

S.No	Hausner' ratio	Flow
1	1-1.2	Free flowing
2	1.2-1.6	Cohesive powder

Solubility

- Freely soluble in water.
- Soluble in alcohol and slightly soluble in acetonitrile and methyl ethyl ketone

Table 3: Results

S.NO	PARAMETER	RESULT
1	Bulk density	0.36 gm/cc
2	Tap density	0.612 gm/cc
3	comp. Index	42
4	Hausner's ratio	1.64
5	Particle size	89 µ

From the above data it was found that Losartan potassium was extremely poor flow, cohesive powder.

Preparation of Mucoadhesive buccal Tablets

Matrix type buccal tablets of losartan potassium were prepared by direct compression method. The buccal tablets were prepared by natural polymers separately. The composition of different formulations is shown in Table.5. The weighed drug, polymers and excipients were mixed homogeneously in a glass mortar for 15 min. The mixture (150 mg) was then compressed using a 7 mm, biconcave punch in double-stroke using 9-station rotary machine.

Table 4: Composition of Losartan Potassium Tablets

	Batch mode			
INGREDIENTS (mg)	**FG1**	**FG2**	**FX1**	**FX2**
Drug	20	20	20	20
Na.Alginate	50	37.5	50	37.5
Guar gum	25	37.5	-	-
Xanthan gum	-	-	25	37.5
Pvp k30	30	30	30	30
MCC	22	22	22	22
Mg Stearate	2	2	2	2
Talc	1	1	1	1
Total	150	150	150	150

Construction of Calibration curve of Losartan Potassium

Accurately weighed 100 mg of Losartan potassium and transferred into 100 ml of volumetric flask and dissolved in small quantity of methanol and diluted with 6.8 phosphate buffer up to the mark to give stock solution 1 mg/ml. 1 ml was taken from stock solution in another volumetric flask and diluted up to 100 ml to give a stock solution 10 µg/ml. Further dilutions were made from 2-40 µg/ml with 6.8 phosphate buffer and absorbance was measured at 235 nm.

Table 5: Calibration curve of Losartan potassium in pH 6.8 phosphate buffer at 235 nm

S.No.	Concentration	Absorbance
1	2 µg/ml	0.122
2	4 µg/ml	0.227
3	6 µg/ml	0.343
4	8 µg/ml	0.450
5	10 µg/ml	0.562
6	12 µg/ml	0.670
7	14 µg/ml	0.779
8	16 µg/ml	0.887
9	18 µg/ml	0.981
10	20 µg/ml	1.074

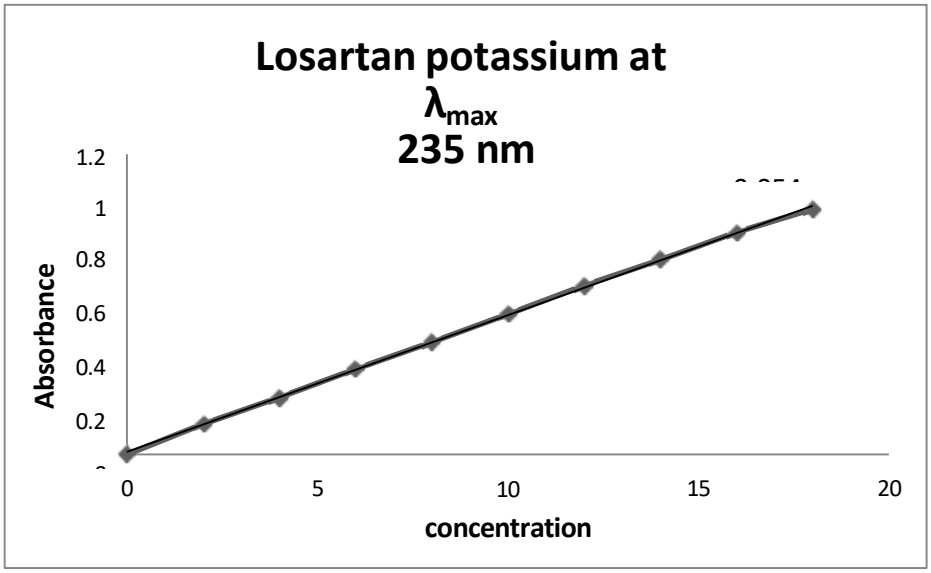

Fig 1: Calibration curve of Losartan potassium

Evaluation of tablets

The formulated tablets were evaluated for the following physicochemical parameters:

Hardness test

The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

Thickness

The thickness of three randomly selected tablets from each formulation was determined in mm using a Vernier Calliper. The mean and standard deviation values were calculated.

Friability test

The friability of tablet was determined by using Roche Friabilator. It is expressed in percentage (%) as per IP.

$$\% \text{ Friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

Weight Variation Test

The weight variation test was performed as per procedure of IP. The weight (mg) of each of 10 individual tablets, selected randomly from each formulation was determined by dusting each tablet off and placing it in an electronic balance. The individual weight was compared with average weight for determination of percent deviation.

Content uniformity

Ten tablets from each formulation were taken, crushed and mixed. From the mixture 20 mg of Losartan potassium equivalent of mixture was extracted thoroughly with 100 ml of pH 6.8 phosphate buffer. The amount of drug present in each extract was determined using UV spectrophotometer at 205 nm. This procedure was repeated thrice and this average was chosen.

Surface pH study

The surface pH of the buccal tablets was determined in order to investigate the possibility of any *in vivo* side effects. An acidic or alkaline pH may cause irritation to the buccal mucosa.Three tablets from each batch were selected and allowed to swell separately by keeping it in contact with distilled water (pH 6.5 ± 0.05) for 2 hrs at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equiliberate for 1 min.

Swelling Index

Three 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 ± 1°C. After every 2 h time interval until 8 h, the tablet was removed from the petri dish and excess surface water was removed careful with blotting paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) were calculated using the formula given in equation.

Swelling Index = [(W2-W1) ÷ W1] × 100

Where,
W1 = initial weight of the tablet.
W2 = final weight of the tablet.

Mucoadhesion strength

The apparatus used for testing bioadhesion was assembled in the laboratory Mucoadhesion strength of the tablet was measured on a modified physical balance employing the method described by Gupta *et al* using Goat buccal mucosa as model mucosal membrane A double beam physical balance was taken, the left pan was removed. To left arm of balance a thick thread of suitable length was hanged. To the bottom side of thread a glass stopper with uniform surface was tied. A clean 100 ml glass beaker was placed below hanging in inverted position. Keep the surface of mucosa moist by phosphate buffer pH 6.8.

***In-Vitro* Residence Time**

The in-vitro residence time was determined using a modified USP disintegration apparatus. The disintegration medium was composed of 900 ml phosphate buffer of pH 6.8 maintained at 37oC±0.5ºC. A segment of goat cheek mucosa 3 cm long was glued to the surface of a glass slab, vertically attached to the apparatus. Mucoadhessive tablets of each formulation were hydrated from one surface using phosphate buffer of pH 6.8 and then the hydrated surface was brought into contact with the mucosal membrane. The glass slab was vertically fixed to the apparatus and allowed to move up and down so that the tablet was completely immersed in the buffer solution at the lowest point and was out at the highest point. The time necessary for compete erosion or detachment of the tablet from mucosal surface were recorded.

***In vitro* drug release profile**

In vitro release study of mucoadhesive buccal tablets of Losartan potassium was carried out using the USP II method at 50 rpm. Medium used for release rate study was 900 ml of phosphate buffer (pH 6.8) solution. The buccal tablet was attached to the glass slide with cyanoacrylate adhesive. The disk was placed at the bottom of dissolution vessel. During the course of study whole assembly was maintained at 37oC. Five ml of the sample was withdrawn at time intervals of 1, 2, and 3 … up to 10 hrs and replaced with the same amount of the fresh medium.

RESULT AND DISCUSSION

Compatibility studies

The incompatibility between the drug and excipients were studied by FTIR spectroscopy. The spectral data of pure drug and various drug-excipient mixtures are presented in Figure.8 (A, B). The results indicate that there was no chemical incompatibility between drug and excipients used in the formulation.

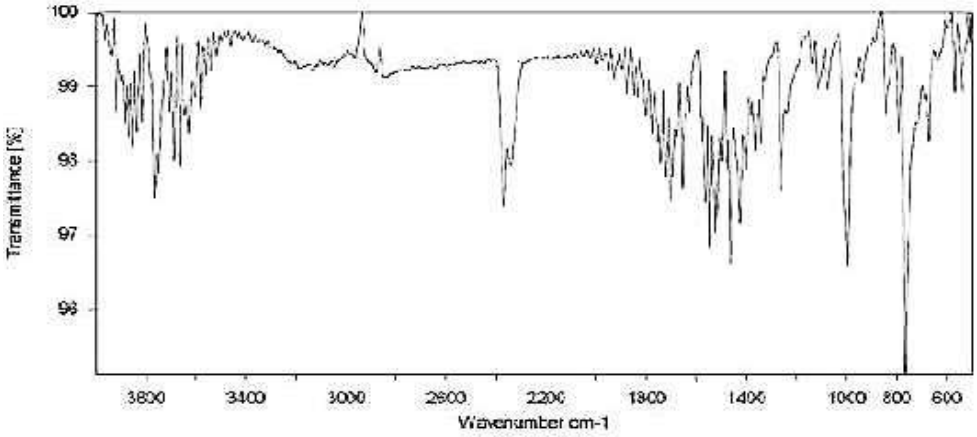

Fig 2: FTIR spectra of A) Losartan potassium

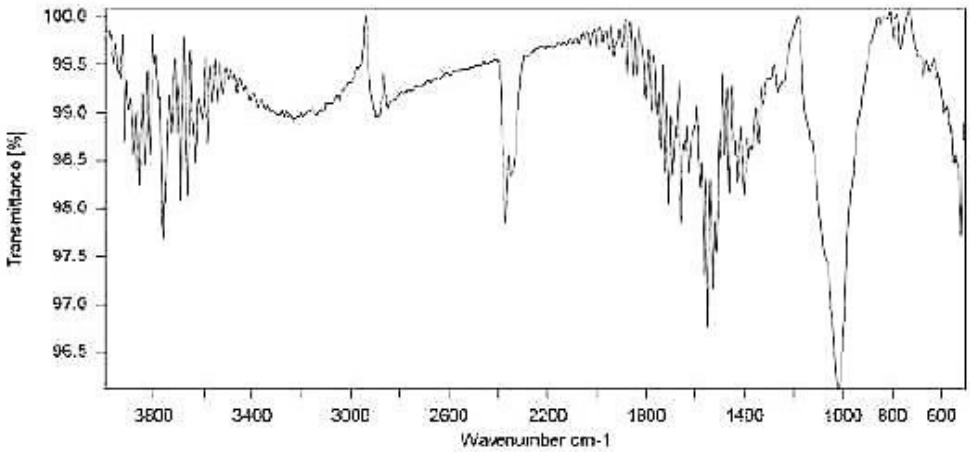

Fig 3: FTIR spectra of B) Losartan potassium+ natural polymers (Sodium alginate, Guar gum and Xanthan gum)

Hardness test

All formulations show hardness in the range of 5.83 to 6.86 kg/cm2.Resultsare shown in Table no: 7

Thickness

The thickness of the tablets was found to be almost uniform in all formulations. The thickness was found to be in the range of 2.46 to 2.5 mm. The results are shown in Table 7.

Friability Test

The friability value for all tablet formulation were found to be less than 1% indicate that the friability is within the prescribed limits and ensuring that the tablets were mechanically stable. Results are shown in Table no: 7.

Weight Variation test

The average weight of ten tablets was calculated for each formulation which varied from 149.3 mg to 151.3 mg that complies with the official requirement as per IP. Results are shown in Table no: 7.

Content Uniformity

The drug content varied from 98.7 % to 99.9 % of all formulations which is within the required limit. The results are shown in the Table no: 7.

Surface pH study

Surface pH of all the formulations was found to be in the range of 6.2 to 6.71 as shown in Table no: 7.

Table 6: Physico-chemical parameters of Losartan Potassium buccal tablets

Batch Code	Evaluation Parameters					
	Hardness (Kg/cm2)	Thickness (mm)	Friability %	Weight variation (gm)	% Drug Content	Surface pH
FG 1	6.26±0.11	2.467±0.1	0.41	150.3±49	98.95±0.7	6.2±0.30
FG2	5.83±0.15	2.5±0.10	0.46	149.5±3.2	99.0±0.65	6.48±0.02
FX 1	6.86±0.05	2.46±0.57	0.52	151±4.8	98.7±0.84	6.36±0.2
FX2	6.46±0.15	2.46±0.05	0.32	149.3±3.3	99.9±1.3	6.71±0.02
	n=3	n=3	n=10	n=10	n=3	n=3

Swelling Index

Swelling Index of all formulation after 8 hrs is in the ranges from 320 % to 378 % as shown in Table no.8. Highest swelling Index 378% was observed of formulation FX2 (Containing Sodium alginate and Xanthan Gum 1:1) among natural polymers

Table 7: Swelling index of all formulations

Batch Code	% Swelling Index					
	Time (hr)					
	0.5	1	2	4	6	8
FG1	49.1±0.2	75.53±0.4	120.7±1.1	213.5±3.04	270.8±1.0	320±1.8
FG2	58.27±0.9	104.2±1.1	187.4±1.6	246.8±1.0	301.1±0.77	341.8±1.0
FX1	51.5±1.3	80.4±0.5	135.8±1.0	236±1.0	310.3±1.5	351±2.7
FX2	77.07±0.8	135±0.9	255.2±0.7	302.8±2.0	351.6±1.0	378.3±1.6

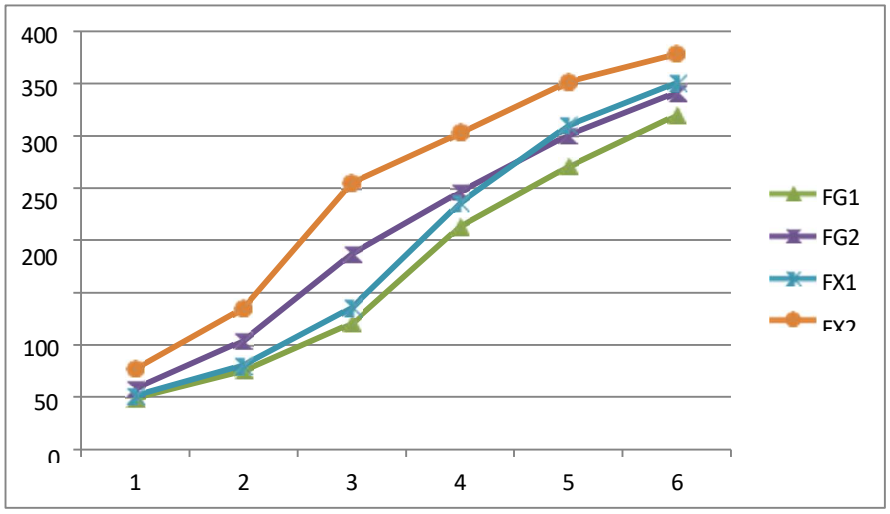

Fig 4: Swelling index of formulation FG1, FG2, FX1, FX2

Mucoadhesive Strength

In vitro Mucoadhesive Strength of all formulations is ranges from 15.03 to 17.77 gm as shown in Table 8. .Mucoadhesive strength of all the formulations was found to be increased as the concentrations of polymers was increased. Natural polymers FX2 shows highest mucoadhesive strength i.e. 17.77 gm respectively.

In vitro Residence Time

In vitro Residence Time of all formulation is ranges from 6 hrs to 8 hrs 15 min. The results are shown in Table no.8. Natural polymers FX2 shows heights results i.e 8hrs 15 min respectively.

Table 8: Mucoadhesive strength study and In vitro Residence Time of all formulations

Batch Code	Mucoadhesive strength (gm)	Force of Adhesion (N)	Time (hrs)
FG1	15.43±0.257	0.151	6 hrs 20 min
FG2	15.03±0.577	0.147	6 hrs
FX1	16.97±0.1528	0.166	7.5 hrs
FX2	17.77±0.3215	0.174	8 hrs 15 min

In vitro Drug release

In vitro % Drug release of all formulations is shown in Table no. 10. Among natural polymers FG1 and FG2 formulations contain sodium alginate and Guar Gum in ratio 2:1 and 1:1 respectively and FX1 and FX2 formulations contain sodium alginate and Xanthan Gum in ratio 2:1 and 1:1 respectively. FX2 shows highest % drug release i.e. 95.28%.

Table 9: Percentage drug release study

Batch Code	% DRUG RELEASE Time (hr)							
	1	2	3	4	5	6	7	8
FG1	7.23	16.32	20.82	28.28	39.74	43.697	74.23	79.16
FG2	3.84	8.95	18.04	23.57	28.11	43.53	64.91	74.54
FX1	9.15	15.65	35.07	49.85	57.59	73.51	84.54	90.31
FX2	13.145	28.023	40.145	53.39	62.56	75.183	83.156	95.28

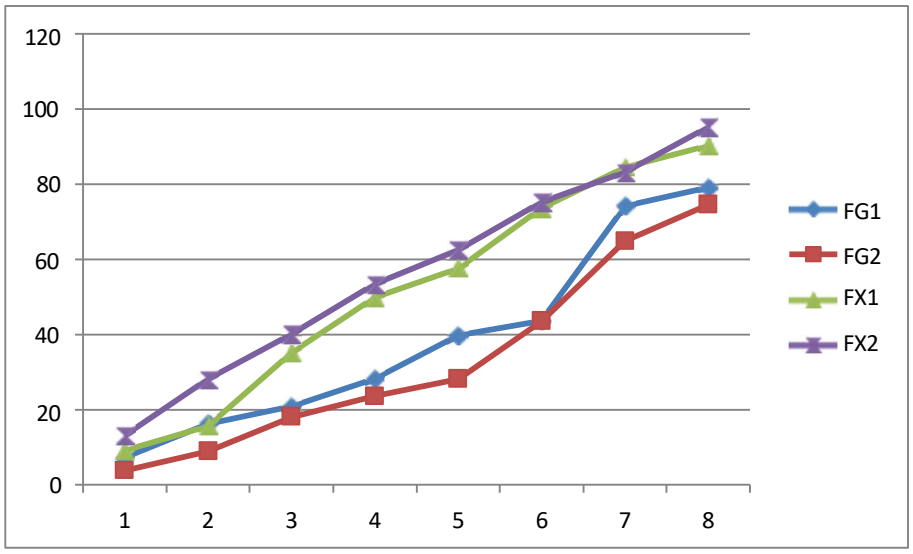

Fig 5: Percentage drug release of batches FG1, FG2, FX1 and FX2 (Containing Natural Polymers)

CONCLUSION AND SUMMARY

In conclusion, the aim of the present study was to develop mucoadhesive drug delivery system for Losartan potassium with a prolonged effect and to avoid first pass metabolism. These mucoadhesive formulations of Losartan potassium, in form of mucoadhesive buccal tablets were developed to a satisfactory level in terms of drug release, mucoadhesive time, physicochemical properties and surface pH. Losartan potassium buccal tablet could be formulated using Drug and and natural polymers, Sodium alginate and xanthan gum in ratio 1:1. increase in results of % Drug release, mucoadhesive strength and *in vitro* residence time. In case of natural polymers sodium alginate as a primary polymer and xanthan gum gives more drug release and mucoadhesive strength than guar gum at same concentration.

REFERENCES

1. Welling, P. G., Barbhaiya, R. H. Effects of food on the pharmacokinetics of Irbesartan/Hydrochlorothiazide combination Tablet. J.Pharm. Sci., 1982*,* 71(6):32.
2. Pandit JK, Vemuri NM, Wahi SP, Jayachandra Babu R. Mucosal Dosage Form of Ephedrine Hydrochloride using Gantrez-AN 139. Eastern Pharmacist 1993;36:169-170.
3. Gupta A, Garg S, Khar RK. Mucoadhesive Buccal Drug Delivery System: A Review. Indian Drugs 1992;29(13):586-93.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;178:11-2.
5. Ponchel G, Irache J. Specific and non-specific bioadhesive particulate systems for oral delivery to the gastrointestinal tract. *Adv Drug Delivery*. 1998;34:191-219.
6. S. J.Hwang, H. Park and K. Park, "Gastric Retentive Drug-Delivery Systems", Crit. Rev. Ther. Drug Carrier Syst. 1998, 15 (3), 243–284.
7. L. Whitehead, J. T. Fell and J H Collett, "Development of a Gastroretentive Dosage Form", Eur. J. Pharma. Sci., 1996, 4 (1),182.
8. P. Mojaverian, P. H. Vlasses, P. E. Kellner and M. . Rocci, "Effects of gender, posture and age on gastric residence time of an indigestible solid: pharmaceutical considerations", Pharm. Res., 1988, 10, 639–644.
9. Singh B, Ahuja N. Response surface optimization of drug delivery system. In: Jain NK, ed. *Progress in Controlled and Novel Drug Delivery Systems.* New Delhi, India: CBS Publishers and Distributors; 2004, 20, 240.
10. Yamagar M, Kadam V, Hirlekar R. Design and evaluation of buccoadhesivedrug delivery system of metoprolol tartrate. Int J Pharm Tech Res. 2010;2(1): 453-462.
11. Vasir JK, Tambwekar K, Garg S.Bioadhesive microspheres as a controlled drug delivery. J Control Release 1998;55:143-52.
12. Semalty A., Bhojwani M., Bhatt G., Gupta G., Shrivastav A. Design and evaluation of mucoadhessive buccal films of diltiazem hydrochloride. Indian J of PharmaceuticalSciences, 2005;67(5):548-552.
13. Guda A, Gudas GK, Bingi B, Debnath S, Rajesham VV. Design and evaluation of controlled release mucoadhesive buccal tablets of lisinopril. Int J Curr Pharm Res. 2010; 2(4): 24-27.
14. K.P.R. Chowdary, B.Suresh, B.Sangeeta and G.Kamalakara Reddy "*Design and Evaluation of Diltiazem Mucoadhesive Tablets for Oral Controlled Release"*of Saudi Pharmaceutical Journal, Vol 11, No. 4,october 2003.
15. Shukla, S., Prasad, S., Sharma, E.K., The Opportunities for Indian Pharma., Out Look , 2002, Oct.-13, 41-49. 5.Nagai, T. and Machida, Y., Mucosal Adhesive Dosage Forms, Pharm. Int., 1985, 196-200.
16. Bodde, H.E., De Vries, M.E.and Junginger, H.E., Mucoadhesive Polymers for the Buccal Delivery of Peptides, Structure-Adhesiveness Relationships, J. Control. Rel., 1990, 13:225-231.
17. Mathiowitz, E., Chickering, D., Jacob, J. S.and Santos, C., In; Mathiowitz, E., Eds, Encyclopedia of Controlled Drug Delivery, Vol. 1, John Willey & Sons, New York, 1999, 9- 44.
18. Squier, C.A.and Wertz, P.W., Structure and Function of the Oral Mucosa and Implications for Drug Delivery, in, M.J. Rathbone, Eds; Oral Mucosal Drug Delivery, 1996, Marcel Dekker, Inc., New York,1-26.
19. Bhaskar U., Patil R., Birajdar R., Mysore S., Bilagi S., Audurti D. Formulation and In-Vitro Evaluation of Mucoadhesive Buccal Tablets of Furosemide. World J of Pharmacy and Pharmaceutical Sciences, 2012; 1(3):1041-1063.