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FORMULATION AND *IN VITRO* EVALUATION OF MUCOADHESIVE BUCCAL TABLET OF LOSARTAN POTASSIUM USING SYNTHETIC AND NATURAL POLYMERS

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ABSTRACT

The objective of this study was to develop mucoadhesive buccal tablets of Losartan Porassium using both Synthetic and Natural mucoadhesive polymers and evaluate results of both polymers. Losartan Potassium is Angiotensin receptor blocker having short biological half-life (2hr), high first-pass metabolism and poor oral bioavailability (33%), hence an ideal candidate for buccal delivery system. The buccal tablets of 150 mg were prepared by using synthetic (Carbopol 934p as primary and HPMC K15M and SCMC as secondary polymer) and natural polymers (Sodium Alginate as primary and Guar Gum and Xanthan Gum as secondary polymers) separately in various concentrations by direct compression method, eight batches were prepared. Estimation of Losartan potassium was carried out spectrophotometrically at 205 nm. FTIR spectroscopy method revealed that there was no interaction between Losartan potassium and polymers. The tablets were evaluated for hardness, thickness, weight variation, friability, drug content, surface pH, swelling index, *in vitro* drug release, mucoadhesive strength and *in vitro* Residence time. Among synthetic polymers FS2 and among natural polymers FX2 batches showed better results. Data of *in-vitro* release from tablets were fed into kinetic models (Zero order, first order, Higuchi and Korsmeyer-Peppas models) to explain release profiles. The optimized formulations showed zero order release.

KEYWORDS: HPMC K15M, Losartan potassium, SCMC, Sodium alginate, Xanthan Gum.

1. INTRODUCTION

Mucoadhesive drug delivery systems offer benefits over conventional delivery methods in terms of extended residence time of the drug at the site of application, a relatively large

permeability of the mucus membranes that allow rapid uptake of a drug into the systemic circulation, and enhanced bioavailability of therapeutic agents resulting from the avoidance of some of the body's natural defense mechanisms. Mucoadhesion, defined as the ability to adhere to the mucus gel layer, is a key element in the design of these drug delivery systems. Buccal mucosa is an attractive route for systemic delivery of drugs since it is relatively permeable, with rich blood supply. The problems such as high first-pass metabolism and drug degradation in the harsh gastrointestinal environment can be circumvented by administering the drug via the buccal route and, buccal drug absorption can be promptly terminated in case of toxicity by removing the dosage form from the buccal cavity. [1]

Losartan potassium is an angiotensin II receptor (type AT1) antagonist. The Losartan is an orally active agent that undergoes substantial first-pass metabolism by cytochrome P450 enzymes. The Losartan is freely soluble in water and 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 2 hours. Hence, it is a suitable candidate for administration via the buccal route. The bioavailability of Losartan is about 33%. [2]

Drugs which are highly water soluble are considered difficult to deliver in the form of sustained or controlled release formulation due to their susceptibility to dose dumping. Hence, an attempt is made to formulate a buccal tablet, to regulate the release process of Losartan potassium using mocoadhesive polymers, with extended clinical effect, reduced dosing frequency and avoid dose dumping. [3]

2. MATERIALS AND METHOD

2.1 Materials

Losartan Potassium (Alkem labs, Mumbai), Carbopol 934P (Ozone International Mumbai), HPMC K15M (Alkem labs. Mumbai), Sodium carboxy methyl cellulose, Sodium Alginate, Xanthan Gum (Gift sample from University Department Nagpur), Guar Gum (Concept pharma Aurangabad).

2.2 Compatibility studies

The drug-excipient compatibility studies were carried out using Fourier Transform Infrared Spectrophotometer (FTIR). Infra red spectra of pure drug and mixture of drug and excipients were recorded.

2.3 Preparation of mucoadhesive buccal Tablets

Matrix type buccal tablets of losartan potassium were prepared by direct compression method. The buccal tablets were prepared by using both synthetic polymers and natural polymers separately. The composition of different formulations is shown in Table 1.

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. (Karnavati Minipress II DL).

2.4 Evaluation of mucoadhesive buccal tablets

2.4.1 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.

2.4.2 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.

2.4.3 Friability test

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

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

2.4.4 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.

2.4.5 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.

2.4.6 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. [4]

2.4.7 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 carefull 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. [5]

2.4.8 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. [6]

Figure 1: Bioadhesion test Assembly

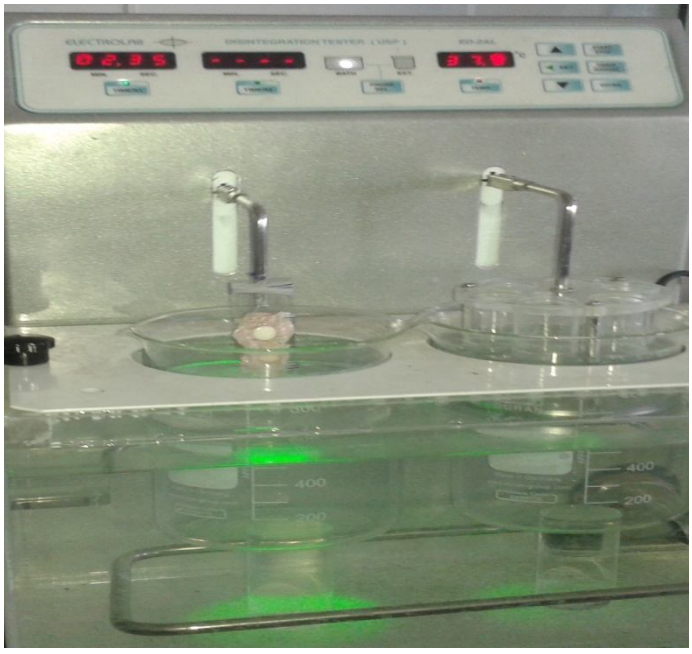


Figure 2: *In vitro* residence time test Assembly

2.4.9 *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 37^{o}C±0.5^{o}C. 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. [7]

2.4.10 *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 37^{o}C. 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.

2.4.11 Release kinetic studies

To find out the mechanism of drug release from hydrophilic matrices, the in vitro release data was treated with different kinetic models, namely zero order, first order, Higuchi and Korsemeyer-Peppas.

Table 1: Composition of Buccal Tablet

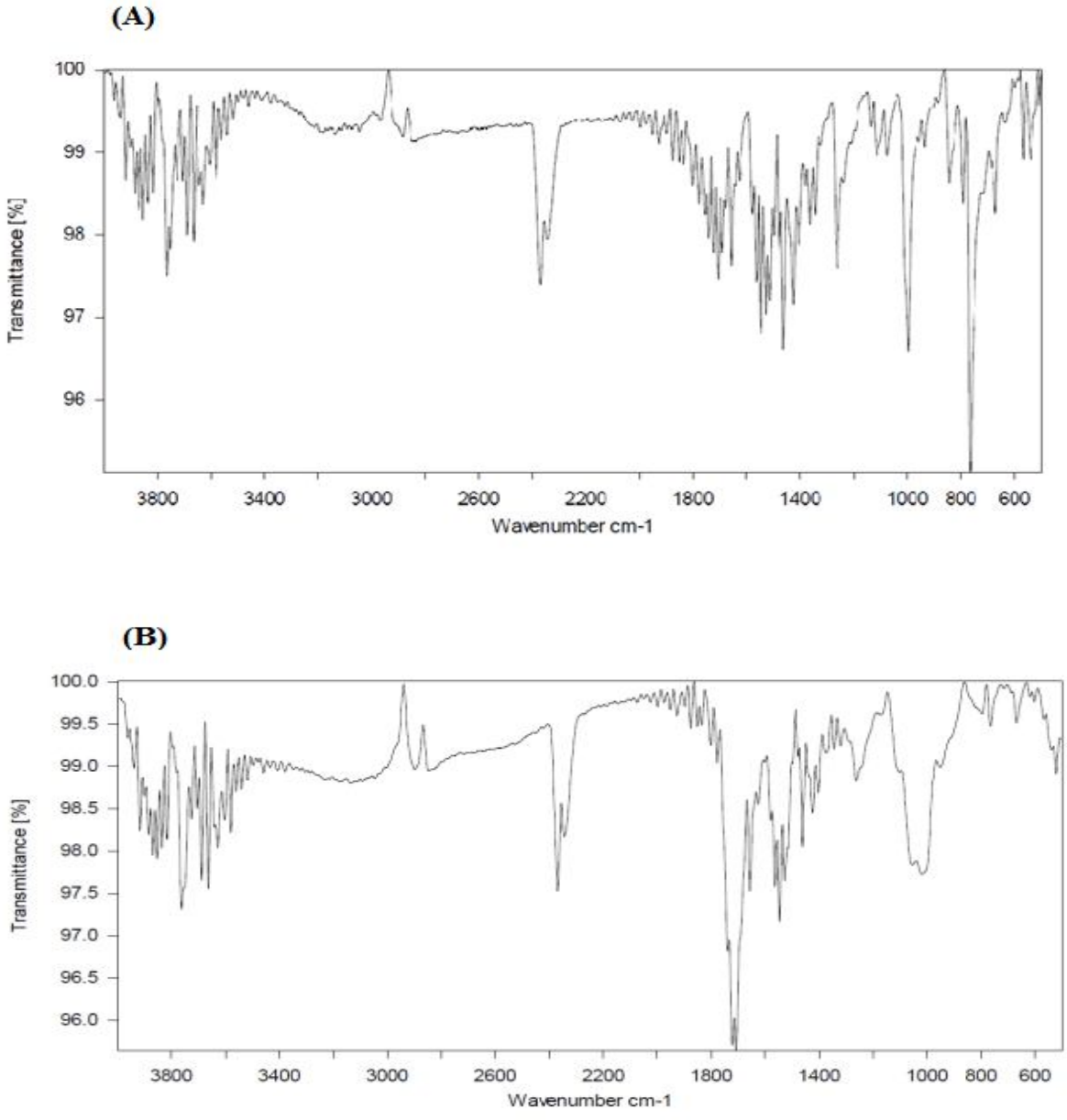
Ingredients (mg)	Batch code							
	FH1	FH2	FS1	FS2	FG1	FG2	FX1	FX2
Drug	20	20	20	20	20	20	20	20
Carbopol 934 P	50	37.5	50	37.5	-	-	-	-
HPMC K15	25	37.5	-	-	-	-	-	-
SCMC	-	-	25	37.5	-	-	-	-
Na.Alginate	-	-	-	-	50	37.5	50	37.5
Guar Gum	-	-	-	-	25	37.5	-	-
Xanthan Gum	-	-	-	-	-	-	25	37.5
PVP K30	30	30	30	30	30	30	30	30
MCC	22	22	22	22	22	22	22	22

Mg Stearate	2	2	2	2	2	2	2	2
Talc	1	1	1	1	1	1	1	1
Total	150	150	150	150	150	150	150	150

3. RESULT AND DISCUSSION

3.1 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 3. The results indicate that there was no chemical incompatibility between drug and excipients used in the formulation.



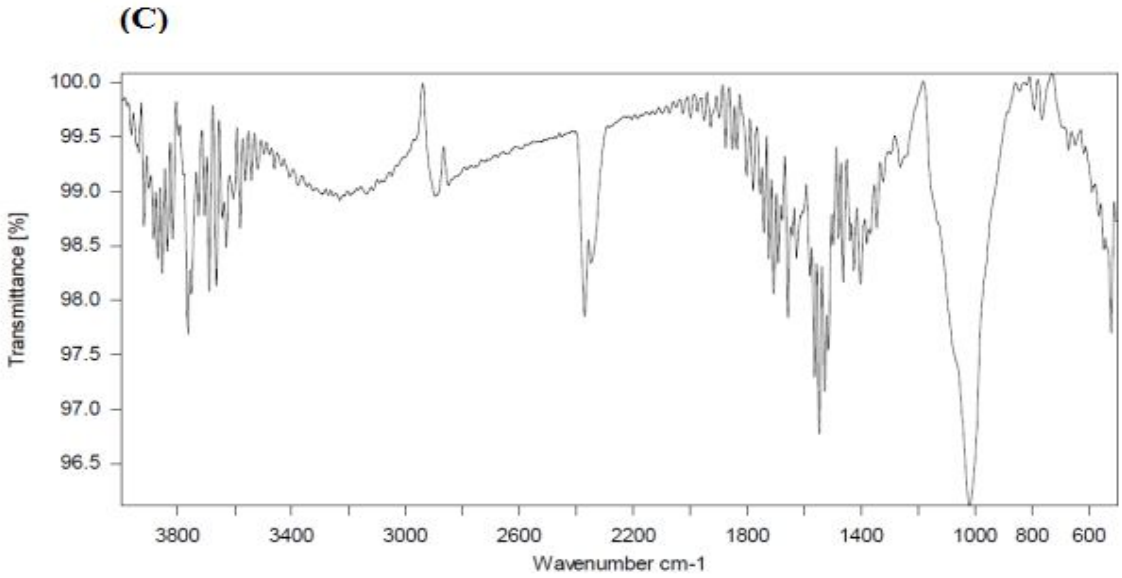


Figure 3: FTIR spectra of A) Losartan potassium B) Losartan potassium+ synthetic polymers (Carbopol 934P, HPMC K15, and SCMC) C) Losartan potassium+ natural polymers (Sodium alginate, Guar gum and Xanthan gum)

Table 2: Physico-chemical parameters of Losartan Potassium buccal tablets.

Batch Code	Evaluation Parameters					
	Hardness (Kg/cm^2)	Thickness (mm)	Friability %	Weight variation (gm)	%Drug Content	Surface pH
FH1	7.0± 0.10	2.46±0.05	0.48	150.8±4.6	98.15±1.7	5.9 ± 0.20
FH2	6.43±0.57	2.5±0.10	0.51	150±3.24	98.30±0.14	6.33 ± 0.05
FS1	6.9±0.57	2.53±0.11	0.39	151.3±4.8	98.45±0.07	6.63 ± 0.15
FS2	7.63±0.15	2.16±0.15	0.35	149.3±3.3	99.8±0.76	6.83 ± 0.05
FG1	6.26±0.11	2.467±0.1	0.41	150.3±4.9	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
FX1	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

Table 3: Swelling index of all formulations

Batch Code	% Swelling Index					
	Time (hr)					
	0.5	1	2	4	6	8
FH1	51.5±1.6	83.3±3.3	134±1.73	233.2±3.3	292.2±1.9	327.5±2.1
FH2	41.8±0.3	84.5±0.4	166.6±0.4	181.9±0.4	218±0.35	299.6±0.7
FS1	61.1±1.9	102±1.7	145±1.7	245.2±1.9	321±3.8	365.5±1.9
FS2	72.83±1.0	110.3±1.1	184.8±1.2	278.8±1.2	341.6±1.5	372.4±0.8
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	2464.8±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

Values are mean± S. D. (n=3)

Table 4: Mucoadhesive strength study and *In vitro* Residence Time of all formulations

Batch Code	Mucoadhesive strength (gm)	Force of Adhesion (N)	Time (hrs)
FH1	16.03 ± 0.0577	0.1572	7.5 hrs
FH2	17.9 ± 0.1732	0.1756	8 hrs
FS1	17.87 ± 0.152	0.1753	8 hrs
FS2	18.47 ± 0.155	0.181	8 hrs 30 min
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

Values are mean± S. D. (n=3)

Table 5: % drug release study

Batch Code	% Drug Release							
	Time (hr)							
	1	2	3	4	5	6	7	8
FH1	14. 13	25.63	41.94	49.52	59.74	72.51	84.66	94.85
FH2	9.04	12.71	23.41	43.55	56.45	69.54	80.89	92.41
FS1	14.58	22.46	35.48	45.06	62.94	74.71	83.60	95.70
FS2	9.15	19.04	33.64	51.09	62.90	74.67	85.82	99.06
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

3.2 Hardness test

All formulations show hardness in the range of 5.83 to 7.63 kg/cm^2. Results are shown in table no. 2.

3.3 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 2.16 to 2.53 mm. The results are shown in Table no. 2.

3.4 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.

3.5 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. 2.

3.6 Content Uniformity

The drug content varied from 98.15 % to 99.99 % of all formulations which is within the required limit. The results are shown in the Table no. 2.

3.7 Surface pH study

Surface pH of all the formulations was found to be in the range of 5.9 to 6.83 as shown in Table no. 2.

3.8 Swelling Index

Swelling Index of all formulation after 8 hrs is in the ranges from 299.6 % to 378 % as shown in Table no. 3. Highest swelling Index 378% was observed of formulation FX2 (Containing Sodium alginate and Xanthan Gum 1:1) among natural polymers and 372.4 % of FS2 among synthetic polymers (containing Carbopol 934 P and SCMC 1:1).

3.9 Mucoadhesive Strength

In vitro Mucoadhesive Strength of all formulations is ranges from 15.03 to 18.47 gm as shown in Table no. 4. Mucoadhesive strength of all the formulations was found to be increased as the concentrations of polymers was increased. Among synthetic polymers FS2 and among natural polymers FX2 shows highest mucoadhesive strength i. e. 18.47 gm and 17.77 gm respectively.

3.10 *In vitro* Residence Time

In vitro Residence Time of all formulation is ranges from 6 hrs to 8 hrs 30 min. The results are shown in Table no. 4. Among synthetic polymers FS2 and among natural polymers FX2 shows heights results i. e. 8hrs 30 min and 8hrs 15 min respectively.

3.11 *In vitro* Drug release

In vitro % Drug release of all formulations is shown in Table no. 5. Formulations containing synthetic polymers show drug release after 8 hrs ranges from 92.41 % to 99.06 %. FH1 and FH2 formulations contain Carbopol 934P and HPMC K15 in ratio 2:1 and 1:1 respectively and FS1 and FS2 formulations contain Carbopol 934P and SCMC in ratio 2:1 and 1:1 respectively. FS2 shows highest % drug release i. e. 99.06%.

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%

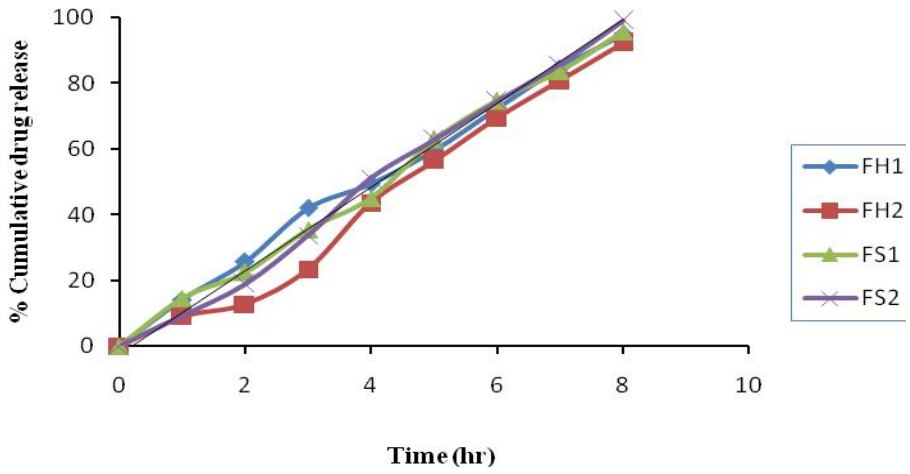


Figure 4: % Drug release of batches FH1, FH2, FS1, and FS2 (Containing synthetic polymers)

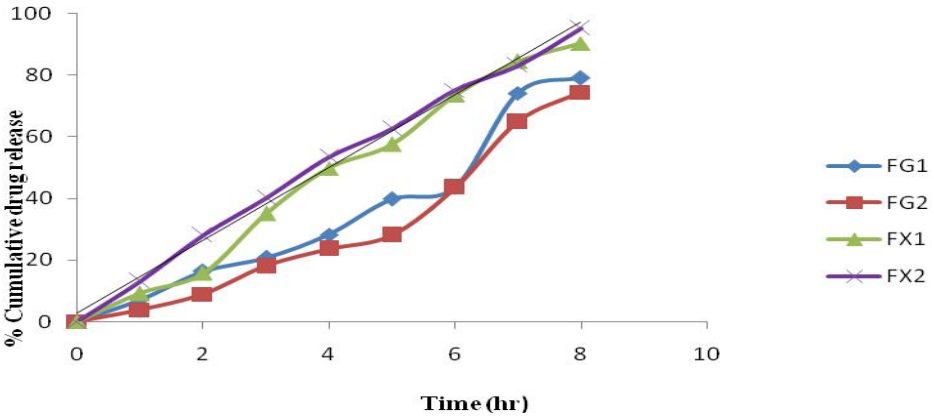


Figure 5: % drug release of batches FG1, FG2, FX1 and FX2 (Containing Natural Polymers)

Table 6: Release kinetics of best formulations FS2 and FX2

Batch code	R^2 Value (correlation coefficient)				
	Zero order	First Order	Higuchi	Korsmeyer-Peppas	
				R^2 value	n value
FS2	0.9961	0.7157	0.8199	0.9622	0.1863
FX2	0.9953	0.8331	0.9548	0.9194	0.2926

4. CONCLUSION

Losartan potassium buccal tablet could be formulated using Drug and synthetic polymers Carbopol 934P and Sodium Carboxy methyl cellulose in ratio 1:1 and also formulated using Drug and natural polymers Sodium alginate and xanthan gum in ratio 1:1. Synthetic polymers shows better results than natural polymers i. e. results of % Drug release, mucoadhesive strength and *in vitro* residence time.

It has concluded that SCMC as secondary polymer with Carbopol 934P increases drug release, mucoadhesive strength than HPMC K15 as secondary polymer with Carbopol 934P at same concentrations, and 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. *In vitro* release kinetic study of formulation FS2 and FX2 shows that both formulations obey Zero Order release kinetics.

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