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FORMULATION AND EVALUATION OF MUCOADHESIVE BUCCAL PATCHES OF LOSARTAN POTASSIUM

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Abstract:

The mucoadhesive Buccal Patches of losartan potassium could be prepared using locustbean gum and HPMC K4M by direct compression method.The IR spectra revealed that, there was no interaction between polymers and drug. All polymers used were compatible with drug.All the prepared tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopoeial specification.The surface pH of prepared Buccal Patches was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation.All the Buccal Patches showed good residence time of 7.2 H to >10 h, indicated good adhesive capacity of polymers used.The CCD was used to find out the effect of independent varibles on the dependable variables. The result of CCD revealed that the locustbean gum and HPMC K4M have significant effect on the mucoadhesion strenth, swelling index, the drug release at 1 h and drug release at 8 h. The observed independent variables were found to be very close to predicted values of optimized formulation which demonstrates the feasibility of the optimization procedure in successful development of buccal tablet containing losartan potassium by using locustbean gum and HPMC K4M. The drug release form the optimized formula was found to be following the zero order kinetics and n value range of the Peppas equation is 0.521, which indicates fickian diffusion mechanism. Thus the release of drug from the dosage form was found to be time dependent.The stability studies revealed that there was no significant change in buccal tablet properties with aging at different storage conditions.Hence, the mucoadhesive Buccal Patches of losartan potassium can be prepared with enhanced bioavailability and prolonged therapeutic effect for the better management of hyper tension.

Keywords: *Losartan potassium, Buccal patches, Mucoadhesive, Formulation, Evaluation*

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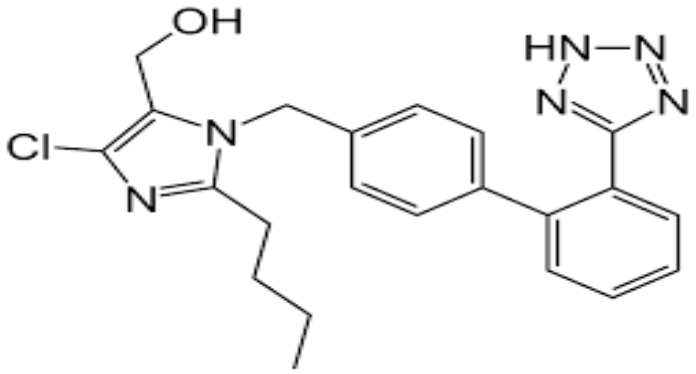
INTRODUCTION:

Amongst the various routes of drug delivery, oral route is perhaps the most preferred to the patient and the clinician alike [1]. Bioadhesion is the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time [2-4]. The biological surface can be epithelial tissue or it can be the mucous membrane adhere on the surface of a tissue. If adhesion is to a mucous coat, the phenomenon is referred to as mucoadhesion. The use of mucoadhesive polymers in buccal drug delivery has a greater application [3].Various mucoadhesive devices, including tablets, films, patches, disks, strips, ointments and gels have recently been developed. However, buccal patch offer greater flexibility and comfort than the other devices. In addition, a patch can circumvent the problem of the relatively short residence time of oral gels on mucosa, since the gels are easily washed away by saliva. Buccal route drug delivery provides the direct entry to the systemic circulation through the jugular vein bypassing the first pass hepatic metabolism leading to high bioavailability [5-7]. Other advantages such as excellent accessibility, low enzymatic activity, suitability for drugs or excipients that mildly and reversibly damage or irritate the mucosa, painless administration, easy withdrawal, facility to include permeation enhancer/ enzyme inhibitor or pH modifier in the formulation, versatility in designing as multidirectional or unidirectional release system for local or systemic action [8-10].

Drug Profile:

Losartan is an angiotensin II receptor blocker (ARB) used to treat hypertension. Angiotensin-converting enzyme (ACE) inhibitors are used for a similar indication but are associated with a cough. When patients with ACE inhibitor associated, coughs are switched to ARBs like losartan, they have an incidence of cough similar to placebo or hydrochlorothiazide. Losartan is available as losartan potassium oral tablets as well as a combination tablet of losartan potassium and hydrochlorothiazide. Patients taking losartan should have their renal function and potassium levels monitored [11]. IUPAC name potassium 5-(4'-{[2-butyl-4-chloro-5-(hydroxymethyl)-1H-imidazol-1-yl] methyl}-[1,1'-biphenyl]-2-yl)-1,2,3,4-tetrazol-2-uide. Molecular formula is $C_{22}H_{22}ClKN_6O$. Molecular weight is 461. Losartan (potassium salt) is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide. The solubility of losartan (potassium salt) in these solvents is approximately 20 mg/ml.

Figure 1: Chemical structure:



The objective of the present research work is to formulate and evaluate bilayered buccoadhesive tablet containing losartan potassium as a drug to achieve unidirectional drug release and to increase bioavailability of the drug.

MATERIALS AND METHODS:

Materials:

Losartan Potassium was received as gift sample from Zydus Cadila Healthcare Ltd, Hyderabad, India. Hydroxy- propylmethyl cellulose K100 (HPMC K100) was obtained as gift sample from Vergo Pharmaceutical, Goa, India. All other chemicals and reagents that were of analytical grade were used.

Methods:

Drug excipients compatibility studies:

The FT-IR spectrum of Losartan Potassium, Physical mixture of Losartan Potassium with Guar Gum and HPMC K100 were analyzed to verify the compatibility between the pure drug and polymers using FT-IR (Make Varian care, Model-510) by KBr disc method. The procedure consisted of dispersing a sample (drug alone or mixture of drug and polymers) in KBr and compressing into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained, to identify functional groups and bands of drug or its mixture. The DSC thermogram of the Losartan Potassium and physical mixtures of Losartan Potassium, with Guar Gum and HPMC K100 were obtained from Shimadzu DSC-60 (Shimadzu Limited Japan) by heating at a scanning rate of 10 °C/ min over a temperature range 50-300 °C under nitrogen environment. DSC thermogram of pure Losartan Potassium and formulation were obtained to verify chemical interaction between drug and excipients (Meyers, 2000).

Formulation of buccoadhesive tablets:

Buccoadhesive tablets of losartan potassium were prepared by wet granulation method using different grades of polymer with varying concentrations (Table 1). Required quantity of drugs, polymers and diluents were mixed thoroughly in a polybag for 10 min sufficient quantity of polyvinyl pyrrolidone (7% w/v of total tablet weight) in isopropyl alcohol was added slowly to get dough mass. The dough mass sieved through 20/35 mesh and dried the granules at 55-60°C for the appropriate period of time till loss on drying is 2% (at 65°C,). Granules were collected in air tight double polythene lined containers. The granules were compressed using 6 mm flat round punches (R & D Tablet Press, Cemach Machineries Limited). The backing layer of ethyl cellulose was added to the one side of compressed tablet (Indian Pharmacopoeia, 2010).

Table 1: Composition of losartan potassium buccoadhesive tablets.

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan Potassium	25	25	25	25	25	25	25	25	25
HPMC K100	-	25	30	35	40	-	-	-	-
Guar Gum	-	-	-	-	-	25	30	35	40
Lactose	54	29	24	19	14	29	24	19	14
Aerosil	1	1	1	1	1	1	1	1	1
Ethyl cellulose Backing Layer	20	20	20	20	20	20	20	20	20
Total	100	100	100	100	100	100	100	100	100

Pre-compression evaluation: Pre-compression para- meters such as Angle of repose, Bulk density, Tapped density, Carr's compressibility index and Hausner's ratio were evaluated (Indian Pharmacopoeia, 2010).

Evaluation of buccoadhesive tablets:
Buccoadhesive tablets of Losartan Potassium were evaluated for their post-compression parameters such as weight variation, hardness, thickness, friability and drug content uniformity.

Surface pH studies:
The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects such irritation to the buccal mucosa, so the pH must maintained to neutral as closely as possible. 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 for 2 h 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 min (Harikrishna et al., 2010).

Determination of ex-vivo mucoadhesive strength:
The mucoadhesive strength of each formulation (n = 3) was determined by using locally assembled apparatus as shown in Figure 5. The device was composed of modified analytical balance. At the time of testing, a section of buccal mucosal membrane was placed on the upper glass stopper using rubber band and tablet was then stuck to the lower beaker using a two-way adhesive tape. The mucosa was lowered onto the tablets under a constant weight of 5 g for a total contact period of 2 min. These are kept in "Krebs-Henseleit buffer solution. Two minutes contact time was given to ensure intimate contact between tissues and tablet, water was then added to the beaker through a pipette until the tablet detached from the buccal mucosal membrane. The water collected in the container was measured and expressed as weight (g) required for the detachment. Mucoadhesive strength was assessed in terms of weight (g) required to detach the tablet from the membrane.

Swelling index studies:
The extent of swelling was measured in terms of percentage weight gain by the tablet. The swelling behaviors of all formulation were studied. One tablet from each formulation was kept in a petri dish containing pH 6.8 phosphate buffer solutions at 37 ± 0.5 °C. At the fix time intervals, the tablets were withdrawn from the petri dish. The tablet were wiped off to remove excess water by using filter paper and then weighed. The weight of swollen tablet was calculated. The swelling index was determined from the following equation (Sellappan and Srinivas, 2013).

S.I. = {(Ws-WI) / WI} X 100 where, S.I = swelling index,
Ws = weight of swollen tablet and WI = initial weight tablet.

***In vitro* dissolution studies:**
The in vitro release rate for buccal tablets was studied using the USP type II (paddle) dissolution test apparatus. Tablets were supposed to release the drug from one side only; therefore an impermeable backing membrane was placed one side of the tablet further tablets was fixed to a 2 × 2 cm glass slide with cyanoacrylate adhesive and immersed into dissolution media. The dissolution test was (Electrolab, TDT-08L, India.) performed using 500 ml of Phosphate buffer pH 6.8 at 37 ± 0.5°C and 50 rpm.

5 ml of samples were periodically withdrawn and replaced with an equal volume of fresh dissolution medium. The Samples were collected at different time intervals up to 08 hr and analyzed after suitable dilution at λmax 250 nm using UV-Visible spectrophotometer (Jasco V-630) (Indian Pharmacopoeia, 2010).

Ex vivo permeation studies:
Ex-vivo permeation study of Losartan Potassium from buccoadhesive tablet through the excised sheep buccal mucosa was performed using a Franz diffusion cell at 37 ± 2°C. Fresh sheep buccal mucosa was obtained from a local slaughter house and used within 2 h of slaughter. The tissue was stored in phosphate buffer pH 6.8 at 4°C after collection. The isolated sheep buccal mucosa was mounted between the donor and receptor compartments of diffusion cell so that the smooth surface of the mucosa faced the donor compartment. The selected prepared buccal tablet was placed on the mucosa and the compartments clamped together. The donor compartment was filled with 1 mL of phosphate buffer pH 6.8. The receptor compartment (7 mL capacity) was filled with phosphate buffer pH 6.8 and the hydrodynamics in the receptor compartment was

maintained by stirring with a magnetic bead at 50 rpm. The diffusion was carried out for 8 h. A 1 mL sample was withdrawn at predetermined time intervals and replaced with an equal volume of phosphate buffer pH 6.8. These aliquots after filtration were diluted suitably and analyzed spectrophotometrically at λmax 250 nm using UV-Visible spectrophotometer (Jasco V-630).

Kinetics of drug release:
In order to study the mechanism of drug release from Losartan potassium buccal tablets, the in vitro release data was treated with different kinetic models, namely zero order and Korsemeyer-Peppas. A criterion for selecting the most appropriate model was based on goodness of fit, high regression coefficient value (Costa and Lobo, 2001).

Statistical analysis:
Results obtained for above swelling index, mucoadhesive strength, permeation studies and in vitro dissolution studies measurement are expressed as mean SEM (Standard Error Mean) and subjected to one-way analysis of variance (ANOVA) with $P < 0.05$ were considered to be statistically significant.

Stability study of optimized formulation:
Stability studies were performed according to ICH guideline. Optimized buccal tablets were sealed in aluminum packing and kept in humidity chamber maintained at 40°C and 75% RH for three month. Samples were analyzed for the drug content, surface pH, in vitro drug release study and other physicochemical properties at regular intervals (ICH, 2013).

RESULTS AND DISCUSSION:

Preformulation Studies:

Organoleptic Properties:
Colour: A small quantity of Losartan potassium powder was taken in butter paper and viewed in well-illuminated place.
Taste and odour: Very less quantity of Losartan potassium was used to get taste with the help of tongue as well as smelled to get the odour.

Table 2: Organoleptic Properties for Losartan potassium

Test	Specification/limits	Observations
Colour	White	White
Taste	Bitter	Bitter
Odour	Odourless	Odourless

Standard plot of Losartan potassium in methanol:

Table 3: Standard graph data of Losartan potassium in methanol at 234 nm

Si no.	Concentration (µg/ml)	Absorbance Mean± SD
0	0	0
1	4	0.144 ± 0.026
2	8	0.262 ± 0.010
3	12	0.405 ± 0.045
4	16	0.506 ± 0.045
5	20	0.628 ± 0.055

All values are mean ± SD, n =3.

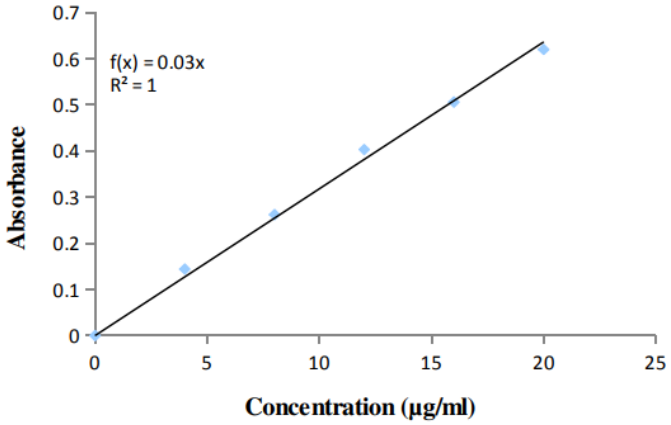


Figure 2: Standard graph of Losartan potassium in methanol

Fourier Transform Infrared spectroscopy:

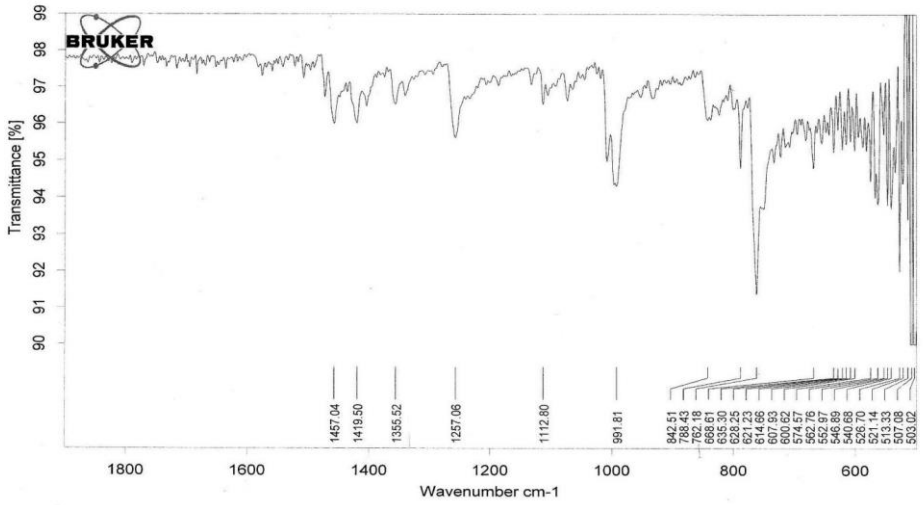


Figure 3: FT-IR Spectra of Losartan potassium

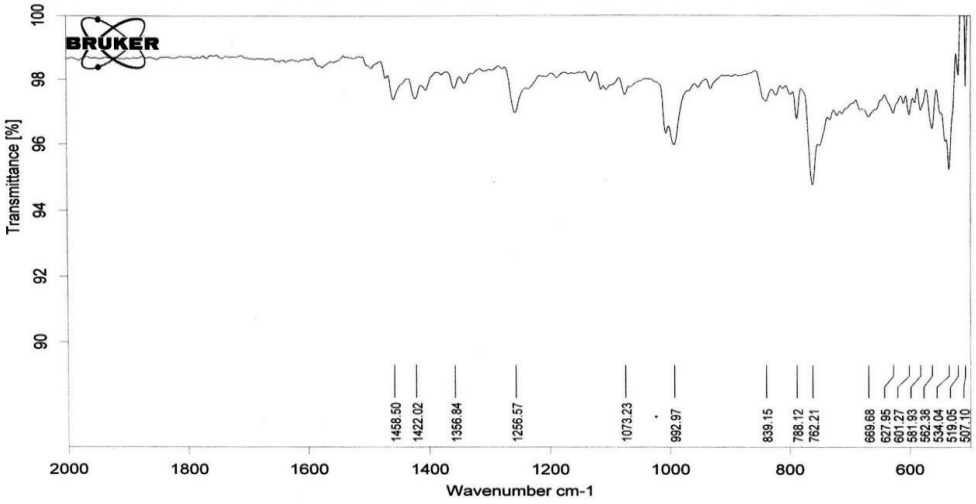


Figure 4: FT-IR spectra of Losartan potassium+ locustbean gum.

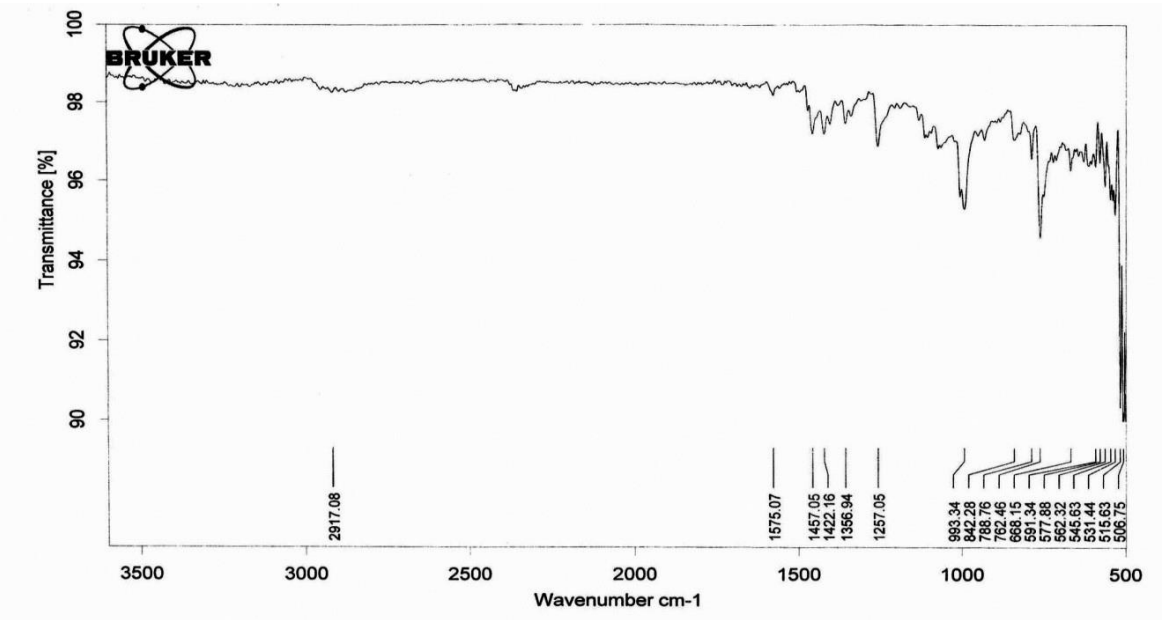


Figure 5: FT-IR spectra of Losartan potassium+ HPMC K4M

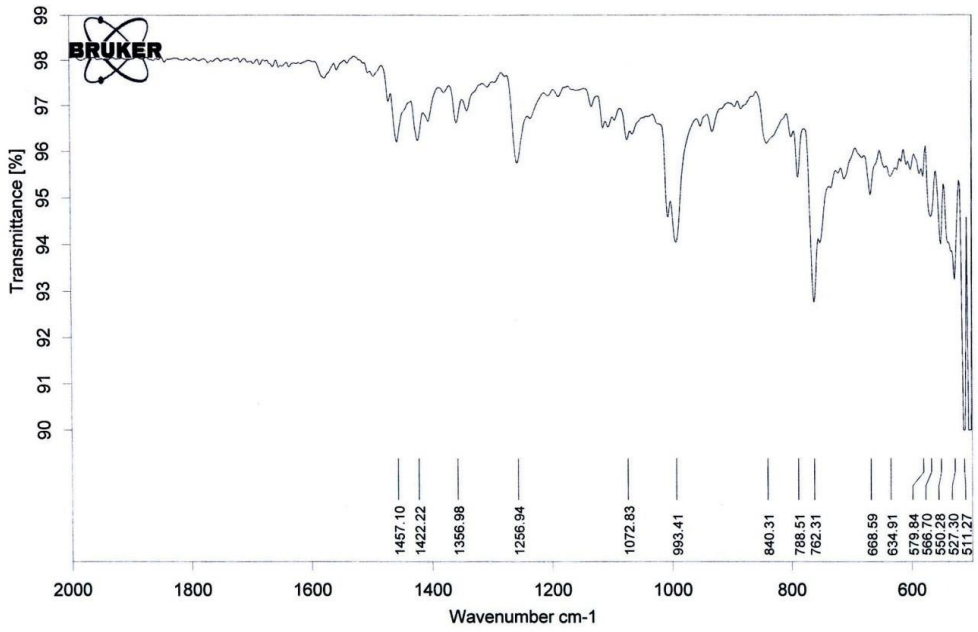


Figure 6: FT-IR spectra of Losartan potassium+ Locustbean gum+ HPMC K4M

Table 4: FTIR Spectral data of Losartan potassium

Pure losartan potassium		
Functional group	Range	Observed range in pure drug
OH	1270-1160	1257.06
1,4 di substituted phenyl ring	850-800	842.51
1,6 substituted phenyls ring	780-720	788.43
C-Cl	850-550	668.61
C-C arometic	1500-1400	1457.04
NH	910-665	762.31

Table 5: interpretation for IR spectra of Losartan potassium and polymers

Name of pure drug	Standard Value of drug(cm^{-1})	Observed value of locustbean gum with drug(cm^{-1})	Observed value of KPMC K4M with drug(cm^{-1})	Observed value of polymer combination with drug(cm^{-1})
	1160 -1270	1256.57	1257.05	1256.94
	800-850	839.15	842.28	840.31
	720-780	788.12	788.76	788.51

Name of pure drug	Standard Value of drug(cm^{-1})	Observed value of locustbean gum with drug(cm^{-1})	Observed value of KPMC K4M with drug(cm^{-1})	Observed value of polymer combination with drug (cm^{-1})
	1160 -1270	1256.57	1257.05	1256.94
	800-850	839.15	842.28	840.31
	720-780	788.12	788.76	788.51
Losartan potassium	550-850	669.68	668.15	668.59
	1500-1400	1458.50	1457.07	1457.10
	910-665	762.21	762.46	762.31

Differential Scanning Calorimetry (DSC):

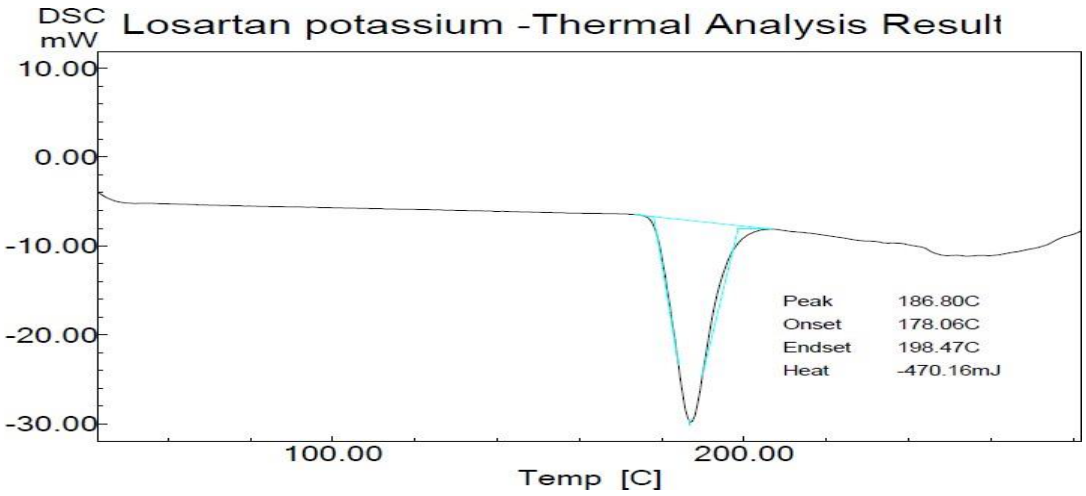


Figure 7: DSC of losatran potassium

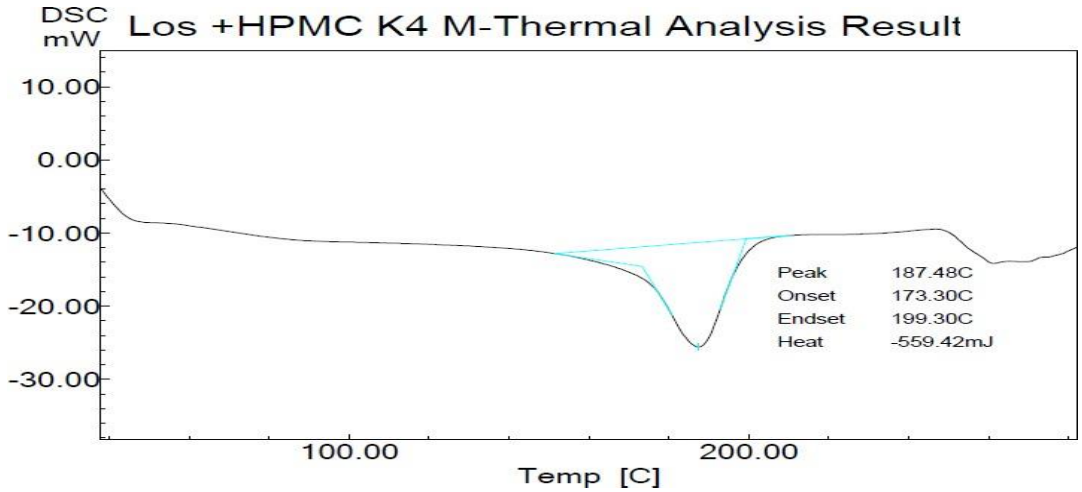


Figure 8: DSC of losartan potassium and HPMC K4M

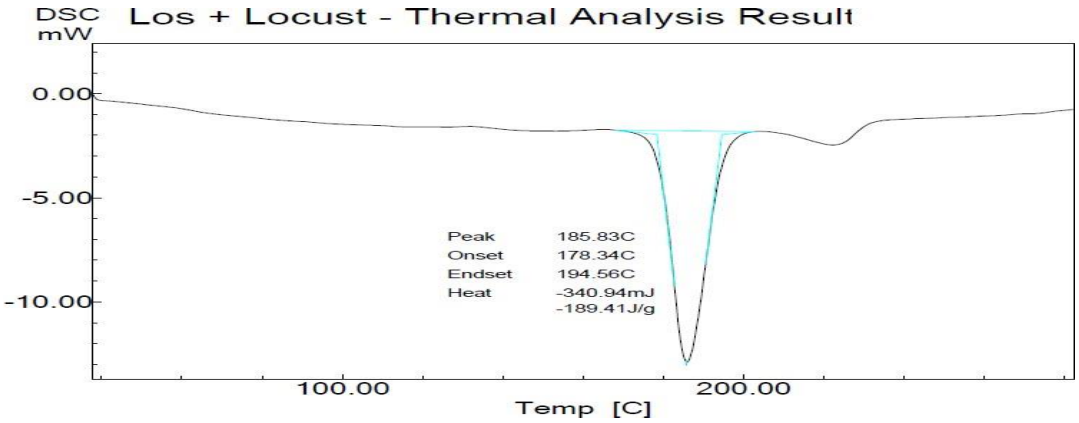


Figure 9: DSC of losartan potassium+ locust bean gum

Precompression parameters for Losartan potassium

Bulk density, tapped density and compressibility index:

Table 6: Data of bulk densiy, tapped density, compressibility index, Hauser's ratio and angle of repose.

BATCH CODE	BULK DENSIY (GM/CM3	TAPPED DENSITY (GM/CM3)	COMPRESSI BILITY INDEX (%)	HAUSNE R'S RATIO	ANGLE OF REPOSE (Θ)
F1	0.443	0.544	18.6	1.23	31.1
F2	0.457	0.552	17.4	1.21	28.5
F3	0.443	0.539	17.9	1.22	29.1
F4	0.453	0.541	16.28	1.19	29.88
F5	0.459	0.538	14.8	1.18	26.8
F6	0.422	0.549	21.4	1.27	31.6
F7	0.459	0.559	17.8	1.22	30.52
F8	0.433	0.513	15.4	1.18	29.62
F9	0.437	0.526	16.76	1.21	28.6

Evaluation of Buccal Patches

Physicochemical parameters

Table 7: Physicochemical parameters of developed Buccal Patches

Formulation	Hardness kg/cm^2	Thickness (mm)	Weight Variation (mg)	Friability (% loss)
F1	3.1 ± 0.42	3.8 ± 0.28	194.2 ± 0.81	0.51 ± 0.27
F2	5.0 ± 0.18	4.2 ± 0.04	235.9 ± 1.62	0.31 ± 0.06
F3	4.2 ± 0.09	4.1 ± 0.15	234.8 ± 0.77	0.29 ± 0.24
F4	7.8 ± 0.26	4.8 ± 0.91	285.3 ± 4.26	0.11 ± 0.43
F5	3.2 ± 0.84	4.0 ± 0.52	209.8 ± 0.98	0.38 ± 0.37
F6	6.0 ± 0.12	4.5 ± 0.22	268.1 ± 1.45	0.25 ± 0.08
F7	3.5 ± 1.53	3.9 ± 0.08	203.9 ± 3.11	0.42 ± 0.09
F8	6.5 ± 2.41	4.6 ± 0.05	274.2 ± 2.81	0.22 ± 0.18

All values are mean ± SD, n =3.

Drug Content uniformity:

Table 13: Amount of drug present and % drug content

Formulation	Amount of drug present (mg)	% Drug content
F1	98.45±0.061	98.45±0.061
F2	98.06±0.031	98.06±0.031
F3	97.10±0.026	97.10±0.026
F4	98.84±0.035	98.84±0.035
F5	99.29±0.025	99.29±0.025
F6	97.42±0.025	97.42±0.025
F7	96.45±0.035	96.45±0.035
F8	97.29±0.042	97.29±0.042
F9	98.71±0.028	98.71±0.028

All values are mean ± SD, n =3.

A. % Swelling index of the developed Buccal Patches

Table 8: % Swelling index of eveloped formulations

% SWELLING INDEX					
Formulation	2h	4h	6h	8h	10h
F1	56	69	75	88	102
F2	85.4	98	110	120	142
F3	78.3	90.2	99	115	120.6
F4	85.2	114.5	125.8	134.4	151
F5	73.7	90	95.6	105	114.6
F6	82	106	118	136	149
F7	61.4	81.5	91.6	100.6	112
F8	57.4	84.4	87	98	121
F9	82.4	103	112	123	144

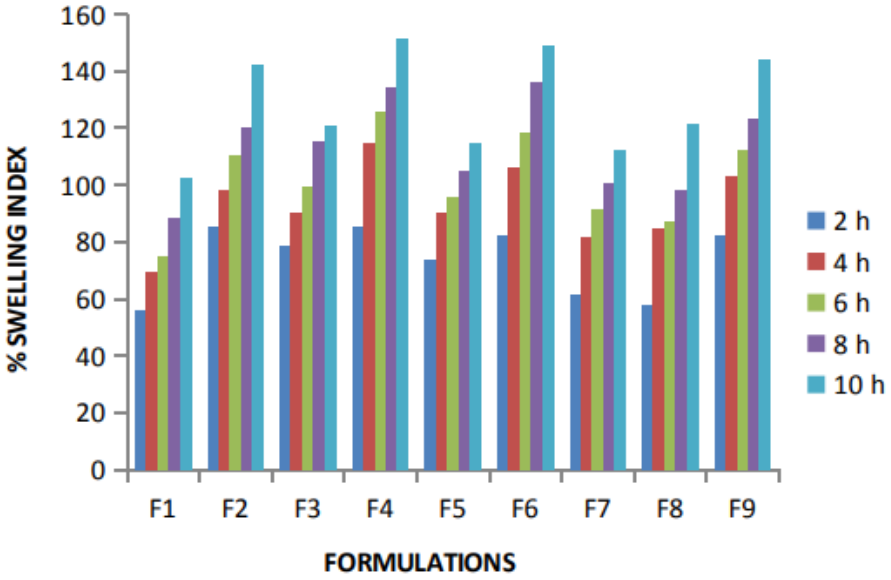


Figure 10: % swelling index graph of 9 formulations

B. Bioadhesive properties

Table 9: Bioadhesive properties of developed Buccal Patches

Formulation	mucoadhesive time (h)	Bioadhesion strength (gm)	Force of adhesion (N)	Surface pH
F1	8.4	20.6 ± 0.05	0.202 ± 0.24	5.6 ± 0.04
F2	>10	30.2 ± 0.24	0.296 ± 0.66	6.1 ± 0.42
F3	9.2	21.6 ± 0.11	0.211 ± 0.047	6.8 ± 0.09
F4	>10	29.1 ± 0.42	0.285 ± 0.52	7.0 ± 0.06
F5	7.2	18.9 ± 0.08	0.185 ± 0.051	5.8 ± 0.52
F6	>10	31.5 ± 0.14	0.309 ± 0.81	6.4 ± 0.08
F7	9.45	25.4 ± 0.37	0.249 ±0.62	5.6 ± 0.05
F8	>10	27.1 ± 0.19	0.266 ± 0.06	6.8 ± 0.11
F9	>10	26.5 ± 0.66	0.259 ± 0.14	6.2 ± 0.22

All values are mean ± SD, n =3.

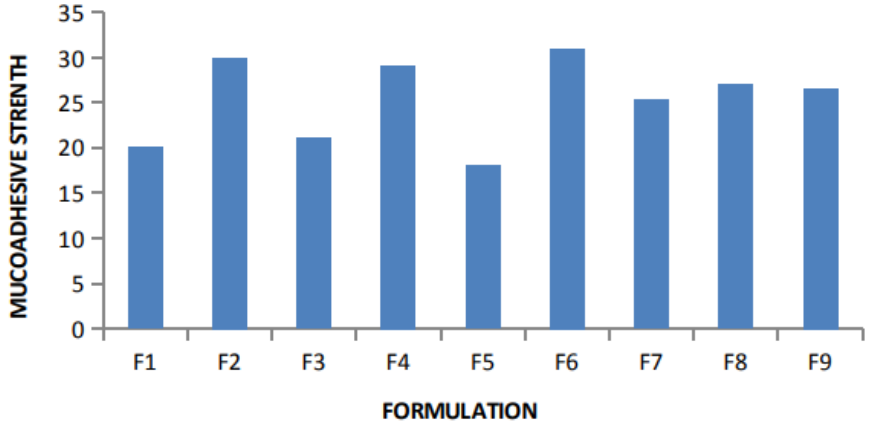


Figure 11: Mucoadhesive strenth of developed Buccal Patches

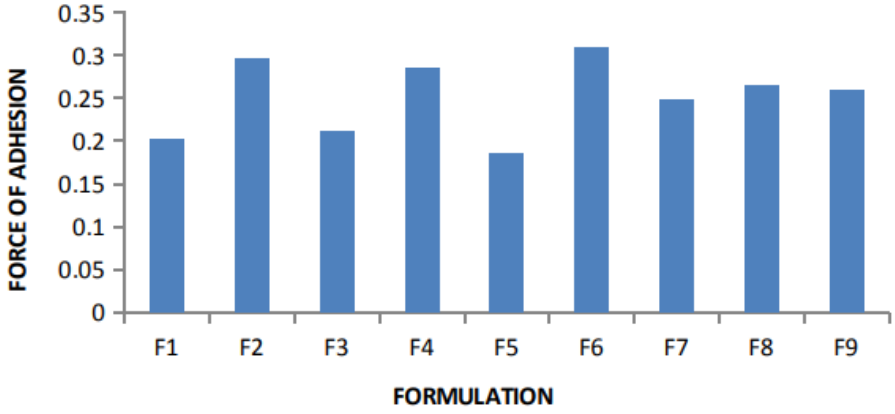


Figure 12: Force of adhesion of developed Buccal Patches

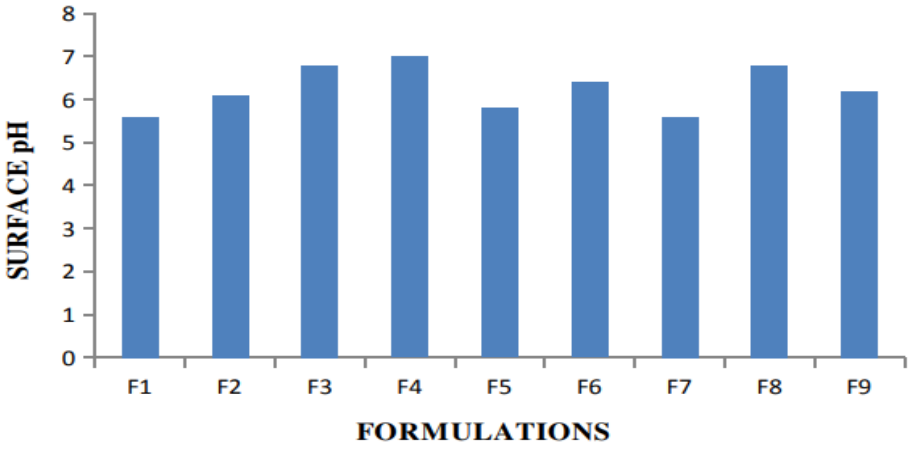


Figure 13: Surface pH of 9 formulations

In-vitro dissolution studies.

Table 10: In-vitro drug release data for formulations F1 - F3

Time (h)	% Cumulative Drug Release		
	F1	F2	F3
0	0	0	0
0.5	25.25±0.08	21.48±0.055	23.22±0.065
1	35.26±0.15	25.96±0.065	34.38±0.124
2	46.49±0.06	31.91±0.082	42.71±0.092
3	60.69±0.11	35.57±0.124	49.91±0.11
4	69.15±0.14	43.89±0.154	58.02±0.064
5	77.39±0.04	52.84±0.086	66.18±0.082
6	86.21±0.16	58.07±0.064	72.63±0.035
7	93.06±0.12	62.74±0.063	79.42±0.0258
8	96.47±0.076	72.37±0162	85.37±0.124
9		87.57±0.115	89.31±0.16
10		94.42±0.214	93.28±0.066

All values are mean ± SD, n =3

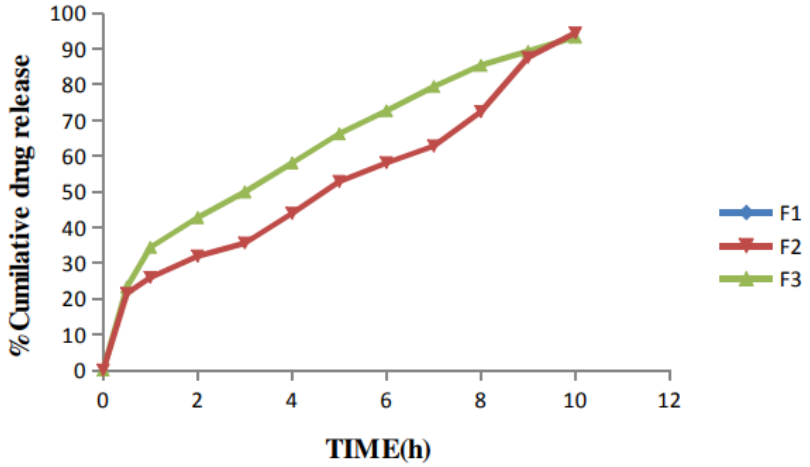


Figure 14: % CDR of Formulations F1-F3

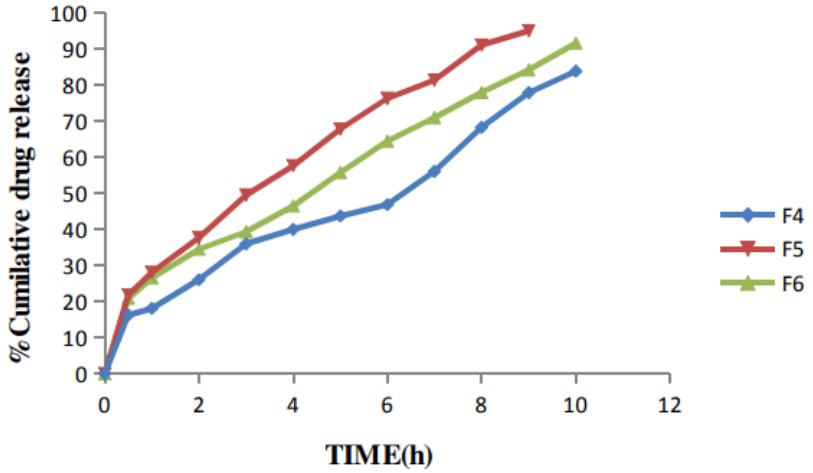


Figure 15: % CDR of Formulations F4-F6

Table 11: In-vitro drug release data for formulations F7 – F9

Time (h)	% Cumulative Drug Release		
	F7	F8	F9
0	0	0	0
0.5	22.06±0.24	18±0.061	20.91±0.042
1	30.32±0.051	23.06±0.025	26.07±0.38
2	40.94±0.24	27.23±0.038	33.36±0.25
3	47.55±0.25	34.64±0.15	40.51±0.16
4	55.65±0.55	40.92±0.42	45.08±0.035
5	68.15±0.081	47.53±0.091	53.46±0.061
6	79.55±0.12	54.47±0.12	58.69±0.028
7	87.82±0.18	60.86±0.062	69.46±0.25
8	95.56±0.62	70.19±0.034	77.090±0.062
9		77.54±0.024	85.35±0.13
10		87.83±0.062	95.97±0.095

All values are mean ± SD, n =3

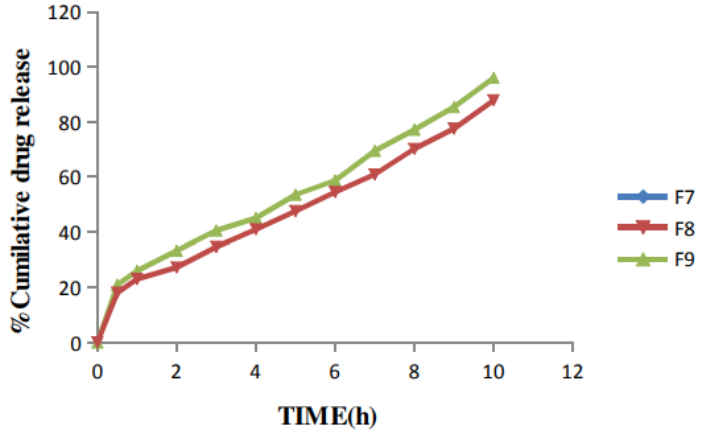


Figure 16: % CDR of Formulations F7-F9

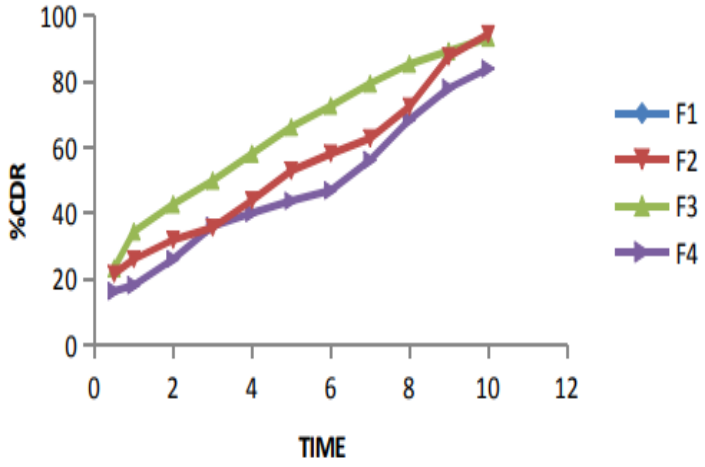


Figure 17: Comparison of zero order of in vitro drug release F1-F4

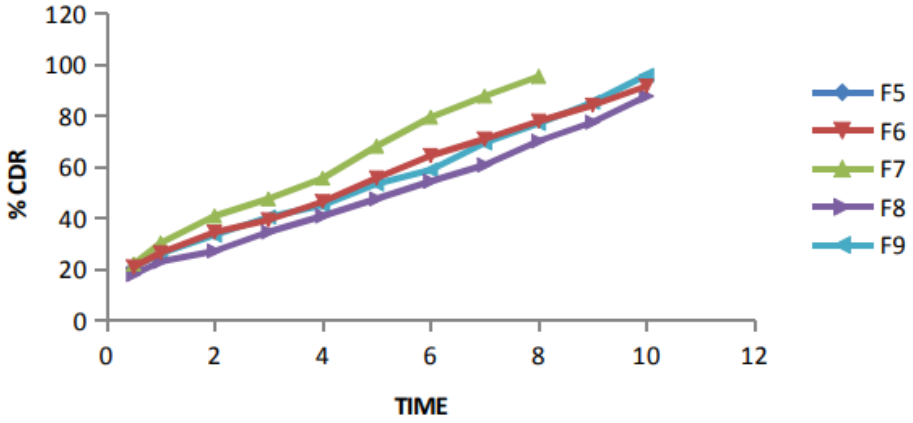


Figure 18: comparison of zero order of in vitro drug release F5-F9

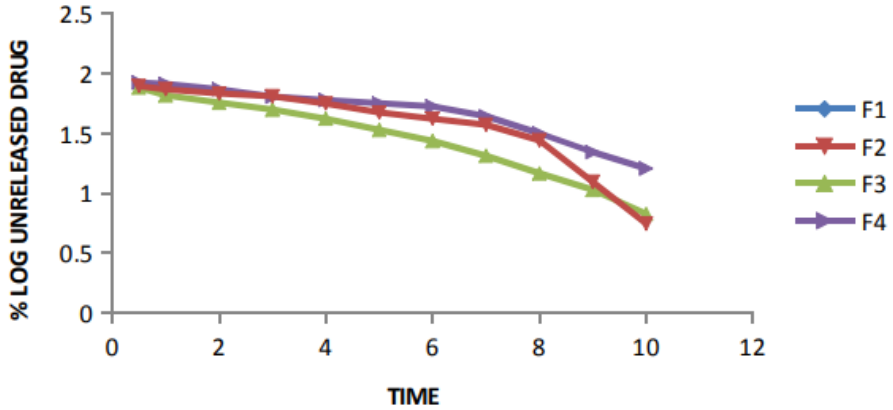


Figure 19: comparison of first order of in vitro drug release F1-F4

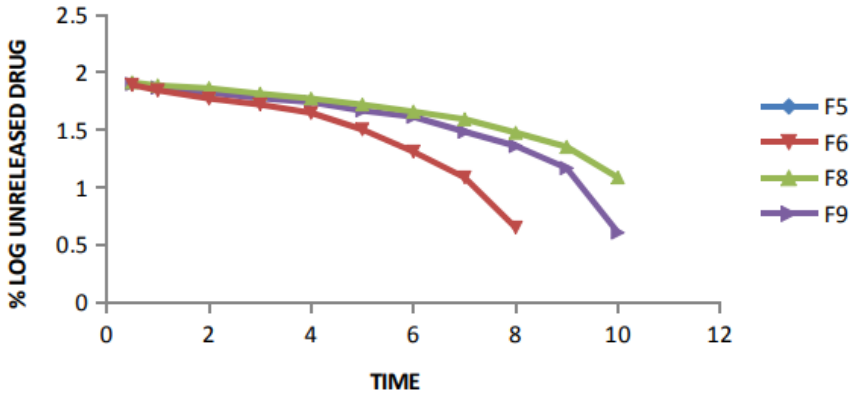


Figure 20: comparison of first order of in vitro drug release F5-F9

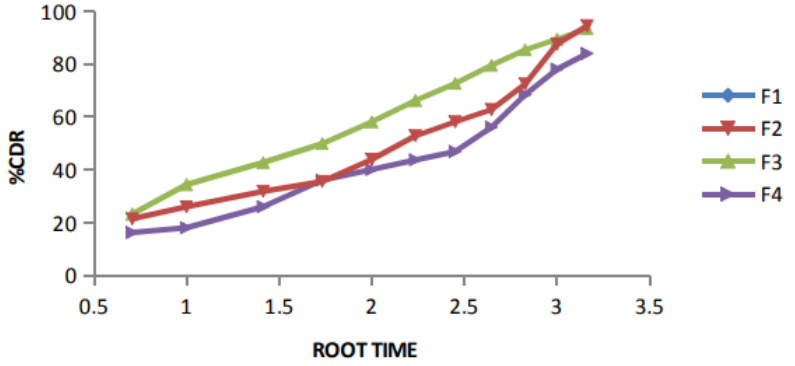


Figure 21: comparison of Higuchi model of in vitro drug release F1-F4

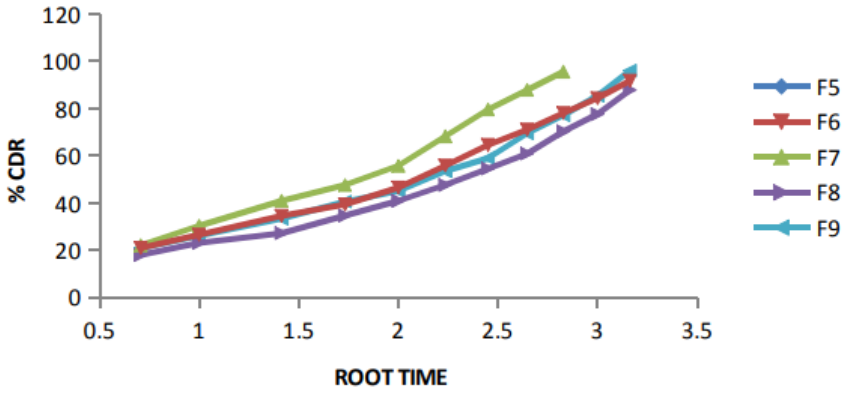


Figure 22: comparison of Higuchi model of in vitro drug release F5-F9

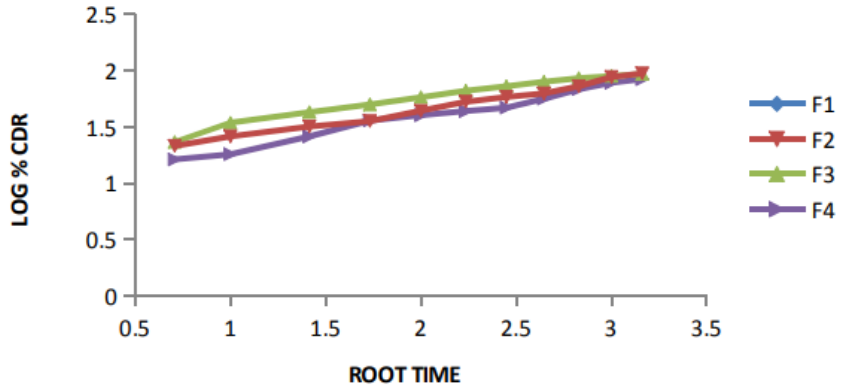


Figure 23: comparison of Korsmeyers-peppas equation of in vitro drug release F1-F4

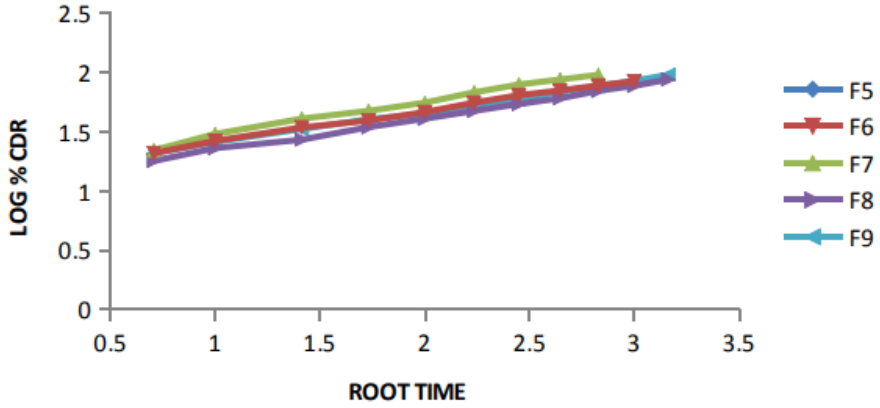


Figure 24: comparison of Korsmeyers-peppas equation of in vitro drug release F5-F9

Table 12: Design and Summary Response Data

OPTIMIZATION

Run	Locustbean gum	HPMC K4M	%CDR at 1st h	%CDR at 8th h	n value	Mucoadhesive strenth gm/cm^2	hardnes gm/cm^2
1	18.00	20.00	35.27	97.93	0.495	20	3.1
2	60.00	20.00	25.96	72.37	0.49	30	5
3	18.00	70.00	34.39	85.37	0.452	21	4
4	60.00	70.00	18.09	68.32	0.56	29	8
5	9.30	45.00	28.11	91.14	0.529	18	3.2
6	68.70	45.00	26.54	78.03	0.501	31	6
7	39.00	9.64	30.32	97.59	0.527	25.4	3
8	39.00	80.36	23.06	70.19	0.525	27.1	6.5
9	39.00	45.00	26.07	77.09	0.502	26.5	6

Response 1: % cumulative drugrelease at 1st houre

Table 13: ANOVA for Response Surface Linear Model

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob >F
Model	142.02	2	71.01	4.86	0.0557
A	96.82	1	96.82	6.62	0.0422
B	45.21	1	45.21	3.09	0.1292
Residual	87.74	6	14.62	-	-
Cor Total	229.76	8	-	-	-

Table 14: Estimated regression coefficient

Factor	Coefficient	STANDARD DF
A-locust bean gum	-3.48	1
B-hpmc k4m	-2.38	1

Factor	Coefficient	STANDARD DF
A-locust bean gum	-3.48	1
B-hpmc k4m	-2.38	1

Final Equation in Terms of Coded Factors:

DRUG RELEASE AT 1 h= +27.53- 3.48* A-2.38* B

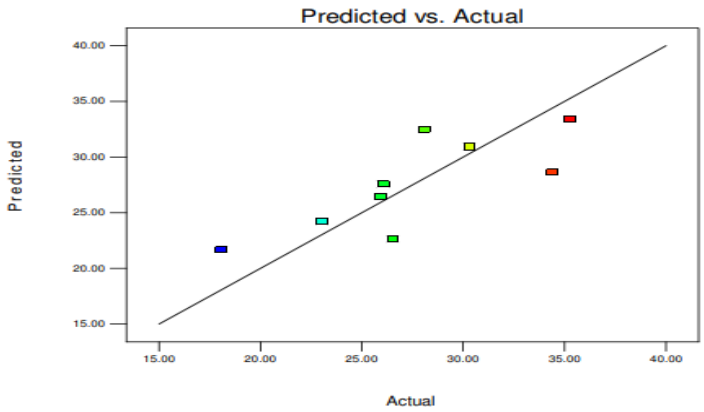


Figure 25: Correlation between actual and predicted values for drug release at 1 h (R1)

Figure 29: 3-D graph showing effect of Locustbean gum and HPMC K4M on drug release at 1 h (R1)
Response 2: % cumulative drug release at 8 th houre

Table 15: ANOVA for Response Surface Linear Model

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob >F
Model	850.50	2	425.25	12.73	0.0069
A	467.42	1	467.42	13.99	0.0096
B	383.08	1	383.08	11.47	0.0147
Residual	200.43	6	33.40	-	-
Cor Total	1050.93	8	-	-	-

Table 16: Estimated regression coefficient Final

Factor	Coefficient Estimate	STANDARD DF
A-locust bean gum	-7.64	1
B-hpmc k4m	-6.92	1

Equation in Terms of Coded Factors:
DRUG RELEASE AT 8 h = +82.00-7.64 * A-6.92* B

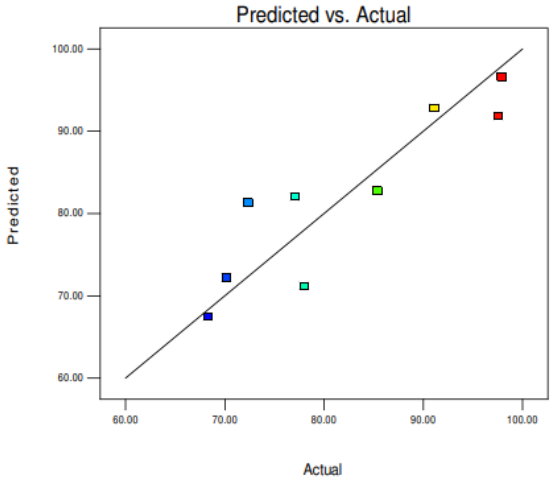


Figure 26: Correlation between actual and predicted values for drug release at 8 h (R2)

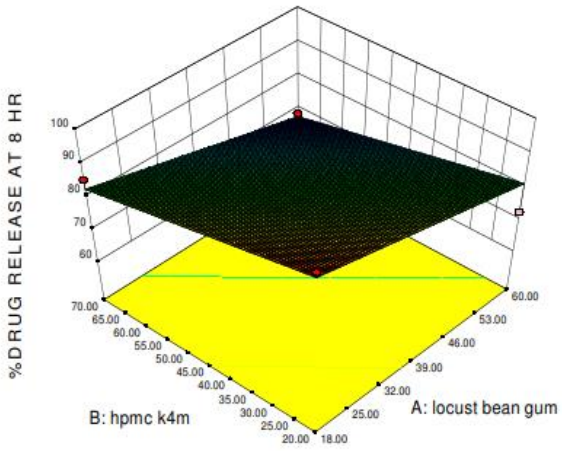


Figure 27: 3-D graph showing effect of Locustbean gum and HPMC K4M on drug release at 8 h (R2)

Response 3: n value

Table 17: ANOVA for Response Surface 2FI Model

Source	Sum of Squares	DF	Mean Square	F Value	p-value Prob >F
Model	3.768E-003	3	1.256E-003	1.68	0.2848
A	5.025E-004	1	5.025E-004	0.67	0.4493
B	7.303E-005	1	7.303E-005	0.098	0.7671
AB^3	3.192E-003	1	3.192E-003	4.28	0.0935
Residual	3.732E-003	5	7.464E-004	-	-
Cor Total	7.500E-003	8	-	-	-

Table 18: Estimated regression coefficient Final

Factor	Coefficient Estimate	STANDARD DF
A-locust bean gum	7.925E-003	1
B-hpmc k4m	3.021E-003	1
AB	0.028	1

SUMMARY AND CONCLUSION:

The study performed on "formulation and evaluation of mucoadhesive Buccal Patches of losartan potassium" reveals following conclusion:

The mucoadhesive Buccal Patches of losartan potassium could be prepared using locustbean gum and HPMC K4M by direct compression method.
The IR spectra revealed that, there was no interaction between polymers and drug. All polymers used were compatible with drug.

All the prepared tablets were in acceptable range of weight variation, hardness, thickness, friability and drug content as per pharmacopoeial specification.
The surface pH of prepared Buccal Patches was in the range of salivary pH, suggested that prepared tablets could be used without risk of mucosal irritation.
All the Buccal Patches showed good residence time of 7.2 H to >10 h, indicated good adhesive capacity of polymers used.

The CCD was used to find out the effect of independent varibles on the dependable variables. The result of CCD revealed that the locustbean gum and HPMC K4M have significant effect on the mucoadhesion strenth, swelling index, the drug release at 1 h and drug release at 8 h. The observed independent variables were found to be very close to predicted values of optimized formulation which demonstrates the feasibility of the optimization procedure in successful development of buccal tablet containing losartan potassium by using locustbean gum and HPMC K4M. The drug release form the optimized formula was found to be following the zero order kinetics and n value range of the Peppas equation is 0.521, which indicates fickian diffusion mechanism. Thus the release of drug from the dosage form was found to be time dependent.

The stability studies revealed that there was no significant change in buccal tablet properties with aging at different storage conditions.

Hence, the mucoadhesive Buccal Patches of losartan potassium can be prepared with enhanced bioavailability and prolonged therapeutic effect for the better management of hyper tension.

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