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FORMULATION AND *IN VITRO* EVALUATION OF FLOATING TABLETS OF LOSARTAN POTASSIUM

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ABSTRACT

The aim of this study was to develop an optimal Gastroretentive drug delivery system (GRDDS) for administering Losartan. Additionally, the influence of optimized GRDDS on the bioavailability of Losartan. Gastroretentive tablets of Losartan potassium were developed by direct compression method using sodium bicarbonate as the effervescent base. HPMC K4M, HPMC K15M and HPMC K100M were used as polymers to prepare the floating tablets and to study the drug release for 12h in stomach. Formulations were evaluated for floating lag time, duration of floating, dimensional stability, drug content, swelling studies and in vitro *drug release profile. It was found that the dimensional stability of the formulations increase with increasing concentration of the swelling agent. The release mechanism of Losartan potassium from floating tablets was evaluated on the basis of Peppas and Higuchi model. The 'n' value of the formulations ranged from 0.5 to 0.7 (0.5<n<1.0) which indicated anomalous (non-Fickian) transport mechanism. FTIR studies indicated the absence of any significant chemical interaction within dug and excipients.*

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KEYWORDS : *Losartan, Gastroretentive, Sodium bicarbonate, non-Fickian transport*

INTRODUCTION

The oral route currently represents the most predominant and preferable route of drug delivery. Unlike majority of parenteral dosage forms, it allows ease of administration by the patient and it's the natural, and therefore a highly convenient way for substances to be introduced into the human body. Oral drug delivery systems have progressed from conventional immediate release to site-specific delivery over a period of time. There are some drawbacks for the conventional dosage forms to over come this, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits.

Over the years, as the expense and complications involved in marketing new drug entities have increased with concomitant recognition of the therapeutic advantages of controlled drug delivery, greater attention has been focused on the development of modified release dosage forms.These systems have been developed to improve the pharmacokinetic profiles of active pharmaceutical ingredients (APIs) and patient compliance, as well as reducing side effects. Oral modified release delivery systems are most commonly used for 1) delayed release (e.g., by using an enteric coating); 2) extended release (e.g., zero-order, first-order, biphasic release, etc.); 3) programmed release (e.g., pulsatile, triggered, etc.) and 4) site specific or timed release (e.g., for colonic delivery or gastric retention).

Gastro retentive dosage forms are drug delivery systems which remain in the stomach for an extended period of time and allow both spatial and time control of drug liberation. Basically, gastro retentive system retains in the stomach for a number of hours and continuously releases the incorporated drug at a controlled rate to preferred absorption sites in the upper intestinal tract. The retention of oral dosage forms in the upper GIT causes prolonged contact time of drug with the GI mucosa, leading to higher bioavailability, and hence therapeutic efficacy, reduced time intervals for drug administration, potentially reduced dose size and thus improved patient compliance. Therefore, Sustained release DDS possessing gastric retention properties may be potentially useful.

Losartan is antagonist of angiotensin type I receptor leading to antihypertensive activity by blocking the effects of angiotensin II which include vasoconstriction and aldosterone-secretion effects. Losartan is slightly soluble in water which is having half life of 2 hrs and the bioavailability of Losartan is 33% . To increase the bioavailability of Losartan it would be beneficial to develop a floating drug delivery system that delays the first pass metabolism prolongs gastric residence time and releases drug in GI tract, where absorption of Losartan is more confined.

Materials and Methods:

MATERIALS

Losartan, HPMC K4M, HPMC K15M, HPMC K100M was obtained as a gift sample from Aurobindo Pharma Limited. Lactose and Sodium bicarbonate was obtained as a gift sample from Zeal Chemicals (P) Ltd. Warangal. Talc and Magnesium Stearate was obtained as a gift sample from Taurus Chemicals (P) Ltd. Secunderabad.

Formulation of floating matrix tablets of Losartan potassium:

The key ingredients included in the formulation are:

Hydrophilic polymers: HPMC K4M, HPMC K15M, and HPMC K100M

Effervescent agent : Sodium carbonate

Filler : Lactose

Anti adherent : Talc

Lubricant : Magnesium Stearate

Accurately weighed quantities of polymer and lactose were taken in a mortar and mixed geometrically to this required quantity of Losartan was added and mixed with the pestle. Accurately weighed quantity of sodium bicarbonate was then mixed with the drug blend. The powder blend was then lubricated with magnesium stearate and talc mixed for about 3 minutes. Finally this mixture was compressed on a 16-station rotary tablet machine using 10-mm standard flat-face punches.

Table1: Composition of floating matrix tablets of Losartan potassium

Ingredient (mg)	Composition(mg)											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Losartan potassium	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4M	75	100	125	-	-	-	-	-	-	50	-	50

HPMC K15M	-	-	-	75	100	125	-	-	-	50	50	-
HPMC K100M	-	-	-	-	-	-	75	100	125	-	50	50
$NaHCO_3$	50	50	50	50	50	50	50	50	50	50	50	50
Lactose	172	147	122	172	147	122	172	147	122	147	147	147
Mg. Stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Total wt (mg)	300	300	300	300	300	300	300	300	300	300	300	300

Evaluation of floating matrix tablets of Losartan potassium

Tablet thickness and Diameter

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using vernier callipers.

Hardness

. In this six tablets were selected at random and the hardness of each tablet was measured with Monsanto hardness tester. The hardness is usually measured in terms of kg/cm^2.

Friability

The friability test was carried out to evaluate the hardness and stability instantly in Roche Friabilator. Here twenty tablets were weighed (Wo) initially and put in a tumbling and rotating apparatus drum. Then, they are subjected to fall from 6 inches height. After completion of 100 rotations i.e., 25 rpm for 4 minutes, the tablets were again weighed (w). The percent loss in weight or friability (F) is calculated by the formula

$$F= (1-W/Wo) \times 100$$

F= friability

Wo= initial weight

Weight variation

This test was performed to maintain the uniformity of weight of each tablet which should be in the prescribed range. This was done by sampling randomly and weighing 20 tablets and average weight is calculated.

Content Uniformity

This test was performed to maintain the uniformity of weight of active ingredient in each tablet which should be in the prescribed range according to the Indian Pharmacopoeia. This test was performed by taking twenty tablets randomly, weighed and powdered. A quantity of powdered tablet equal to 100 mg of losartan is dissolved in 0.1 N HCL in 100ml volumetric flask. It is diluted and the absorbance is measured at 224 nm using 0.1 N HCL as blank.

Buoyancy / Floating Test:

The tablets were placed in a 100-mL beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

In vitro dissolution studies

Dissolution studies were carried out using USP II dissolution apparatus. The stirring speed was 50 rpm. 0.1 N hydrochloric acid is used as dissolution medium (900ml). It was maintained at 37 ± 1˚C. Samples of 5ml were withdrawn at predetermined time intervals. The collected samples were suitably diluted with dissolution fluid wherever necessary and were analyzed at 224 nm by using a double beam UV spectrophotometer.

Kinetic studies:

Mathematical models, zero order, first order, Higuchi & Peppas were applied to analyze the release rate mechanism and pattern.

Stability Studies:

The optimized formulation was subjected to stability studies as per ICH guidelines. Samples were kept at accelerated conditions **(**40°C±2°C/75%RH) and analyzed for post compression parameters for every month for a period of 3 months.

RESULTS & DISCUSSION:

The thicknesses of tablets in all formulations were ranged from 3.51±0.05 mm to 3.58±0.05 mm. The weight variation of tablets in all formulations were ranged from 352±9.4% to 349±9.2%.The hardness of all the formulations F1-F9 was found to be 4±0.2 (kg/cm^2) to 4.3±0.3 (kg/cm^2). The friability of all the F1-F9 formulations was found to be 0.36% to 0.45% respectively. Drug content of all the formulations were ranged from 101±1.03% to 86.6±0.56%. The buoyancy lag time of all the formulations were ranged from 80 Sec to 52 Sec.Table 3 gives the percentage swelling index of all the formulations. Figure 1-3 gives the graphical presentation of percentage swelling index of all the formulations.

Table2: Physical parameters of floating matrix tablets of Losartan potassium

Batch No	Tablet Thickness (mm)	Weight Variation(mg)	Hardness Kg/cm^2	Drug content (%)	Friability (%)	Lag time (sec)	Total floating time(sec)
F1	3.52±0.05	350±7.2	4.0±0.4	98.78±1.2	0.44	65	>12
F2	3.53±0.07	350±8.3	4.1±0.3	97.6±0.98	0.45	68	>12
F3	3.55±0.06	352±7.1	4.06±0.6	96.6±0.43	0.36	70	>12
F4	3.53±0.03	352±9.4	4.02±0.4	93.3±1.43	0.51	80	>12
F5	3.51±0.08	351±7.8	4±0.2	86.6±0.56	0.52	73	>12
F6	3.52±0.04	350±9.4	4.3±0.2	99.9±1.43	0.27	70	>12
F7	3.56±0.07	351±8.6	4.0±0.2	98.1±0.97	0.37	52	>12
F8	3.55±0.05	349±11.6	4.3±0.3	101±1.03	0.38	45	>12
F9	3.51±0.05	349±10.5	4.0±0.2	99.3±1.02	0.42	45	>12
F10	3.59±0.05	349±9.2	4.2±0.5	99.3±1.32	0.45	75	>12
F11	3.53±0.08	352±1.4	4.2±0.2	97.37±2.6	0.45	55	>12
F12	3.58±0.05	351±8.6	4.1±0.5	97.5±2.31	0.43	70	>12

SWELLING STUDIES:

Table 3 : Percent swelling of formulations with HPMC K4M and K15M

Sampling time(hr)	F1	F2	F3	F4	F5	F6
1	15.41	21.83	23.53	16.97	22.87	22.45
2	19.96	34.33	37.65	22.47	35.73	36.42
3	42.19	52.33	56.63	48.34	53.68	54.66
4	60.22	71.26	75.64	69.19	72.34	78.76
6	79.89	84.74	88.78	81.83	90.42	99.38
8	68.26	79.28	80.27	79.59	82.69	88.14
10	61.15	72.36	76.85	76.02	76.93	82.64
12	59.35	68.48	71.36	70.99	73.29	78.54

All values represent mean ± standard deviation (SD) n=3.

Figure1: Percent swelling of formulations with HPMC K4M&K15M

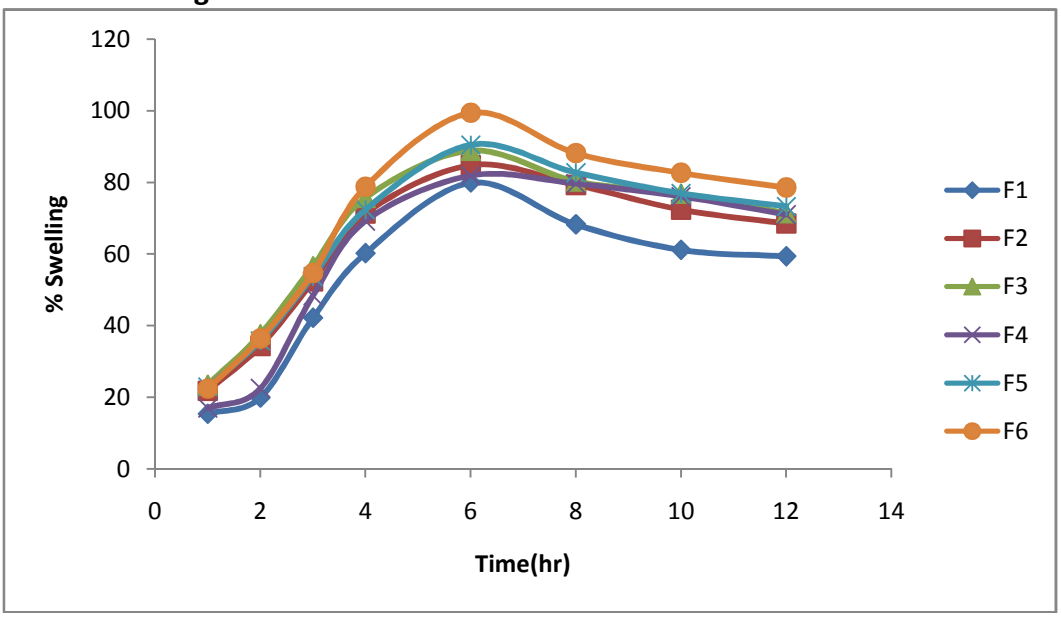
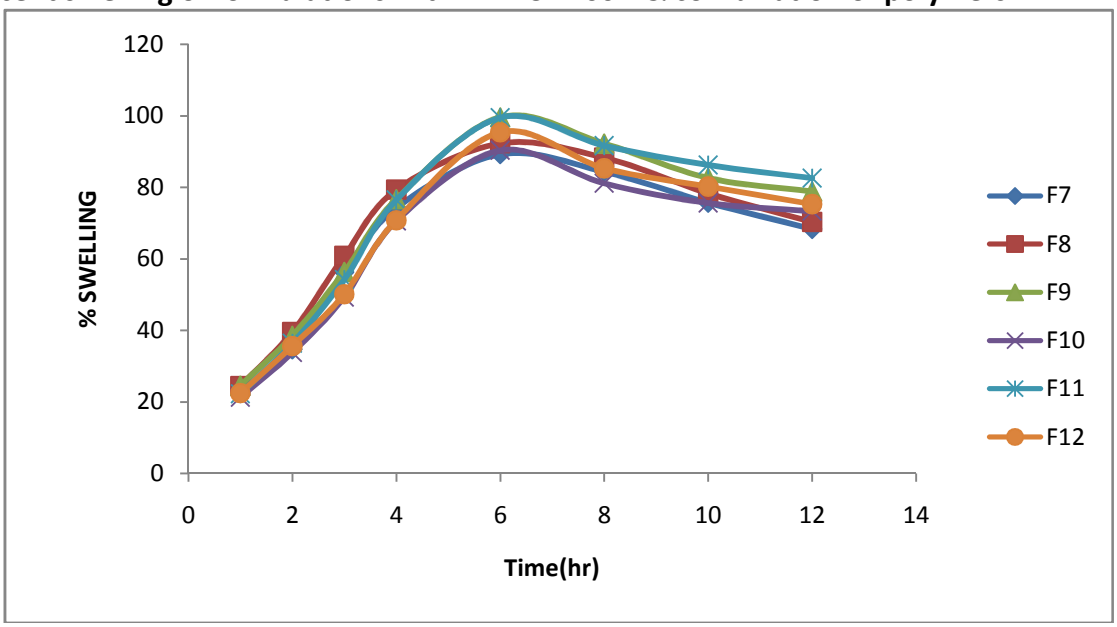


Table 4: Percent swelling of formulations with HPMC K100M and polymer combinations

Sampling time(hr)	F7	F8	F9	F10	F11	F12
1	22.56	24.45	24.48	21.27	22.26	22.47
2	34.73	39.57	38.46	33.76	36.38	35.64
3	56.26	60.84	56.37	49.27	54.18	50.15
4	74.28	79.36	76.72	70.56	76.45	70.84
6	89.27	92.34	99.64	90.36	99.48	95.42
8	84.38	88.34	92.27	81.16	91.65	85.37
10	75.74	78.38	82.64	75.64	86.24	80.25
12	68.34	70.37	78.84	73.34	82.56	75.32

All values represent mean ± standard deviation (SD)

Figure2: Percent swelling of formulations with HPMC K100M& combination of polymers



***IN VITRO* DRUG RELEASE STUDY:**

Table5: Cumulative Percentage drug release of formulations with HPMC K4M (F1, F2, F3)

S. No	Time(hrs)	F1	F2	F3
1	0	0	0	0
2	1	21.22	19.97	18.50
3	2	33.13	29.13	26.70
4	4	50.56	47.00	40.36
5	6	73.18	64.46	62.83
6	8	99.91	73.61	75.07
7	12	-	99.33	92.88

All values represent mean ± standard deviation (SD) n=3

Figure 3: Cumulative percentage drug release of formulations containing HPMC K4M

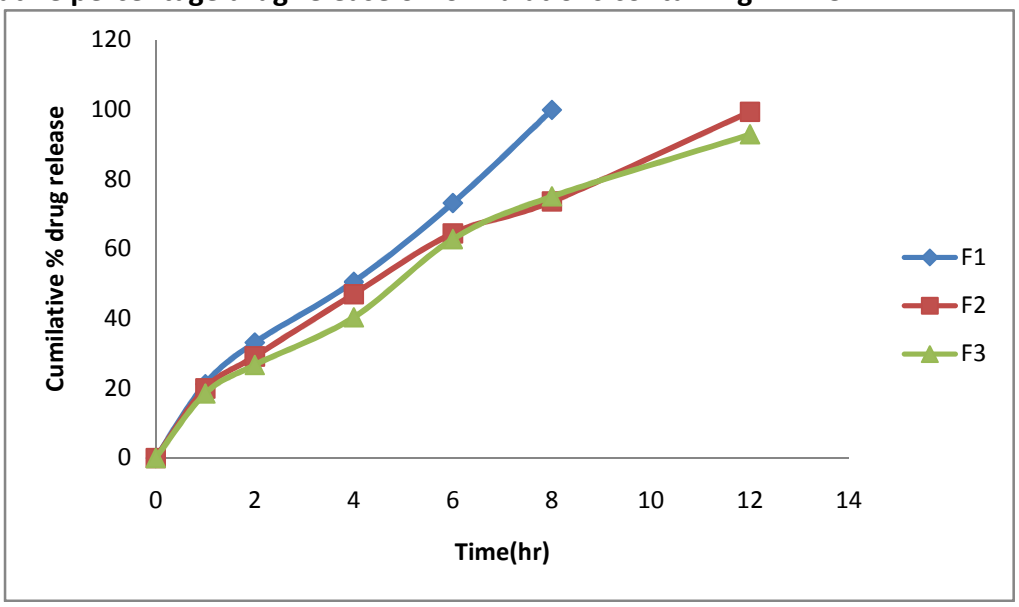


Table 6: Cumulative percentage drug release of formulations with HPMC K15M

S. No	Time(hrs)	F4	F5	F6
1	0	0	0	0
2	1	17.98	15.17	14.83
3	2	29.98	24.41	20.57
4	4	47.55	41.41	36.70
5	6	63.52	55.66	50.41
6	8	76.57	69.32	61.12
7	12	95.84	85.33	83.81

All values represent mean ± standard deviation (SD) n=3.

Figure4: Cumulative percentage drug release of formulations containing HPMC K100M

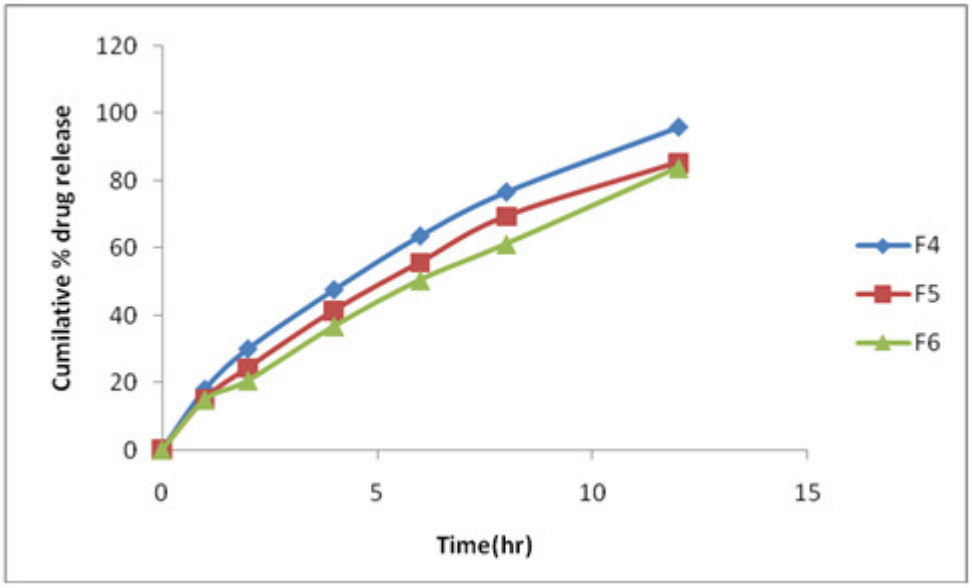


Table 7: Cumulative percentage drug release of formulations with HPMC K100M

S. No	Time(hrs)	F7	F8	F9
1	0	0	0	0
2	1	11.99	10.10	9.29
3	2	23.71	15.17	14.89
4	4	40.68	29.87	23.71
5	6	57.02	47.52	44.52
6	8	72.97	60.95	57.72
7	12	90.47	74.01	61.55

All values represent mean ± standard deviation (SD) n=3.

Figure4: Cumulative percentage drug release of formulations containing HPMC K100M

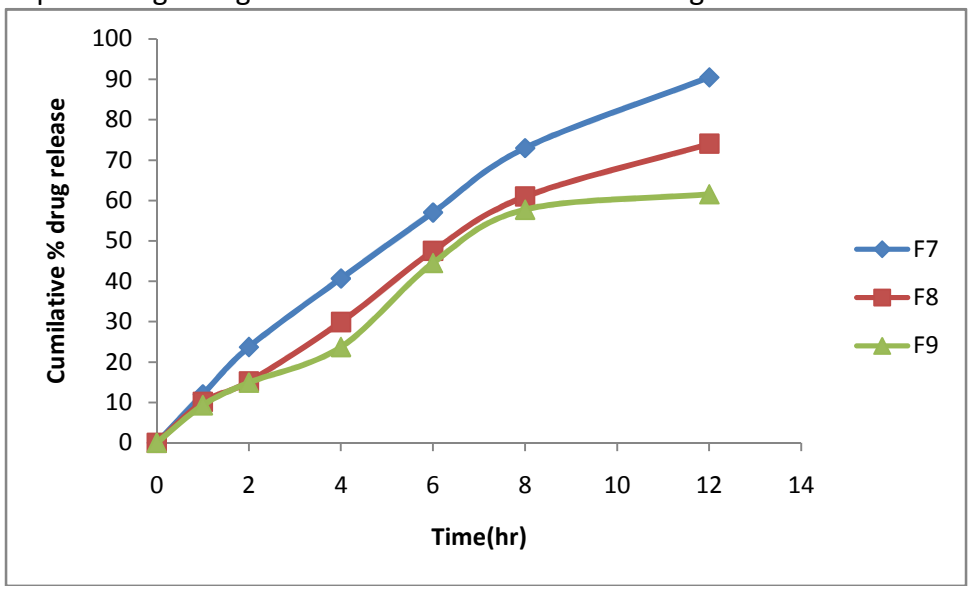
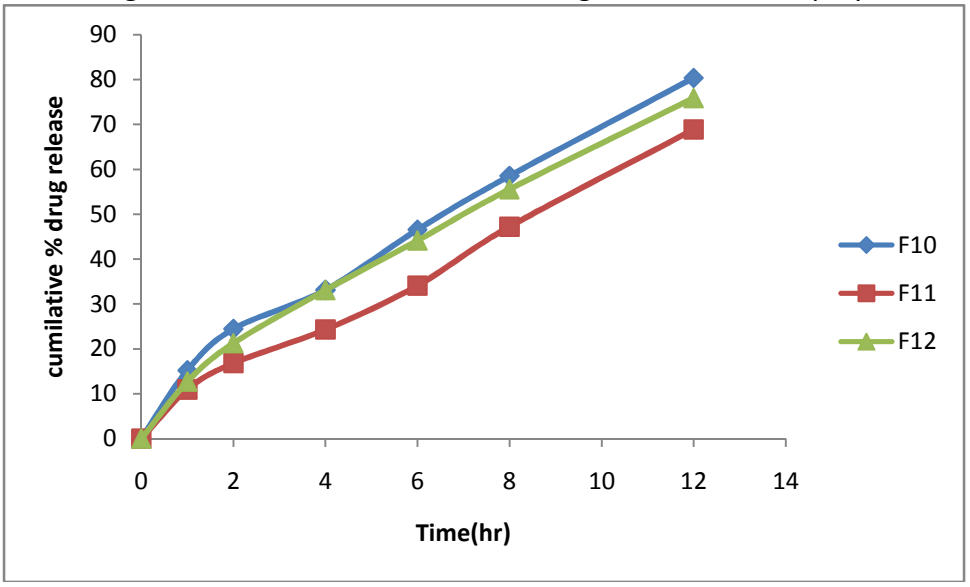


Table 8: Percent drug release of formulations with combination of polymers

S. No	Time(hrs)	F10	F11	F12
1	0	0	0	0
2	1	15.20	10.94	12.69
3	2	24.43	16.79	21.26
4	4	33.11	24.29	33.08
5	6	46.56	34.07	44.13
6	8	58.53	47.18	55.57
7	12	80.36	68.84	75.86

All values represent mean ± standard deviation (SD) n=3.

Figure 5 : Cumulative % drug release of formulations containing combination of polymers



DRUG RELEASE MECHANIS

Table 9: Release kinetics of the optimum formulation F2

S.no	Time (hr)	√T	Log T	Cumulative %drug dissolved	Cumulative %drug un dissolved	Log Cumulative %drug dissolved	Log Cumulative %drug un dissolved
1	0	0	0	0	100	0	2.0
2	1	1.0	0	19.97	80.03	1.03	1.903
3	2	1.414	0.30	29.13	70.87	1.46	1.85
4	4	2.0	0.60	47.00	53.00	1.67	1.72
5	6	2.4	0.778	64.46	35.54	1.809	1.55
6	8	2.8	0.90	73.61	26.39	1.867	1.42
7	12	3.16	1.0	99.33	0.67	1.99	-0.17

Figure 6: Zero order plot (F2) Formulation

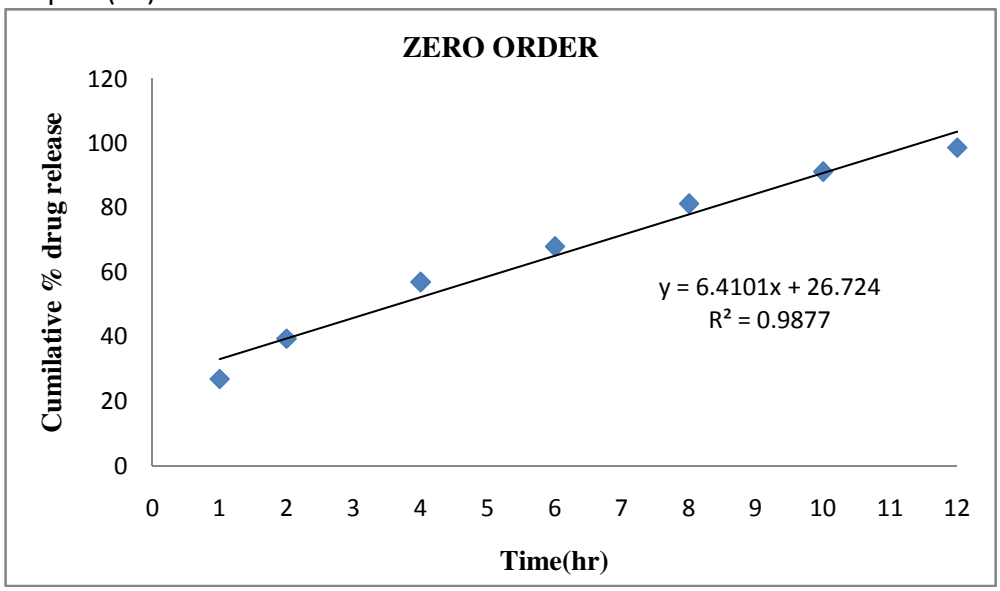


Figure 7: First order plot (F2)

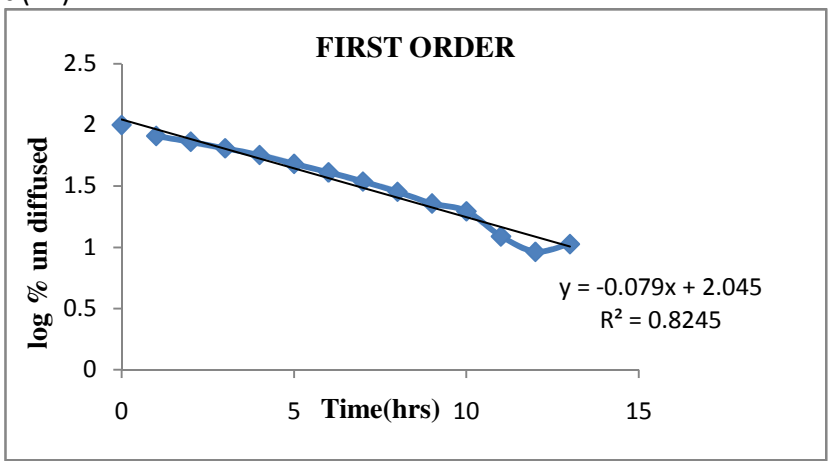


Figure 8 : Higuchi Plot (F2)

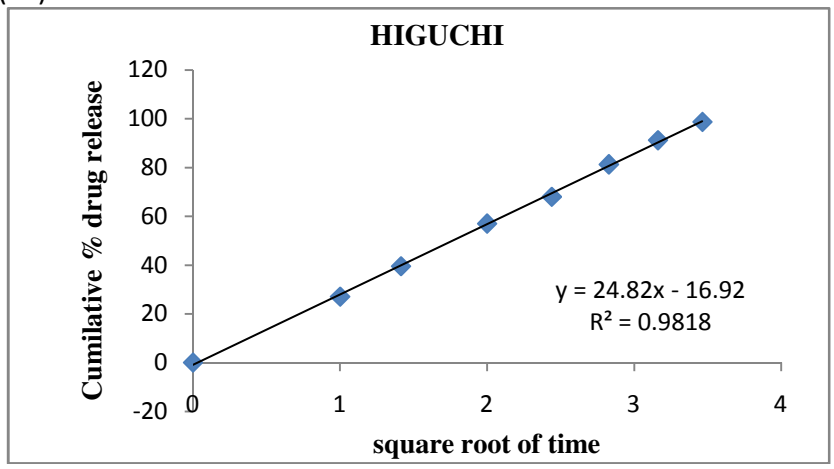
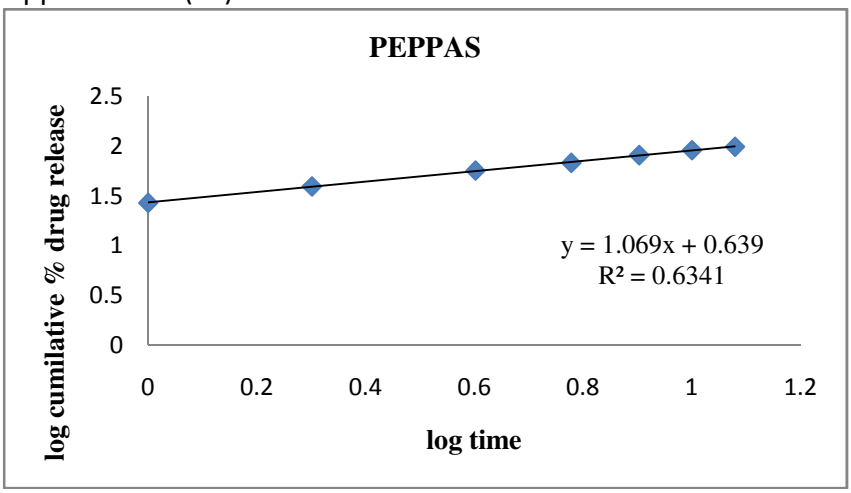


Figure 9: Korsemeyer Peppas Model (F2)



CONCLUSION:

This study discusses the preparation of floating tablets of Losartan Potassium. The gastro retentive floating drug delivery is a promising approach to achieve *in vitro* buoyancy and there by longer gastric retention time by using polymers like HPMC K4, HPMC K15, HPMC K100 and gas generating agent sodium bicarbonate.The tablets containing HPMC K4M (F2) showed satisfactory results with short floating lag time (68 sec) total buoyancy time more than 12 h, cumulative % drug release (99.33) and controlled drug release up to 12 h. So F2 was taken for kinetic studies.The kinetic studies were carried for formulation F2 and it follows zero order and non-Fickians diffusion drug release mechanism.

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