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FORMULATION AND EVALUATION OF GASTRORETENTIVE DRUG DELIVERY SYSTEM OF LOSARTAN

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Abstract

The study's goal was to formulate a Losartan drug delivery method with improved gastro retention. The tablets were prepared using Guar Gum, Micro Crystalline Cellulose, HPMC K4M and HPMC K100 LV in a direct compression process. To shorten the floating lag time, sodium bicarbonate was employed as the gas-generating agent. The tablets' hardness, weight fluctuation, thickness, floating capacity, swelling index, medication content, and in vitro dissolution study all underwent evaluation. Losartan Potassium tablet formulation with code LF4 could only sustain the release of respective drug till 12 hours.

Keywords: Anti-hypertensive, Losartan, Guar Gum, Micro Crystalline Cellulose, HPMC K4M and HPMC K100 LV.

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INTRODUCTION

Oral sustained release systems are the most popular drug delivery systems because they offer advantages over conventional ones like minimal steady state plasma level fluctuation, which aids in the treatment of diseases effectively, maximum drug utilization, which enables a reduction in the total dose administered, and lower health care costs through improved therapy [1-3]. Due to the reduced dosage, it is also possible to accomplish the shorter treatment period while simultaneously boosting patient compliance and comfort [4-5]. On the other hand, a continuous release dosage form's gastric residence time is decreased by rapid gastrointestinal transit (typical intestinal transit time is only 6 hours), which also lowers the level of absorption of drugs with limited absorption windows (upper GI track), decreases solubility at simple pH (above 6), and allows depletion or metabolization throughout the intestine [7-8]. In order to boost absorption and extend the time a medicine stays at the absorption site, a gastroretentive dosage type was developed [9-10]. Losartan is an angiotensin receptor blocker (ARB) in the imidzaole subclass and primarily used as an antihypertensive. Losartan is a selective, competitive angiotensin II receptor type 1 (AT1) antagonist, reducing the end organ responses to angiotensin II. Losartan is considered class 3 in the biopharmaceutics classification system, because it has high solubility and low permeability. Losartan is well absorbed following oral administration and undergoes significant first-pass metabolism to produce the 5-carboxylic acid metabolite. Losartan's bioavailability is about 33%. The most common adverse effects for Losartan in adults are upper respiratory infections, dizziness, and back pain. People with type 2 diabetes and kidney disease may experience diarrhea, fatigue, low blood pressure, low blood glucose, elevated potassium, chest pain, or allergic reaction.

The aim of the present research work was to formulate and evaluate gastroretentive sustained release tablets of Losartan.

MATERIAL AND METHODS

All the chemicals were procured from Rajsthan Lifescience, Jaipur, India were of were of the highest purity and analytical grade

Preparation of tablets of Losartan

Accurately weighed quantity of Losartan potassium, Guar gum and Lactose were taken in a Motor, mixed well and sifted through 40-mesh screen**.** Then others materials were added one by one and finally granulated with water. Wet mass was sieved using 16 mesh screen and granules obtained were air-dried in oven at 50 º c for 2 hrs. Dried granules were sifted using 14 mesh screen. Moisture contents of dried granules was controlled and maintained between 2-3%. If it was not within the limit then the granulation was further reprocessed. Above blend with the target weight of 340mg weight was compressed using 8.0 mm normal concave punches.

Table 4.4: Composition of different floating matrix tablet formulation of Losartan potassium

Formulation Code		**LF1**	**LF2**	**LF3**	**LF4**	**LF5**	**LF6**	**LF7**	**LF8**
S. No.	**Ingredients**	**QTY / tab (mg)**							
1.	Losartan potassium	50	50	50	50	50	50	50	50
2.	Guar Gum	100	100	100	100	100	100	100	100
3.	Lactose	90	40	60	40	40	25	40	20
4.	Micro Crystalline Cellulose (Avicel PH-101)	-	50	30	-	-	15	-	40
5.	Hydroxy Propyl Methyl Cellulose (Methocel K4M)	-	-	-	50	-	-	-	-
6.	HPMC K100 LV	-	-	-	-	50	50	50	30
7	$NaHCO_3$	70	70	70	70	70	70	70	70
8	Citric acid	30	30	30	30	30	30	30	30
9.	Magnesium stearate	6	6	6	6	6	6	6	6
10.	Talc	4	4	4	4	4	4	4	4
	Total weight	340 mg	340 mg	340 mg	340 mg	340 mg	340 mg	340 mg	340 mg

Evaluation of Losartan tablets

Pre-compression parameters

Tablets were prepared by wet granulation methods. Prepared granule was subjected to various characterization viz. angle of repose, bulk density, tapped density, compressibility index and Hausners ratio [17-18].

Angle of Repose

Angle of Repose was determined using the funnel method. The blend was poured through a funnel that can be raised vertically until a maximum cone height (h) was obtained. The radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula [19-20].

$$\tan\theta = \frac{h}{r}$$

Bulk Density

Apparent bulk density (ρb) was determined by pouring the blend into a graduated cylinder. The bulk density was calculated using the formula [19-20]

$$Bulk\ density = \frac{M}{V_b}$$

Whereas, M is the weight of the powder and V_b is the bulk volume of powder [19-20].

Tapped Density

The measuring cylinder containing a known mass of the blend was tapped for a 100 times using density apparatus. The minimum volume (Vt) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the formula [19-20].

$$Tapped\ density = \frac{M}{V_t}$$

Hausner ratio

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

Compressibility Index

$$Compressibility\ Index = \frac{Tapped\ density\ - Bulk\ density}{Tapped\ density}$$

Determination of λ_{max} of Losartan

A standard solution of Losartan having a concentration of 10 µg/ml was prepared by dissolving Losartan in 0.1N HCl. This solution was scanned in UV Visible spectrophotometer in the wavelength range of 200 – 400nm [21-22].

Calibration curve

An accurately weighed amount of Losartan corresponding to 100 mg was dissolved in a small amount of 0.1 N HCl in 100 ml volumetric flask and volume made up to 100 ml with the same 0.1 N HCl. Further 10 ml of prepared solution was made up to 100 ml with 0.1 N HCl. From this solution, 1 ml, 2 ml, 3 ml, 4 ml, 5 ml, 6 ml, 7 ml, 8 ml, 9 ml and 10 ml were withdrawn and diluted up to 10 ml with the 0.1 N HCl in 10ml volumetric flask to get concentration of 1 µg/ml, 2 µg/ml, 3 µg/ml, 4 µg/ml, 5 µg/ml, 6 µg/ml, 7 µg/ml, 8 µg/ml, 9 µg/ml and 10 µg/ml respectively. The optical density of every solution was calculated by UV-Visible Spectrophotometer at 234 nm, using 0.1 N HCl as blank [21-22].

Hardness

Randomly sampled five tablets from each batch of formulations were used for the determination of hardness with the help of the Monsanto type hardness tester. The sample mean and standard deviation were reported for each batch [16-20].

Weight Variation

Ten tablets selected at random were weighed accurately and the average weight of the tablets was calculated. Then the deviation of individual weight from the average weight and the standard deviation were calculated [16-20].

Thickness

The individual crown-to-crown thicknesses of ten tablets were determined using screw gauge micrometer for each batch. The sample mean and standard deviation of each tablet were calculated [16-20].

Measurement of Floating Capacity

Three individual tablets were put in individual flask containing 400ml of 0.1 (N) HCl solutions as per earlier reported method. Then the time in min for each tablet to go from the bottom to the top of the flask (floating lag time) and the timetables constantly float on the water surface (duration of floating) were

measured. The sample mean and standard deviation were calculated [16-20].

Swelling Index

Losartan tablets were weighed individually (W0) and placed in 900ml of dissolution medium (0.1 N HCl). The temperature was maintained at 37°C. At regular intervals, the samples were removed using a small basket and swollen weight (Wt) of each tablet was determined at predefined time intervals. The swelling index was calculated by the following equation [16-20]

$$Swelling\ Index = \frac{W_t - W_0}{W_0} \times 100$$

Where W_0 is the initial weight of tablet, and W_t is the weight of tablet at time t [16-20].

Drug Content

Three tablets from each batch were selected randomly and transfer to a 100ml volumetric flask, and the flask was filled with distilled water and 0.1(N) HCl respectively, kept it for 48 hours. Then, 1ml from each of the volumetric flask was transferred to the test tubes. The sample was then filtered, suitably diluted and analyzed spectrometrically at 234 nm.

In vitro Dissolution Study

USP-II type dissolution apparatus (paddle type) was used to study the release characteristic of floating systems. The release study was performed at 50 rpm in 900ml-distilled water and 0.1(N) HCl. 1ml of sample was withdrawn at a predetermined intervals and the volume of dissolution medium was maintained by adding the same volume of fresh dissolution medium. The absorbance of withdrawn sample was measured spectrometrically with suitable dilution and the corresponding concentrations were determined from the respective calibration curve. All the studies were performed in triplicate, and the temperature was maintained at 37 ± 0.5°C throughout the studies [16-20].

RESULTS AND DISCUSSION

Percentage purity of Losartan was performed by UV spectrophotometry and the drug was found to be 98.8 % pure. Melting point of pure Losartan was found to be 182-186 °C (178-185 °C reported). The result of melting points of Losartan was in the range of reported melting point by pharmacopoeia. It also inferred the purity of drugs. Further IR analysis of the sample was carried out for qualitative compound identification. Infrared study was performed by using ATR sampling technique on Tensor bruker. The sample scanned at wavelength 4000 – 667 cm^{-1}.

Pure Losartan displays sharp peaks corresponding to its melting point of pure drug suggested that there is no interaction between the Losartan and polymers.

For preparing tablets of Losartan Potassium, quantities of Lactose was varied. In formulation LF4, HPMC K4M was added and its quantity was varied, whereas, in formulation, LF5 – LF8, HPMC K100 LV was added and its quantity was varied. Quantities of Guar gum was common in all the formulation. For gas formation to make tablet float, $NaHCO_3$ and citric acid was added into the formulation.

Tablets were made from blends by direct compression, dry granulation and wet granulation methods. The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. The characterization of mixed blend done for the flow property of powder that is bulk density, tapped density, Hausners ratio, Compressibility index, angle of repose [16-20].

Table 2: Result of evaluation of precompression parameters of Losartan tablets

Formulations	Angle of Repose	Bulk density (g/cm3)	Tap density (g/cm3)	Compresibility Index (%)	Hausner's Ratio
LF1	21.18±0.16	0.40±0.84	0.42±0.15	20.70	1.10
LF2	22.89±0.75	0.42±0.93	0.52±0.49	21.82	1.22
LF3	20.47±0.49	0.44±0.24	0.54±0.61	21.15	1.29
LF4	23.58±0.38	0.46±0.19	0.56±0.54	22.58	1.67
LF5	23.88±0.24	0.42±0.53	0.50±0.27	19.30	1.98
LF6	22.37±0.34	0.44±0.49	0.56±0.41	19.10	1.28
LF7	22.12±0.66	0.46±0.21	0.58±0.69	20.12	1.23
LF8	24.94±0.78	0.48±0.68	0.62±0.55	19.82	1.68

Values are mean ± S.D.

Angle of repose for Losartan granules ranges from 20.47±0.49 to 24.94±0.78. Bulk density of Losartan was found to be from 0.40±0.84 -0.48±0.68 and the tapped density was found to be 0.42±0.15 to 0.62±0.55. Compressibility index and Hausner's ratio of Losartan granules were found to be 19.10-22.58 and 1.10-1.98 respectively. Compressibility index and Hausner's ratio of both the set of formulation indicates better to excellent flow properties [16-20].

Table 3: Properties of compressed tablets of Losartan

Batch code	Thickness* (mm)	Deviation in Weight Variation† (%)	Drug Content* (%)	Hardness* (kg/cm^2)	Friability† (%)
LF1	3.46±0.03	0.88±0.18	96.36±0.07	4.65±0.22	0.32±0.04
LF2	3.53±0.04	1.42±0.25	97.24±0.14	5.70±0.12	0.50±0.06
LF3	3.14±0.04	1.96±0.12	95.43±0.07	4.85±0.14	0.44±0.08
LF4	3.96±0.05	1.78±0.83	96.95±0.14	4.90±0.35	0.26±0.04
LF5	3.88±0.06	2.42±0.37	96.83±0.75	4.65±0.27	0.44±0.04
LF6	3.82±0.07	1.22±0.86	96.27±0.86	5.20±0.58	0.64±0.03
LF7	4.18±0.08	3.36±0.90	95.89±0.35	5.45±0.24	0.36±0.06
LF8	4.09±0.09	2.82±0.32	98.85±0.66	4.70±0.36	0.42±0.12

* All values are expressed as mean ± SE, n = 5

† All values are expressed as mean ± SE, n = 20

The thickness of Losartan tablet was found to be in the range of 3.14±0.04 to 4.18±0.08. Deviation of weight variation of Losartan was found to be in the range of 0.88±0.18 to 3.36±0.90. Weight variation was well within the limit as reported in United State Pharmacopoeia. Drug content was found to be from 95.43±0.07 to 98.85±0.66 which is well accepted. Hardness of tablet was found to be from 4.65±0.22 to 5.70±0.12. Friability was found to be from 0.26±0.04 to 0.64±0.03. Friability of all formulation is well within accepted limit of 1%.

The standard calibration curve of Losartan was prepared for determining the unknown concentration of drug. The standard calibration curve was prepared in 0.1 (N) hydrochloric acid (HCl) solution.

Table 4: Absorbance by Losartan drug

Conc. (µg/ml)	Absorbance 234 nm
1	0.026
2	0.054
3	0.078
4	0.103
5	0.136
6	0.166
7	0.196
8	0.224
9	0.246
10	0.264

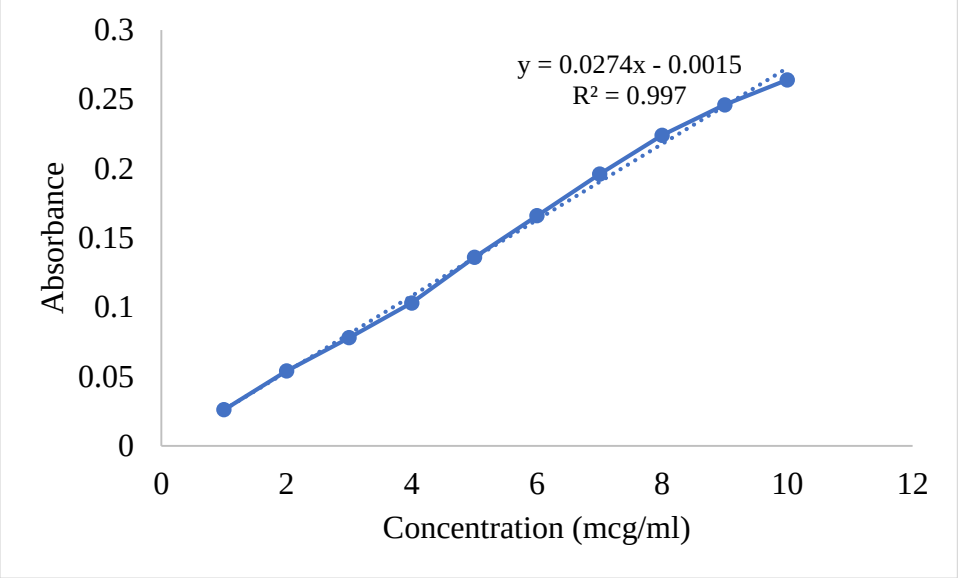

Figure 1: Calibration curve of Losartan drug

When immersed in 0.1 N HCl solution at 37±0.5 °C, all losartan floating tablets floated immediately and remained buoyant for more than 12 hours without disintegration. Sodium bicarbonate ($NaHCO_3$) was added as a gas-generating agent which induced carbon dioxide in the presence of dissolution medium (1/10 N HCl). Table 5 shows the buoyancy properties of various formulation matrix tablets. The buoyancy delay times for losartan tablets range from: 19.3±0.52 to 39.4±0.77 seconds. This indicate that the tablets were taking very lesser time to initiate gas formation that enables floating of tablets. All the batches of tablets were found to exhibit short floating lag times in the presence of citric acid and sodium bicarbonate.

Table 5: Buoyancy Lag Time and total floating time of Losartan tablets

Formulations	Buoyancy time (sec)	Total Floating time (hr)
LF1	37.2±0.84	>12
LF2	32.1±0.39	>12
LF3	24.7±0.16	>12
LF4	25.5±0.93	>12
LF5	39.4±0.77	>12
LF6	37.8±0.54	>12
LF7	33.1±0.69	>12
LF8	19.3±0.52	>12

Table 6: Swelling index of Losartan tablets

Formulations	Swelling index (%)
LF1	81.4±0.27
LF2	85.6±0.54
LF3	89.2±0.71
LF4	96.7±0.64
LF5	98.4±0.23
LF6	98.3±0.41
LF7	99.8±0.51
LF8	104.2±0.68

Values are mean ± S.D.

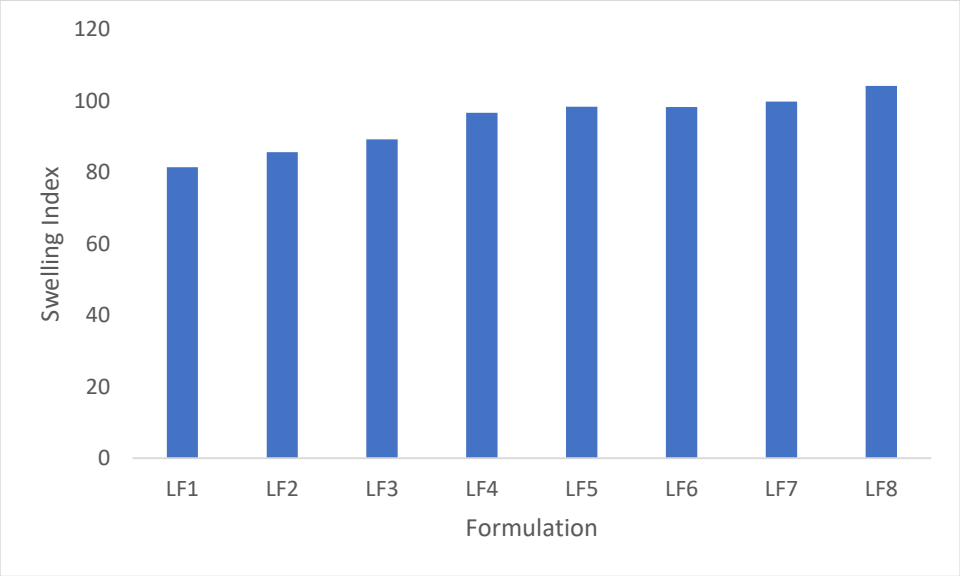

Figure 2: Swelling index of formulation of Losartan

Table 7: Cumulative % Drug release of Losartan floating tablets

Time in hr	Cumulative percentage drug release							
	LF1	**LF2**	**LF3**	**LF4**	**LF5**	**LF6**	**LF7**	**LF8**
1	29.91±0.856	23.4±0.44	18.27±0.13	18.67±0.47	23.44±0.62	24.64±0.19	25.25±0.57	21.38±0.56
2	41.79±0.41	32.68±0.67	24.32±0.64	23.47±0.73	31.12±0.54	35.12±0.84	33.57±0.38	27.44±0.18
3	53.38±0.63	38.97±0.28	33.53±0.85	31.71±0.55	41.82±0.36	43.44±0.45	45.14±0.82	35.63±0.35
4	64.88±0.69	45.28±0.53	39.18±0.25	38.84±0.97	50.61±0.52	50.96±0.21	51.94±0.59	43.56±0.63
5	76.14±0.64	55.55±0.44	43.65±0.55	44.46±0.24	57.72±0.74	62.87±0.34	62.48±0.64	52.17±0.45
6	84.55±0.52	64.78±0.39	51.44±0.35	52.12±0.36	63.54±0.29	73.82±0.59	73.74±0.86	61.95±0.87
7	91.87±0.88	73.86±0.86	62.87±0.37	57.34±0.53	71.62±0.94	82.47±0.65	81.48±0.71	72.76±0.64
8	98.16±0.53	82.58±0.15	67.12±0.43	66.86±0.32	81.22±0.33	88.93±0.36	87.17±0.43	84.77±0.13
9		91.23±0.64	74.86±0.57	74.92±0.16	88.36±0.46	92.54±0.84	92.27±0.53	93.25±0.84
10		97.15±0.52	85.56±0.74	85.47±0.23	92.77±0.67	97.86±0.66	96.88±0.26	99.22±0.68
11			97.82±0.16	91.11±0.36	98.92±0.26			
12				96.88±0.43				

Formulation LF1, release drug till 8 hours only and could not sustain the release of drug beyond 8 hours where formulation LF2, sustains the release of drug till 10 hours. However, formulation LF3 could sustain the release of drug till 11 hours only. Formulation LF4 can was only the formulation that could sustain the release of drug till 12 hours. Formulation LF5 could sustain the release of drug till 11 hours. Formulation LF6, LF7 and F8 could sustain the drug till 10 hours only.

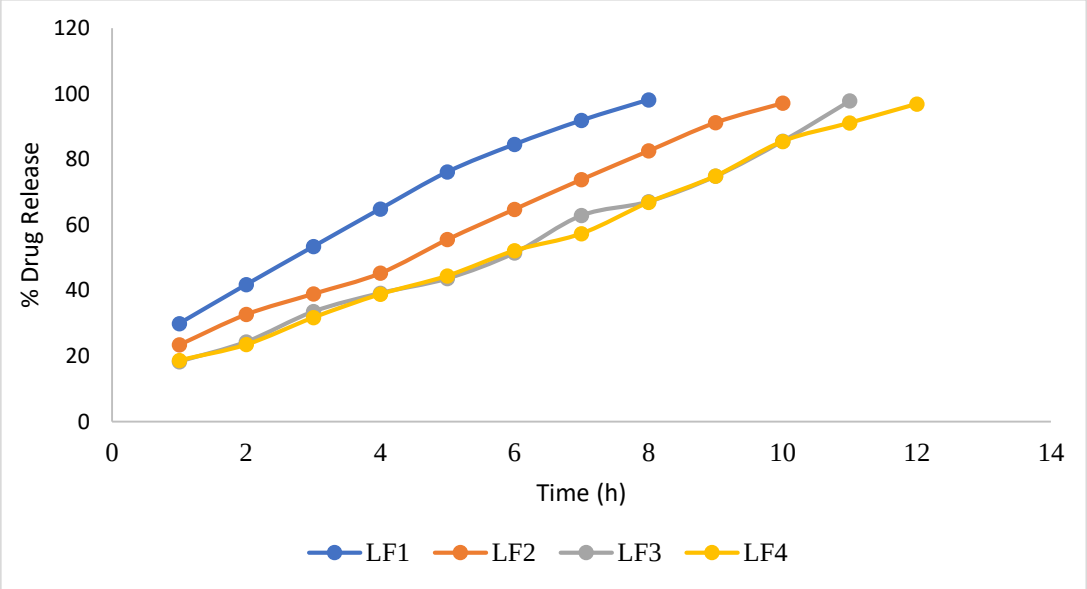

Figure 3: % Drug release of Losartan floating tablets, LF1 – LF4

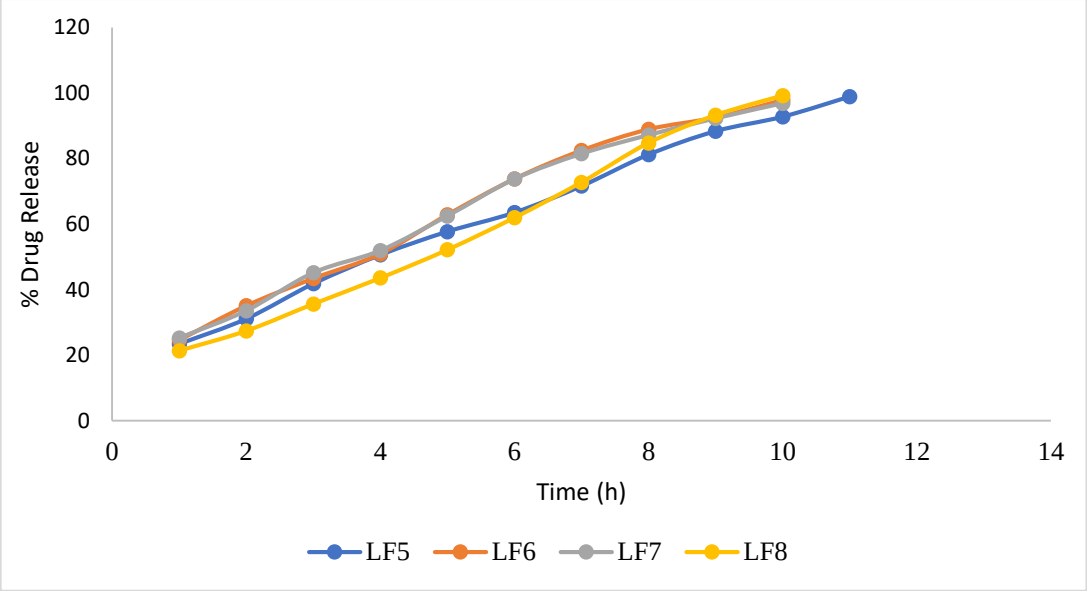

Figure 4: % Drug release of Losartan floating tablets, LF5 – LF8

The release data found after dissolution studies was fitted into different kinetic models viz. zero order kinetics, first order kinetics, Higuchi model and Krosmeyer Peppas equation model. The correlation coefficient (R^2) values in various models are given in Table 8 for Losartan tablets.

Table 8: Release kinetics of Losartan tablets

Formulation	Zero Order model		First order model		Higuchi model		Korsmeyer Peppas Equation	
LF1	R^2	0.996	R^2	0.771	R^2	0.996	R^2	0.997
	K (mg/h^{-1})	9.178	K (hr^{-1})	0.486	K_H ($h^{-1/2}$)	38.338	n	0.584
LF2	R^2	0.998	R^2	0.819	R^2	0.975	R^2	0.985
	K (mg/h^{-1})	8.427	K (hr^{-1})	0.325	K_H ($h^{-1/2}$)	35.584	n	0.651
LF3	R^2	0.991	R^2	0.598	R^2	0.949	R^2	0.973
	K (mg/h^{-1})	7.644	K (hr^{-1})	0.282	K_H ($h^{-1/2}$)	33.280	n	0.681
LF4	R^2	0.992	R^2	0.822	R^2	0.968	R^2	0.985
	K (mg/h^{-1})	7.247	K (hr^{-1})	0.261	K_H ($h^{-1/2}$)	33.406	n	0.734
LF5	R^2	0.992	R^2	0.944	R^2	0.988	R^2	0.986
	K (mg/h^{-1})	7.596	K (hr^{-1})	0.226	K_H ($h^{-1/2}$)	33.706	n	0.608
LF6	R^2	0.981	R^2	0.851	R^2	0.983	R^2	0.987
	K (mg/h^{-1})	8.158	K (hr^{-1})	0.362	K_H ($h^{-1/2}$)	34.812	n	0.584
LF7	R^2	0.991	R^2	0.889	R^2	0.988	R^2	0.981
	K (mg/h^{-1})	8.304	K (hr^{-1})	0.351	K_H ($h^{-1/2}$)	35.433	n	0.606
LF8	R^2	0.996	R^2	0.895	R^2	0.968	R^2	0.982
	K (mg/h^{-1})	8.955	K (hr^{-1})	0.245	K_H ($h^{-1/2}$)	37.691	n	0.785

When the release data were analyzed as per zero and first order models, the 'R^2' values (Table 5.18) of zero order kinetics was in the range of 0.981 – 0.998 whereas R^2 values of first order kinetics was found to be in the range of 0.598 – 0.944. The R^2 values were relatively higher in zero order model with all the floating tablets formulated indicating that the drug release from all these tablets (LF1 to LF8) followed zero order kinetics. Values of zero order rate constant for formulation LF1 – LF8, ranges from, 7.247 – 9.178 whereas first release rate constant ranges from 0.226 – 0.486.

Release data of Losartan Potassium floating tablets obeyed Higuchi and Peppas equation models with R^2 values greater than 0.949. When cumulative percent drug release was plotted against square root of time, linear regressions with 'R^2' > 0.949 were observed with all the floating tablets prepared indicating that the drug release from all these tablets was diffusion controlled.

When the release data were analyzed as per Korsmeyer Peppas equation, the release exponent 'n' was found in the range 0.584 to 0.785. Formulations were following nonfickian (anamalous) diffusion as the release mechanism from all the floating tablets prepared with various polymers.

CONCLUSION

In the present work floating tablets of Losartan were prepared by direct compression. For preparing tablets of Losartan Potassium, quantities of Lactose was varied. In formulation LF4, HPMC K4M was added and its quantity was varied, whereas, in formulation, LF5 – LF8, HPMC K100 LV was added and its quantity was varied. Quantities of Guar gum was common in all the formulation. For gas formation to make tablet float, $NaHCO_3$ and citric acid was added into the formulation. The drug-polymer interaction was evaluated by Fourier Transform Infrared Spectroscopy (FTIR) and DSC study. The FTIR and DSC study indicated the lack of drug-polymer interaction. The formulated tablets were evaluated for hardness, weight variation, thickness, floating capacity, swelling index, drug content, *in vitro* dissolution study. Losartan Potassium tablet formulation with code LF4 could only sustain the release of respective drug till 12 hours.

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