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FORMULATION AND EVALUATION OF STABLE FLOATING TABLET OF LOSARTAN POTASSIUM FOR ORAL CONTROLLED DRUG DELIVERY SYSTEM

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ABSTRACT

The present study was to prepare a gastro retentive drug delivery system of Losartan floating tablets, was designed to increase the gastric residence time, thus prolong the drug release. The different type formulations were prepared by using polymers like HPMC K100M, ethyl cellulose, talc and lactose. In the present study Sodium bicarbonate and citric acid were incorporated as a gas generating agent. The Floating tablets were evaluated for precompression and post compression parameters are solubility, uniformity of weight, hardness, friability, drug content, in vitro buoyancy, swelling index, dissolution studies. The drug release profile and floating properties was investigated. The prepared tablets exhibited satisfactory physico-chemical characteristics. All the prepared batches showed good in vitro buoyancy. The tablet swelled radially and axially during in vitro buoyancy studies. It was observed that the tablet remained buoyant for 8-12 hours. From the study it is concluded that the developed formulation has good appearance with good handling condition, therapeutically efficacious, stable.

Keywords: Losartan, Floating, Gastro retentive

1. INTRODUCTION:

Oral administration is the most versatile, convenient and commonly employed route of drug delivery for systemic action. Indeed, for controlled release system, oral route of administration has received more attention and success because gastrointestinal physiology offers more flexibility in dosage form design than other routes [1]. Oral controlled release dosage forms have been developed for the past three decades due to their considerable therapeutic advantages and applications. The high level of patient compliance in taking oral dosage forms is due to the ease of administration and handling of these forms [2]. The controlled release drug delivery systems possessing the ability of being retained in the stomach are called Gastro Retentive Drug Delivery Systems and they can help in optimizing the oral controlled delivery of drugs by continuously releasing drug prior to absorption window for prolonged period of time[3]. Since that, various approaches such as floating, bioadhesive, swelling and expanding systems have been developed to increase the gastric retention time of a dosage form[1]. Among all the systems the floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time [3].

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Losartan potassium (2-butyl-4-chloro-1-{[2'- (1*H*-tetrazol-5-yl) biphenyl-4-yl] methyl}-1*H*imidazol- 5-yl) methanol is used in the treatment of hypertension.

Losartan potassium is an angiotensin II receptor antagonist [4, 5]. It is readily absorbed orally undergoes rapid hepatic metabolism. The peak concentration is 1 hour and mean elimination half-lives achieved after 2.1 hours. The absorption of time of controlled release dosage form of losartan was increased by its enhanced gastric retention time. So in the present study supports the gastroretentive floating system improves its bioavailability of losartan potassium.

2. MATERIALS AND METHODS:

Materials: Losartan potassium. HPMC K100M, ethyl cellulose, sodium bicarbonate and citric acid were obtained as a gift samples from BMR Pharma, Hyderabad. Magnesium stearate, talc lactose and hydrochloric acid were purchased from S.D. Fine Chem Ltd, Mumbai.

Preparation of floating tablet of losartan:

The floating tablets of Losartan Potassium were prepared by direct compression technique. All the ingredients used in the formulation were initially passed through sieve #40 separately before mixing. The required quantity of Losartan Potassium and other ingredients except talc and magnesium stearate were weighed accurately and transferred to a mortar and triturated for thorough mixing. To the above mixture, talc and magnesium stearate was added and further mixed for 2 minutes. Finally the mixture was compressed into tablets of 320 mg each using approx.10 mm punches in Shiv Pharma Engineers ten station tablet punching machine.

METHODS:

Evaluation of granules properties:

Angle of repose

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and horizontal plane. The angle for the granules of each formulation was determined by the funnel method suggested by Neumann. The granules were allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper by substituting the values of the base radius 'R' and pile height 'H' in the following equation, the angle of repose was calculated as, tan Θ=H/R therefore, Θ= tan-1 (H / R)

Bulk Density

It is ratio of mass and bulk volume. Bulk density may influence compressibility, tablet porosity, dissolution, and other properties and depends on the particle size, shape and tendency of particles to adhere together. It helps to decide appropriate packing of dosage form. Accurately weighed 20 g granules were allowed to flow in fine stream into a graduated cylinder and final volume was noted. The bulk density is obtained by dividing the weight of the sample in grams by final volume in cm3.

Bulk density = Bulk mass / Bulk Volume

Tapped density

Tapped density helps to determine packing geometry and flowability of powder blend. 20 gm granules were allowed to flow in fine stream into a graduated cylinder 0f mechanical tapping device. The measuring cylinder was tapped for 100 times and final tapped volume noted. The tapped density was obtained by dividing the weight of sample powder taken by final tapped volume.

Tapped density = Bulk mass / Tapped volume

Carr's Index

An indirect method of measuring powder flow from bulk densities was developed by Carr's. The percentage compressibility of a powder was a direct measure of the potential powder arch or bridge strength and stability. Carr's index of each formulation was calculated according to equation given below

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

Hausner ratio

It is essential to determine the compressibility strength of powder. Hausner's ratio is simple method to evaluate stability of powder column and to estimate flow properties. Tapped density and bulk density were measured and Hausner ratio was calculated using following formula.

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

Evaluation of tablet properties:

Thickness and Hardness:

Thickness and diameter of tablets were important for uniformity of tablet size. Thickness and diameter were measured using digital verniercallipers. The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of tablet of each formulation was measured by Monsanto hardness tester. The hardness was measured in terms of kg/cm2 [6].

Friability:

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 rpm dropping the tablets through a distance of six inches with each revolution. After 4 min., the tablets were weighed and the percentage loss in tablet weight was determined.

$$\% \text{ loss} = \frac{\text{Initial wt. of tablets} - \text{Final wt. of tablets}}{\text{Initial wt. of tablets}} \times 100$$

Weight Variation:

Weigh 20 tablets selected at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in Table.2 and none deviates by more than twice that percentage.

S. No	Avg. wt. of tablet	% of deviation
1	80mg or < 80	10
2	>80 to < 250mg	7.5
3	>250 or more	5

Drug Content uniformity:

This test was applicable to tablets that contain less than 10 mg or less than 10 % w/w of active ingredient. Content of active ingredient in tablets and capsules, taken at random, was determined. Crush tablets and powder equivalent to weight of tablet dissolved in 0.1 NHCl. Drug content was calculated by measuring absorbance at wavelength 320 nm. The tablet comply with the test if not more than one of the individual values thus obtained was outside the limits 85 to 115 % of the average value and none is outside the limits 75 to 125 % of the average value. If two or three of the individual values are outside the limits 85 to 115.5 of the average value and none is outside the limits 75 to 125 %, repeat the determination using another 20 tablets. The tablet comply with the test if in the total sample of 30 tablets not more than three of the individual values are outside the limits 85 to 115 % and none is outside the limits 75 to 125 % of the average value[7].

Swelling index:

The swelling properties of HPMC matrices containing drug were determined by placing the tablet matrices in the dissolution test apparatus, in 900 ml of 0.1 N HCl at 37 ± 0.5 0C. The tablets were removed periodically from dissolution medium. After draining free water these were measured for weight gain, thickness and diameter. Swelling characteristics were expressed in terms of percentage water uptake (WU %) according to the equation,

$$WU\ \% = \frac{\text{Wt. of swollen tablet} - \text{Initial wt. of the tablet}}{\text{Initial wt. of the table}} \times 100$$

Floating Lag Time & Floating Time:

This test was performed in beaker containing 100 ml 0.1 N HCl as a testing medium maintained at 37^0C [8]. The time required for the tablet to rise to the surface and float was determined as floating lag time. Floating time was the time, the tablet floats in dissolution medium (including floating lag time) [9].

***In vitro* drug release profile:**

In-vitro dissolution studies were carried out in USP type-II tablet dissolution apparatus using 900ml hydrochloric acid buffer pH 1.2 as dissolution media. The paddle was rotated at 50 rpm and the temperature was maintained at 37±0.5^{0}C throughout the study. At predetermined time intervals 5 ml of the samples were withdrawn by means of an auto sampler machine with a pre filter. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium maintained at 37±0.5^{0}C. The samples were analysed for drug releases by measuring the absorbance at 205 nm using UV-Visible spectrophotometer. All the studies were conducted in triplicate.

RESULTS:

Solubility studies of Losartan: The Losartan potassium was freely soluble on water and methanol. Soluble in 0.1 N HCL and slightly soluble in isopropyl alcohol (Table 1).

Precompression parameters of Losartan potassium granules

The Carr's index ranged from 11.32 to 17.39 for Formulations 1 to 18. Hausner ratio ranged from 1.11 to 1.21 for different formulations of losartan and the tapped density and bulk density ranges from 0.37 to 0.53 and 0.31to 0.47 respectively. Angle of repose ranged from 22.29 to 27.91 values indicates good flow property of the granules.

Post compression parameters:

The drug content in formulations ranges from 98.07±0.61% (F9) to 100.07±0.1% (F5). The hardness of the prepared GRDDS of Losartan potassium was found to be in the range of 5.2±0.2 (F7) to 5.6±0.2 (F11) kg/cm^2. The % friability values ranges from 0.21± 0.5 (F7) to 0.45± 0.4 (F12). The thickness of the GRDDS of losartan potassium ranges from 3.84±0.012mm (F13) to 3.98±0.051mm (F7). The weight variation ranges from 319±0.010 (F2) to 321±0.018 (F3) were shown in Table 3.

Floating property and swelling index: Swelling index:

The floating lag time ranges from 22 to 33 for all GRDDS of Losartan potassium. The swelling index of F1-F18 was found to be ranging in between 45.36± 0.011% (F13) to 84.26± 0.196% (F16).

***In vitro* drug release profile:**

In vitro dissolution studies were performed for all the batches of GRDDS of Losartan potassium using USP XXIII dissolution test apparatus-II at 50rpm, 900ml of 0.1N HCl used as dissolution media. The *In vitro* drug release data was given in graph 3, 4.

The cumulative drug release of formulations were found to be F1 (83.27), F2 (85.75), F3 (90.15), F4 (89.33), F5 (94.77), F6 (92.46), F7 (98.44), F8 (95.35), F9 (92.62), F10 (92.91), F11 (93.120), F12 (94.11), F13 (82.25), F14 (96.62), F15 (90.26), F16 (97.52), F17 (90.42) and F18 (93.21).

IR Interpretation:

The IR spectrum of the pure Losartan Potassium sample recorded by FTIR spectrometer is shown in figure 1. This was compared with mixture of complex of Losartan Potassium as shown in figure 2.

From FTIR study, the characteristic peaks of drug such as of OH (3218.85 cm^{-1}), C-H Stretching Aromatic (3375.57 cm^{-1}), C-H stretching Aliphatic (2954.62 cm^{-1}), C=o (1642.01 cm^{-1}), Ar-CH Out plane bending (994.12 cm^{-1}) appeared for the pure drug Losartan Potassium. For the mixture of Losartan Potassium with HPMC K100M and Ethyl cellulose, the peaks which have been obtained for the pure drug were available at the same wavelength for OH (3249.95 cm^{-1}), CH stretching Aromatic (3399.06 cm^{-1}), CH stretching Aliphatic (2933.70 cm^{-1}) C=O (1642.16 cm^{-1}), Al-CH bend (1460.31 cm^{-1}), Ar-CH In plane Bending (1110.77 cm^{-1}), Ar-CH Out plane Bending (949.75 cm^{-1}).

DISCUSSION:

Losartan potassium is a potent, highly specific angiotensin II type 1 (AT1) receptor antagonist with antihypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 hr. Therefore an attempt was made to increase oral bioavailability of Losartan by retaining the dosage form in stomach for longer period of time. This is achieved by developing gastroretentive floating drug delivery system. These floating tablets were prepared to increase the bioavailability of the drugs by utilizing the drugs to full extent avoiding unnecessary frequency of dosing and subsequently first pass metabolism. Therefore, it was selected for the design of a gastro-retentive floating drug delivery system with aview to improve its oral bioavailability.

In the present study, an attempt was made to design and optimize GFDDS of Losartan Potassium using hydroxypropyl methylcellulose (HPMC K100M) and ethyl cellulose as the polymers and sodium bicarbonate as a gas generating agent, to reduce floating lag time. The compatibility evaluations were performed by Fourier transforms infra-red spectroscopy studies implied that polymers and drug were compatible with each other. There was no interaction found between polymer and drug. The preformulation studies of all the formulations were tested by various studies including angle of repose (ranging from 23.01° to 28.21°), bulk density (ranging from 0.41 to 0.47gm/ml),tapped density (ranging from 0.48 to 0.56gm/ml), Hausner's ratio (ranging from 1.11 to1.24) and Carr's index (ranging from 10.00 to 19.64 %). All the results showed good flow property. The tablets were prepared by direct compression method, eight batches of preliminary trial formulations were designed and from the results of evaluation data, the constraints for independent variables X1 (HPMC K100M), X2 (Ethyl Cellulose) and X3 (Sodium bicarbonate) were fixed. A full 2^3 factorial design was

used for final optimization of Losartan Potassium formulations. For the formulation of floating tablets, HPMC K100M was used as matrix forming gelling agent, ethyl cellulose used as release retardant. Other excipients used were Lactose (Diluent), Sodium bicarbonate (gas generating agent), citric acid (to provide acidic media) Magnesium stearate (lubricant) and talc (glidant). Fourier transform Infrared spectroscopy confirmed the absence of any drug/polymers/excipients interactions.

The floating tablets were compressed using 10 mm circular flat faced punches using Shiv Pharma 10 station rotary punching machine. Direct compression method was employed to formulate the tablets, because of its effectiveness and due to reduced number of manufacturing steps. The prepared floating tablets were evaluated for hardness, weight variation, thickness, friability, drug content uniformity, buoyancy lag time, total floating time, water uptake (swelling index), *in-vitro* dissolution studies. All formulations were subjected for five different models viz. Zero order, First order, Higuchi, Korsemeyer-Peppas model and Hixson-Crowell models[10]. Floating lag time, total floating time, swelling index and *in-vitro* drug release pattern of tablets of F1 to F8 formulations were determined. Among all formulations F2 showed highest swelling index. The hardness of the prepared tablets of Losartan Potassium was found to be in the range of 5.2 to 5.6 Kg/cm^2. The friability of all tablets was less than 1% i.e., in the range of 0.15 to 0.41%. The percentage deviations from the mean weights of all the batches of prepared HBS were found to be within the prescribed limits as per IP. The swelling index of the tablets increases with an increase in the polymer content and the content of gas generating agent $NaHCO_3$. *In-vitro* floating studies were performed by placing tablets in USP type II paddle dissolution apparatus containing 900 ml of 0.1N hydrochloric acid maintained at a temperature of 37±0.5ºC. The floating lag time and floating time was noted visually. For all (trial and factorial) formulations, lag time was in the range of 20 to 32 seconds [11]. For formulation F8 it was lowest (20 sec) as the polymers such as HPMC K100M and ethyl cellulose and gas generating agent sodium bicarbonate were in highest proportion among all formulations, while for formulation F1, floating lag time was highest(32 seconds) as the polymers HPMC K100M and ethyl cellulose and sodium bicarbonate were in lowest proportion. All the designed formulations had displayed a floating time of more than 12 hours.

Among the various floating tablet formulations studied, formulation F7 containing drug polymer ratio (1:3) prepared with HPMC K100M & ethyl cellulose showed promising results releasing98.44% of the drug in 12 hours with a floating lag time of 22 seconds and floating time of more than 12 hours has been considered as an ideal formulation. After 12 hours study, it was observed that nearly 83.27 to 98.44%drug was released from all the formulations. The release data was then fitted to mathematical models such as Zero order, First order, Higuchi, Korsemeyer-Peppas and Hixon Crowell model and the coefficients of regression value were compared [12]. It was observed that the formulations F1, F2, F3, and F7 followed Korsemeyer-peppas model, F4, F5, and F8 followed zero order models and formulation F6 followed Higuchi model. Among the eight formulations, F7 was selected as the best formulations as its coefficient of regression value was more near to unity. Then data was subjected to Korsmeyer-Peppas equation for determination of release mechanism. The acceptable linearity was observed (r2>0.969-0.996) for all developed formulations. The release exponent "n" varied from 0.527-0.838 that indicates anomalous non-fickian diffusion Banker[13].

Table 1: Solubility profile of Losartan Potassium in different media:

Medium	Solubility
Water	Freely soluble
Methanol	Freely soluble
0.1 N HCl	Soluble
Isopropyl alcohol	Slightly soluble

Table 2: Pre compression parameters of various formulations

Angle of Repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Hausner's ratio	Carr's Index (%)	Formulation code
23.01	0.45	0.51	1.13	11.76	**F1**
24.86	0.44	0.52	1.18	15.38	**F2**
22.29	0.45	0.53	1.18	15.09	**F3**
26.36	0.47	0.52	1.11	9.61	**F4**
28.11	0.42	0.48	1.14	12.5	**F5**
28.21	0.43	0.51	1.19	15.68	**F6**
27.62	0.42	0.48	1.14	12.5	**F7**
24.32	0.41	0.48	1.17	14.58	**F8**
25.23	0.33	0.39	1.18	15.38	**F9**
26.15	0.39	0.45	1.15	13.33	**F10**
26.98	0.42	0.48	1.14	12.50	**F11**
26.95	0.48	0.56	1.17	14.28	**F12**
25.64	0.31	0.37	1.19	16.21	**F13**
24.67	0.41	0.49	1.19	16.32	**F14**
26.31	0.47	0.53	1.13	11.32	**F15**
27.91	0.38	0.46	1.21	17.39	**F16**
24..71	0.36	0.41	1.14	12.19	**F17**
27.15	0.41	0.48	1.17	14.58	**F18**

Table 3: Post compression parameters of formulation F1-F18

Formulation code	Evaluation Parameters				
	Drug content (%)	Weight variation (n=20)	Friability(%) (n=10)	Hardness±SD (Kg/cm^2) (n=10)	Thickness ± SD (mm) (n=10)
F1	98.29±0.22	320±0.011	0.29± 0.5	5.2±0.4	3.94±0.093
F2	99.41±0.13	319±0.010	0.30± 0.4	5.4±0.2	3.90±0.046
F3	98.16±0.31	321±0.018	0.41± 0.6	5.3±0.2	3.93±0.035
F4	99.63±0.22	320±0.013	0.25± 0.7	5.6±0.1	3.94±0.023
F5	100.07±0.1	319±0.014	0.41± 0.6	5.5±0.6	3.96±0.048
F6	99.24±0.26	321±0.009	0.24± 0.5	5.5±0.3	3.95±0.039
F7	100.52±0.2	319±0.021	0.29± 0.3	5.2±0.2	3.98±0.051
F8	98.52±0.19	321±0.011	0.21± 0.5	5.5±0.3	3.92±0.025
F9	98.07±0.61	320±0.017	0.33± 0.5	5.4±0.3	3.85±0.016
F10	99.17±0.16	320±0.021	0.39± 0.4	5.5±0.2	3.85±0.017
F11	99.52±0.52	319±0.015	0.44± 0.5	5.6±0.2	3.86±0.019
F12	98.12±0.16	320±0.001	0.45± 0.4	5.5±0.1	3.85±0.025
F13	98.17±0.45	319±0.017	0.39± 0.6	5.5±0.3	3.84±0.012
F14	99.17±0.25	321±0.011	0.38± 0.5	5.4±0.2	3.84±0.015
F15	99.15±0.62	321±0.002	0.36± 0.1	5.4±0.2	3.85±0.016
F16	98.18±0.14	319±0.028	0.35± 0.1	5.4±0.3	3.85±0.021
F17	99.15±0.42	320±0.026	0.38± 0.3	5.3±0.3	3.85±0.023
F18	99.18±0.15	320±0.042	0.39± 0.2	5.4±0.3	3.85±0.012

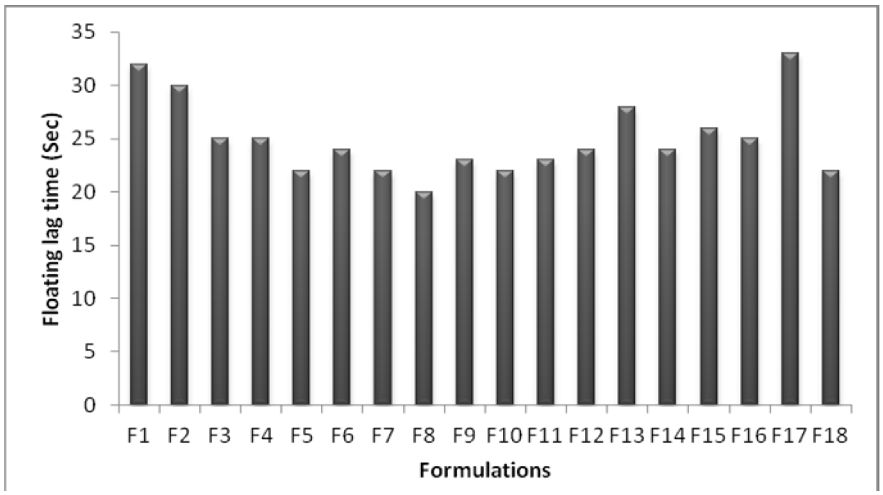
Table 4: Comparison of Peaks with pure drug (Losartan) and physical mixture

Losartan Potassium Mixture	Losartan Potassium	Functional Group
3249.95	3218.85	OH
3399.06	3375.57	CH Stretching Aromatic
2933.70	2954.62	CH Stretching Aromatic
1642.16	1642.01	C=O
1591.12	1574.17	C=C
1460.31	1460.54	Al-CH bend
11110.77	1106.17	Ar-CH (In plane bending)
949.75	994.12	Ar-CH (Out plane bending)

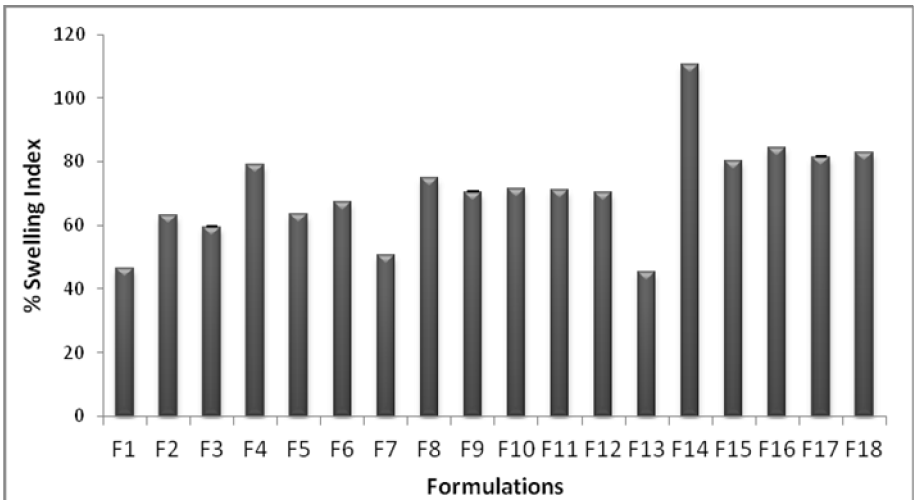
Table 5: Kinetic analysis of dissolution data of formulations F1-F18

Formulation code	Korsemeyer-Peppas		Higuchi	First order	Zero order	Best fit model
	n	R^2	R^2	R^2	R^2	KorsemeyerPeppas
F1	0.838	0.9983	0.9361	0.9526	0.9974	KorsemeyerPeppas
F2	0.653	0.9959	0.9722	0.9594	0.9799	KorsemeyerPeppas
F3	0.535	0.9966	0.9960	0.9765	0.9434	Zero
F4	0.783	0.9852	0.9368	0.9353	0.9964	Zero
F5	0.647	0.9755	0.9513	0.8842	0.9851	Higuchi
F6	0.527	0.9962	0.9964	0.9624	0.9402	KorsemeyerPeppas
F7	0.602	0.9788	0.9688	0.8528	0.9770	Zero
F8	0.758	0.9696	0.9067	0.8442	0.9886	KorsemeyerPeppas
F9	0.652	0.9870	0.9615	0.9190	0.9815	KorsemeyerPeppas
F10	0.668	0.9937	0.9647	0.9071	0.9831	KorsemeyerPeppas
F11	0.624	0.9865	0.9628	0.8924	0.9805	KorsemeyerPeppas
F12	0.647	0.9846	0.9544	0.8718	0.9845	Zero order
F13	0.694	0.9613	0.9248	0.9361	0.9895	KorsemeyerPeppas
F14	0.634	0.9912	0.9735	0.8730	0.9773	KorsemeyerPeppas
F15	0.654	0.9984	0.9819	0.9648	0.9695	KorsemeyerPeppas
F16	0.690	0.9994	0.9738	0.8607	0.9794	KorsemeyerPeppas
F17	0.668	0.9967	0.9695	0.9233	0.9794	KorsemeyerPeppas
F18	0.695	0.9994	0.9802	0.9392	0.9711	KorsemeyerPeppas

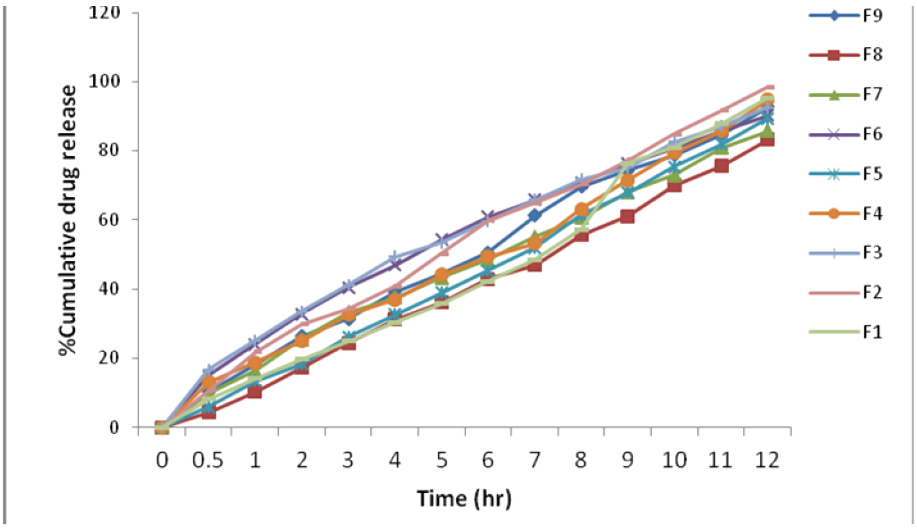
Graph 1: Floating property of Losartan floating tablets



Graph 2: Swelling index of different formulation



Graph 3: Percentage of drug release at different time interval (F1 to F9)



Graph 4: Percentage of drug release at different time interval (F10 to F18)

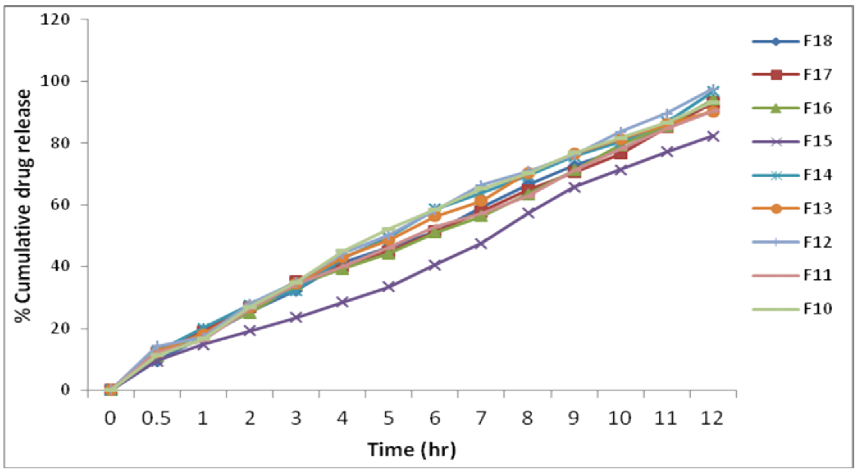


Figure 1: IR Spectra of pure Losartan Potassium

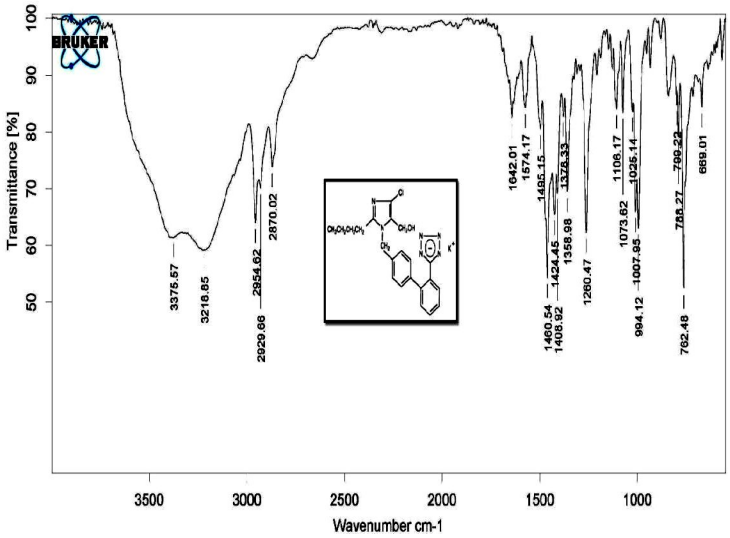
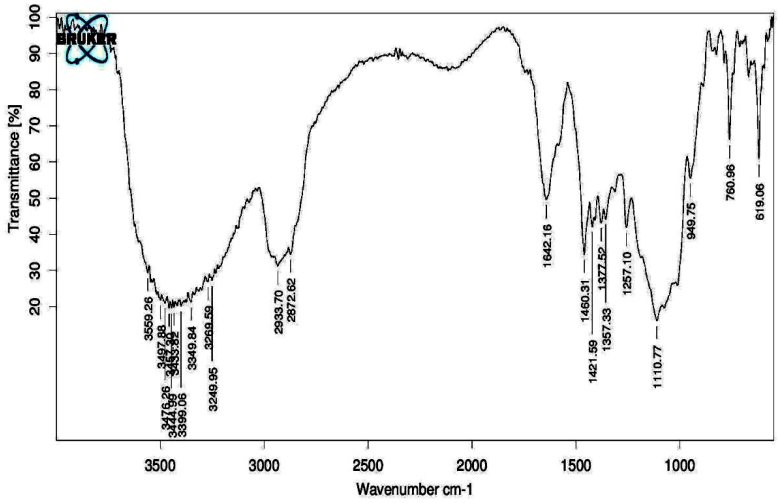


Figure 2: IR Spectra of Losartan Potassium mixture



CONCLUSIONS:

Thus the objective of gastroretentive floating drug delivery system of an antihypertensive drug Losartan Potassium with extended release profile was achieved.Characterization, *in vitro* evaluation of these developed drug delivery system of Losartan Potassium showed good correlation with USP standards.Gastroretentive sustained release dosage forms of Losartan Potassium might be beneficial to produce improved patient compliance reducing the dosing frequencies and increased oral bioavailability.

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