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FORMULATION AND IN-VITRO EVALUATION OF FLOATING DRUG DELIVERY SYSTEM OF LOSARTAN POTASSIUM.

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Abstract

Objective In the present study, Gastro Retentive Floating Drug Delivery systems (GRDDS) of Losartan potassium, an antihypertensive drug, with an oral bioavailability of only 33% (because of its poor absorption from lower gastrointestinal tract) have been designed to increase the therapeutic efficacy & gastric residence time and to reduce frequency of administration. Losartan potassium having a short biological half-life of 1.5 -2 h is eliminated quickly from the body leading to low therapeutic efficacy[1].

Method The tablets were prepared by direct compression method, by employing semi-synthetic and natural polymers like HPMCK100M, HPMC K4M, and Guar gum respectively in various concentrations. Carbopol 934 and sodium bicarbonate as gas generating agent to reduce floating lag time[1].

Result Precompression parameters are evaluated including bulk density, tapped density, Carr's index, Hausner's ratio, angle of repose for powder material. Prepared tablets were evaluated for hardness, thickness, friability, weight variation, drug content, swelling index.. *In-vitro* drug release was tested in phosphate buffer pH 2.1 in time upto 12 hrs.[2]

Conclusion Among all these formulations F3 shows maximum drug release up to 96.02% Optimized tablet formulation was subjected Accelerated stability studies (AST) was carried for optimized formulation F3 by exposing it to 40°C/75% RH for one month and analyzed the sample at the interval of 7,14,21,28 days. Kinetics of formulation purely follows the Anomolous transport mechanism

Keywords Losartan potassium, HPMCK100M, HPMCK4, Carbopol 934.

Introduction

The present scenario of pharmaceutical technology has been changed just because of promising delivery of medicament to the body systems. The various dosage forms are being produced, it is not just because of to deliver the drug within proper concentration but the patient's compliance and a safe drug delivery is also the interest of researcher to develop such dosage form.[3]

Oral drug, delivery is the largest and the oldest segment of the total drug delivery market. It is the fastest growing and most preferred route of drug delivery due to the ease of administration, patient compliance and flexibility in formulation One of the most feasible approaches for achieving a prolonged and predictable drug delivery profile in the GI tract is to control the gastric residence time (GRT)Effective oral drug delivery may depend upon the factors such as gastric emptying process, gastrointestinal transit time of dosage form, drug release from the dosage form and site of absorption of drugs. Dosage forms with a prolonged GRT i.e. gasroretentive dosage forms (GRDFs) will provide us with new and important therapeutic options. Since many drugs are well absorbed in the upper part of the gastrointestinal tract, high variability in these factors may lead to non-uniform absorption and makes the bioavailability unpredictable. Hence, a beneficial delivery system would be one which possesses the ability to control and prolong the gastric emptying time and can deliver drugs in higher concentrations to the absorption site[4] (i.e. upper part of the small intestine).

Drugs that are easily absorbed from the gastrointestinal tract (GIT) and have a short half-life are eliminated quickly from the blood circulation, require frequent dosing. To avoid this problem, the oral controlled release (CR) formulations have been developed in an attempt to release the drug slowly into the GIT and maintain a constant drug concentration in the serum for longer period of time.[4, 5]

Some drugs have narrow absorption window in upper part of GI tract i.e. stomach and small intestine, which is due to short transit time of dosage form. Formulation of these drugs leave upper part of GI tract and reaches to non-absorbing distal regiment, resulting lesser bioavailability. Losartan potassium having a short biological half-life of 1.5 -2 h is eliminated quickly from the body leading to low therapeutic efficacy. [6, 7, 8]

Materials and Methods

Materials

Losartan potassium (drug), HPMC K4M, HPMC K100, Carbopol P-934, Sodium bicarbonate, Citric acid, Lactose, Talc, Magnesium stearate.

Methods

The direct compression method

Preliminary study

This study was carried out for the selection of suitable polymer and excipients for the proposed formulations. The composition of all preliminary batches were shown in table no.1,2,3 Losartan potassium, polymer, lactose, sodium bicarbonate and citric acid were passed through sieve no.40 separately. The drug was mixed with the polymers and other ingredients. The powder blend was then lubricated with magnesium stearate(1%w/w) persisted through 40#), talc (2%w/w) and this lubricated blend was compressed into tablet using 9 mm flat-face tooling on a tablet compression machine. Each formulation contains 50 mg Losartan potassium, 20%sodium bicarbonate, 5% citric acid, 1% magnesium stearate, 2% talc and lactose q.s.

Table No.1 Composition of tablet in preliminary study (F1- F9)

Ingredients/Batches	F1	F2	F3	F4	F5	F6	F7	F8	F9
Losartan potassium	50	50	50	50	50	50	50	50	50
HPMC K4M	60	90	120	-	-	-	-	-	-
Guar Gum	-	-	-	15	30	45	-	-	-
HPMC K100M	-	-	-	-	-	-	15	30	45

Table No.2 Composition of tablet in preliminary study (F10- F17)

Ingredients/Batches	F10	F11	F12	F13	F14	F15	F16	F17
Losartan potassium	50	50	50	50	50	50	50	50
HPMC K4M	60	60	90	90	60	60	90	90
Guar Gum	15	45	15	45	-	-	-	-
HPMC K100M	-	-	-	-	15	45	15	45

Table No.3 Composition of tablet in preliminary study (F18-F25)

Ingredients/ Batches	F18	F19	F20	F21	F22	F23	F24	F25
Losartan potassium	50	50	50	50	50	50	50	50
HPMC K4M	75	75	75	75	90	90	90	90
HPMC K100M	15	15	30	30	15	15	30	30
Carbopsol 934P	9	15	9	15	9	15	9	15

Formulation for preliminary trials

Floating tablets of Losartan potassium were prepared using different polymers like HPMC K4M, Guar gum and HPMC K100M alone (F1-F9 batches). These batches have less floating lag time (2-3 min) but remained buoyant for only 2-3 hrs. After 2-3 hrs these tablets were dispersed. Therefore, formulations using different combinations of these polymers were developed. Formulations of HPMC K4M and Guar gum have less floating time (F10-F13 batches). Formulations of HPMC K4M and HPMC K100M gives better results (F14-F17 batches). These batches have floating lag time of 3-4 min and remained buoyant for more than 12 Hrs. but, the % drug release was more therefore, Carbopol 934P was used as a drug release retardant (F18-F25 batches).

Table No.4 Composition of tablet in final formulations (F1- F8)

Sr No	Ingredients (mg/tablet)	F1	F2	F3	F4	F5	F6	F7	F8
1	Losartan Potassium	50	50	50	50	50	50	50	50
2	HPMC K4M	75	75	75	75	90	90	90	90
3	HPMC K100M	15	15	30	30	15	15	30	30
4	Carbopol 934P	9	12	9	12	9	12	9	12
5	Sodium bicarbonate	60	60	60	60	60	60	60	60
6	Citric acid	15	15	15	15	15	15	15	15
7	Mg Stearate	3	3	3	3	3	3	3	3
8	Talc	6	6	6	6	6	6	6	6
9	Lactose	66	64	51	49	51	49	36	34
	Total	300	300	300	300	300	300	300	300

Evaluation Of Precompression Parameters Of Drug Polymeric Blend

Physical properties of drug, polymers and excipients[9]

Excipients, polymers and drug were characterized for their physical properties such as angle of repose, density, compressibility, Hausner's ratio.

1. Angle of repose

The powder was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured. The angle of repose was calculated by substituting the values of the base radius 'R' and pile height 'H' in the following equation.

$$\tan\theta = H/R$$

Where, H = Pile height and R = Radius of Pile

Therefore, $\theta = \tan^{-1} H/R$

2. Bulk density

The sample equivalent to 25g was accurately weighed and filled in a 100 ml graduated cylinder and the powder was leveled and the unsettled volume, V_o was noted. The bulk density was calculated by the formula.

$$\text{Bulk density } (\rho_o) = M/V_o$$

Where,

M = mass of powder taken

V_o = Apparent unstirred volume

3. Tapped density

The tapped density was determined by mechanically tapping the measuring cylinder and the volume was noted.

$$\text{Tapped density } (\rho_t) = M / V_t$$

Where,

ρ_t = tapped denssity

M = weight of granules

V_t = tapped volume of granules in cm.

4. Compressibility index

The bulk volume and tapped volume was measured and compressibility index was calculated using the formula.

$$\text{Compressibility index} = 100\ (V_o - V_f)/V_o$$

Where,

V_o = Bulk volume

V_f = Tapped volume

5. Hausner's ratio

Tapped volume and bulk volume were measured and the hausner's ratio was calculated using the formula

Hausner's ratio = V_o/V_f

Where, V_o = Bulk volume

V_f = Tapped volume

Evaluation Of Floating Tablets

A) Physical Parameters

1. Thickness

The thickness of the tablets was determined using a Vernier caliper. Five tablets from each type of formulation were used and average values were calculated. It is expressed in mm.

2. Hardness

The resistance of tablets to shipping, breakage, under conditions of storage, transportation and handling before usage depends on its hardness. For each formulation, the hardness of 6 tablets was determined using the Monsanto hardness tester. The tablet was held along its oblong axis in between the two jaws of the tester. At this point, reading should be zero kg/cm^2. Then constant force was applied by rotating the knob until the tablet fractured. The value at this point was noted.

3. Friability

This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm, dropping the tablets to a distance of 6 inches in each revolution. A sample of pre-weighed 6 tablets was placed in Roche friabilator which was then operated for 100 revolutions i.e. 4 minutes. The tablets were then dusted and reweighed. A loss of less than 1 % in weight in generally considered acceptable. Percent friability (% F) was calculated as follows.

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

4. Weight variation test

To find out weight variation, 20 tablets of each type of formulation were weighed individually using an electronic balance, average weight was calculated, and individual tablet weight was then compared with average value to find the deviation in weight.

5. Matrix Integrity

The prepared tablets were visually checked for matrix integrity and uniformness. The tablets were checked for matrix integrity during dissolution.

6. Floating Behavior

The *in-vitro* buoyancy was determined by floating lag time and floating time. The tablets were placed in dissolution vessel containing 900 ml of 0.1N HCl. The time required for the tablet to rise to the surface and afloat was determined as floating lag time. The duration for which the tablet remains afloat on surface of solution is known as floating time.[10]

7. Swelling Behavior of tablets

The swelling of the polymers can be measured by their ability to absorb water and swell. Water uptake studies of the formulation were performed using USP dissolution apparatus II. The medium used was 0.1 N HCl (900mL) rotated at 50 rpm and maintained at 37 ± 0.5°C through- out the study. After a selected time interval, the formulation is withdrawn, blotted to remove excess water and weighed. Swelling characteristics of the tablets expressed in terms of water uptake (WU) are calculated as follow.[11]

$$WU\ \% = \frac{\text{Swollen weight} - \text{Initial weight}}{\text{Initial weight}} \times 100$$

B) Chemical Parameters

1. Uniformity of drug content[12]

Five tablets of each type of formulation were weighed and crushed in mortar and powder equivalent to 50 mg of Losartan potassium was weighed and dissolved in 100 ml of 0.1N HCl (pH 1.2). This was the stock solution from which 0.2 ml sample was withdrawn and diluted to 10 ml with 0.1N HCl. The absorbance was measured at wavelength 226 nm using double beam UV-Visible spectrophotometer.
Content uniformity was calculated using formula

% Purity = 10 C (Au / As)

Where, C - Concentration,

Au and As - Absorbance's obtained from unknown preparation and standard

2. *In-vitro* dissolution studies[13]

Details of dissolution test

Dissolution test apparatus USP (Type II), Speed: 100 RPM, Stirrer: Paddle type Volume of medium: 900 ml, Sample withdraw at each time intervals: 10 ml, Medium used: 0.1N HCl (pH1.2) Temperature 37 ± 0.5 ^{0}C

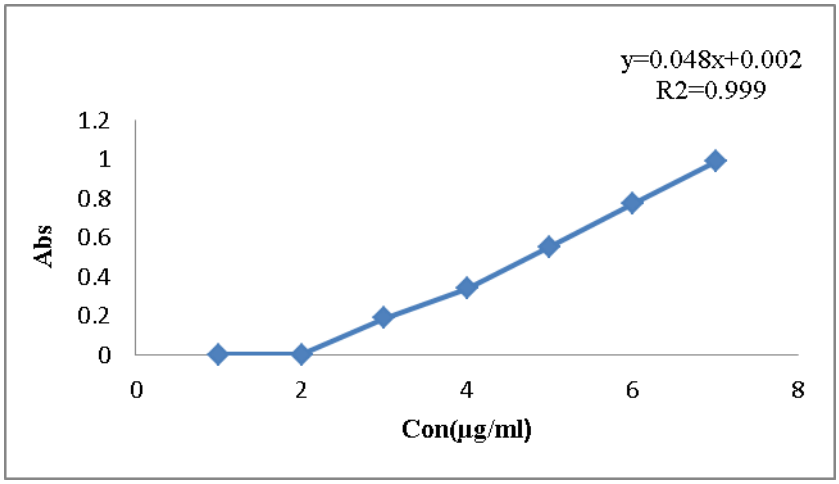
5. Stability Studies

It is the responsibility of the manufacturers to see that the medicine reaches the consumer in an active form. So, the stability of pharmaceuticals is an important criteria. Wherever possible, commercial pharmaceutical products should have a shelf-life of 3 years. The potency should not fall below 95% under the recommended storage conditions and the product should still look and perform as it did when first manufactured.

Accelerated Stability Testing[12, 13]

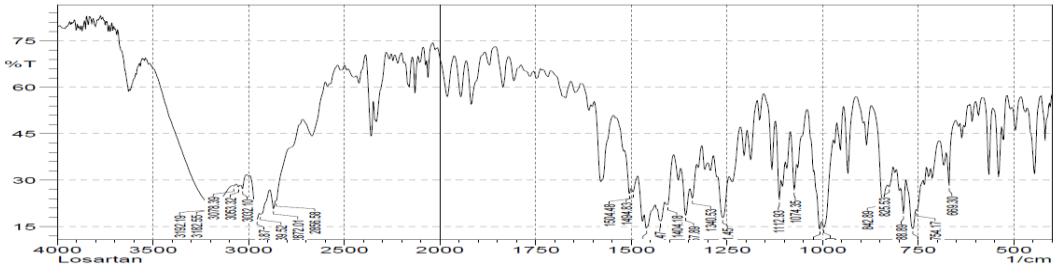
Stability testing of formulation batch was carried out to determine the stability of drug and carrier and also to determine the physical stability of formulation under accelerated storage condition at 45ºC/70%RH. The prepared tablets were placed in borosilicate screw capped glass containers. The samples were kept at condition of 45°C/70% RH and were analyzed at 7th, 14^{th,} 21st and 28th days for drug content, hardness and *in-vitro* dissolution study.

Result and Discussion



Graph 1: Standard curve of Losartan potassium in 0.1 N HCI (pH 1.2)

Infrared Spectroscopy:



Graph2: FT-IR spectrum of Losartan potassium.

Table No.5: Physical parameters of powder blend

Parameters Formulations	Bulk Density (g/ml) ±SD	Tapped Density (g/ml) ±SD	Angle of Repose ±SD	Carr's Index (%)±SD	Hausner's Ratio ±SD
F1	0.620±0.01	0.696±0.01	23.30±0.79	13.79±0.25	1.139±0.03
F2	0.607±0.01	0.713±0.02	23.61±1.16	14.13±0.43	1.176±0.005
F3	0.623±0.01	0.740±0.03	25.40±0.49	14.63±0.47	1.187±0.006
F4	0.624±0.03	0.690±0.02	26.10±0.50	9.37±0.50	1.104±0.007
F5	0.553±0.02	0.624±0.01	23.31±0.83	11.59±1.11	1.123±0.002
F6	0.603±0.01	0.662±0.04	24.42±1.56	9.06±0.52	1.094±0.006
F7	0.581±0.03	0.684±0.02	21.53±0.86	13.54±0.63	1.167±0.007
F8	0.572±0.02	0.642±0.01	25.01±0.77	10.90±0.89	1.127±0.003

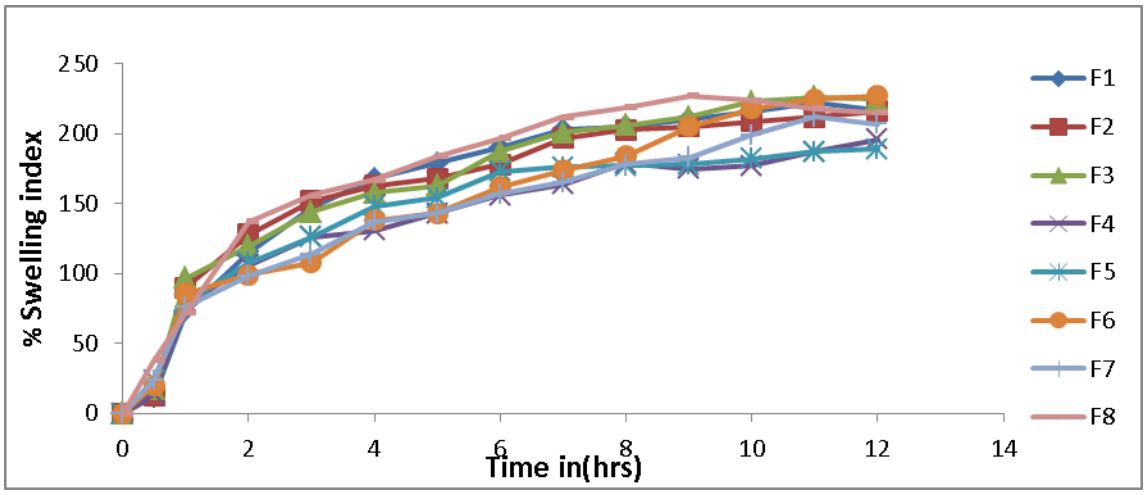
n=3

Evaluation of Floating Tablets

Table No.6: Physical parameters of tablets

Parameters Formulations	Hardness (kg/cm^2± SD)	Thickness (mm ± SD)	% Friability (± SD)	Wt. Variation (± SD)
F1	4.05±0.122	3.347±0.04	0.554±0.315	302.9±1.678
F2	4.22±0.11	3.212±0.03	0.7845±0.157	292.8±1.607
F3	4.32±0.18	3.234±0.05	0.6172±0.105	301.05±1.118
F4	4.04±0.14	3.40±0.02	0.4959±0.131	301.14±1.356
F5	4.25±0.12	3.53±0.04	0.6304±0.190	298.09±1.941
F6	4.68±0.13	3.360±0.03	0.7341±0.273	293.01±2.024
F7	4.33±0.12	3.524±0.03	0.4042±0.162	297.25±1.712
F8	4.03±0.12	3.486±0.05	0.6555±0.230	298.6±2.261

(n=3)



Graph No. 3: Plot of percent water uptake (% swelling) by tablets from batches F1- F8 as a function of

Chemical Parameters[12]

1. Uniformity of drug content

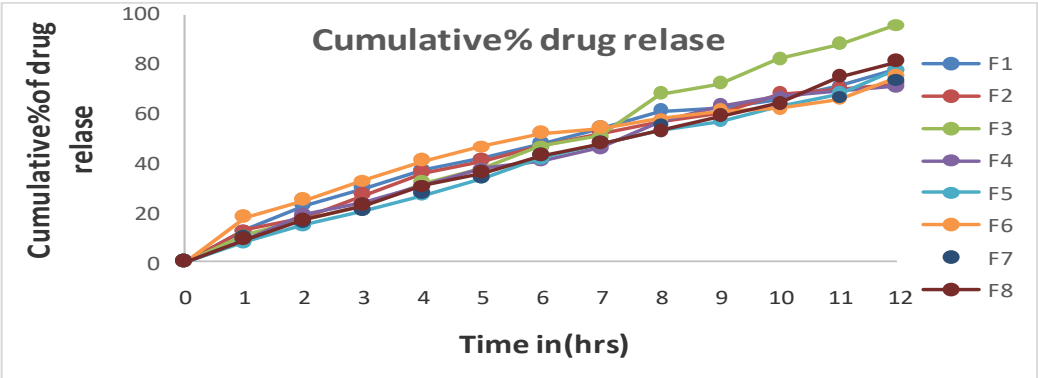
Table No.7: Uniformity content of formulations F1 to F8

Formulations	Uniformity of Content ± SD (%)	Formulations	Uniformity of Content ± SD (%)
F1	98.34±3.02	**F5**	101.67±1.84
F2	102.7±3.0	**F6**	104.08±4.57
F3	96.81±3.06	**F7**	100.05±3.43
F4	105.32±4.05	**F8**	94.87±2.32

Tablets from each batch showed uniformity of content in the range 94.87% to 105.32% which is within pharmacopoeial specifications. All the formulations complies the test for uniformity of content as it found to be within the limit of 91- 109%.

2. *In-Vitro* drug release study

Besides the satisfactory buoyancy, the Floating tablets are required to release Losartan potassium gradually over prolonged period. Hence, they were tested for release kinetics by conducting *in-vitro* dissolution test.



Graph No.4: Graphical representation of *in-vitro* drug release profile of F1-F8 formulation

Kinetic Modeling[14, 15]

In order to predict the drug release mechanism from formulations, kinetics treatment was applied to *in-vitro* drug release data as follows:

Table No. 8:- Kinetic data for the prepared batches

Batch code	Zero Order (R)	First Order (R)	Higuchi Model (R)	Hixson-Crowell (R)	KorsmeyerPeppas (n)
F1	0.9662	0.9942	0.9928	0.9867	0.6866
F2	0.9687	0.9895	0.9900	0.9812	0.6687
F3	0.9823	0.9887	0.9970	0.9967	0.7832
F4	0.9787	0.9954	0.9933	0.9915	0.7204
F5	0.9847	0.9947	0.9976	0.9874	0.8321
F6	0.9564	0.9882	0.9912	0.9806	0.6071
F7	0.9825	0.9882	0.9975	0.9984	0.7852
F8	0.9842	0.9998	0.9981	0.9987	0.7498

n=3

Table No.9:- Best fit model for the prepared batches

Formulations	Best Fit Model	R	K	n (Peppas)
F1	1st Order	0.9942	13.17	0.6866
F2	Higuchi matrix	0.9986	13.83	0.6687
F3	1st Order	0.9887	10.92	0.7832
F4	1st Order	0.9954	10.31	0.7204
F5	1st Order	0.9947	8.46	0.8321
F6	Higuchi matrix	0.9911	19.38	0.6071
F7	1st Order	0.9987	9.84	0.7852
F8	1st Order	0.9998	10.64	0.7498

n=3

The drug release data of all he formulations were fitted into different models namely zero order, first order, Higuchi model, Hixson-Crowell model and Peppas model. The rate constant and r^2 values for zero order, first order, Higuchi, Hixson-Crowell and the n values of Peppas model was considered.

Considering the correlation (r^2) as obtained from the different kinetics equation, the drug release of the formulations was found to follow different models but the best fit model were selected. First order and Higuchi matrix model showed the highest r^2 values compare to other models but, it follows first order for most of the formulations. The release components of "n" for the different formulations ranged from 0.5081s-0.6071.

Table No. 10 Release exponent and drug release mechanism

Release Exponent (n)	**Drug Release Mechanism**
0.5	Fickian diffusion
0.5<n<1.0	Anomolous transport
1.0	Case-II transport
1.0	Super Case-II transport

So, it can be concluded that the formulation purely follows the Anomolous transport mechanism. All the formulation shows first order kinetics as shown in table. The best fit model was found to be first order.

Optimized formulation F3 shows the greater r^2 value than the other, and was best fitted in first order kinetics and value is more than 0.5 which shows the first order release kinetics which met the requirements of sustained drug delivery system.

9. Stability Study

Accelerated stability studies (AST) was carried for optimized formulation F3 by exposing it to 40°C/75% RH for one month and analyzed the sample at the interval of 7,14,21,28 days. The sample was analyzed for drug content, hardness and cumulative percentage drug release.[12]

F3 Formulations

Table No. 11 Accelerated stability studies of F3 formulation

n=3

Parameters	**Days**			
	7	**14**	**21**	**28**
Hardness	4.27±0.12	4.07±0.1	4.3±0.12	4.1±0.11
Drug content (%)	97.67±3.78	96.5±2.54	98.67±1.79	95.98±2.32
In-vitro dissolution study	81.33±0.61	81.00±0.61	81.98±0.42	81.97±0.49

Conclusion

The present study was carried out to develop the floating drug delivery with sustained release of studies showed good percent yield, good buoyancy and release for more than 12hrs, results of the current study clearly indicate, a promising potential of the Losartan potassium floating system as an alternative to the conventional dosage form. However, further clinical studies are needed to assess the utility of this system.

The investigation carried out in this work so far has concluded the following conclusion.

- The value of absorbance maxima 226nm obtain during this study corroborates with the literature value 226nm.
- Melting point of losartan potassium was found to be 278^{0}C Which was within the literature range 283.5-284.5^{0}C
- Floating tablet of losartan potassium was prepared by Carbopol-934.the first order was found to be F1>F2>F3>F4>F5>F6>F7>F8 for F1 toF8 batch.
- All formulation show increasing swelling tablet with in time.
- *In-vitro* release was studied using USP dissolution apparatus II (using paddle) at constant temperature of 37^{0}C stirred at 100rpm, 900ml dissolution media using 0.1N HCL (pH1.2).
- Stability data indicate that there is no decrease in the drug content was observed for a period of 2 month therefore it was ascertain that, the tablet of losartan potassium could be stored for a period of at last 2 years.

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