

FORMULATION AND EVALUATION OF EFFERVESCENT FLOATING TABLETS OF LOSARTAN POTASSIUM

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ABSTRACT

Objective: The Losartan potassium floating tablets were prepared using different low density polymers (Gur gum, HPMC different grades, Carbopol, Xanthan gum, Sodium alginate and Gum acacia) in various proportions for prolongation of gastric residence time and to improve the patient compliance.

Methods: The Losartan potassium floating tablets were prepared by direct compression method. The losartan floating tablets were evaluated for friability, thickness, hardness, weight variation test, drug content, swelling index and *in vitro release*, floating properties and *in vivo* studies. The drug excipients compatibility was evaluated by DSC study.

Results: All the batches showed compliance with pharmacopoeial standards. Formulation F11 containing HPMC K100 showed controlled drug release for 12h (84%) emerging as best formulation. Among all the formulations, formulation F11 which contains HPMC K100 releases the drugs which follow Zero order kinetics via, swelling, diffusion. Percentage swelling index studies reveals that increasing polymer concentration percentage swelling was also increased. An *in vitro* buoyancy study reveals that all batches showed good *in vitro* buoyancy. The DSC study revealed that there was no strong interaction between Losartan potassium and excipients. Stability studies were carried out for optimized formulation F11 (HPMC K100M 35%) according to ICH guidelines. Stability studies ($40\pm 2^{\circ}\text{C}/75\pm 5\% \text{RH}$) for 3 months indicated that Losartan potassium was stable in floating tablets. *In vivo* radiographic studies revealed that F11 tablets remained in the stomach for 480 min, which indicated that GRT was increased by the floating principle and was considered desirable for improving bioavailability of the absorption window drugs.

Conclusion: Hence different low density polymers such as HPMCK100M, Carbopol and Xanthan gum in various proportions can be used to prepare Losartan potassium floating tablets for prolongation of gastric residence time with enhanced patient compliance.

Keywords: Losartan potassium, Floating Tablets, HPMC K100, Carbopol, Xanthan gum, Sustained Release.

INTRODUCTION

Oral sustained or controlled drug delivery system is complicated by restricted gastric residence time. Faster gastrointestinal transit can prevent complete drug release in the absorption window zone and reduce the efficacy dose since the majority of drugs are absorbed in stomach or the upper part of small intestine [1]. One of the most realistic technology for achieving prolonged and predictable drug delivery profile in the GI tract is to control gastric residence time (GRT). The Gastroretentive drug delivery system can be retained in the stomach and assist in improving the oral sustained or controlled delivery of drugs that have an absorption window in a particular region of the gastro-intestinal tract [2, 3]. These systems help in continuously releasing the drug before it reaches the absorption window, thus ensuring optimal bioavailability. Gastric retention improves bioavailability, reduces drug waste, and drugs that are poorly soluble or unstable in the intestinal fluid. It has applications also for local drug delivery to the stomach and upper part of the small intestine [4-7]. There are several approaches that can be used currently to prolong gastric retention time, such as floating drug delivery systems, also known as hydrodynamically balanced systems, swelling and expanding systems, raft system, polymeric bioadhesive systems, modified-shape systems, high-density systems, and other delayed gastric emptying devices [8-10]. Floating drug delivery system has bulk density lower than gastric fluids and thus remains buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric content, the drug is released slowly at a desired rate from the system, which results in increased gastric retentive time and reduces fluctuation in plasma drug concentration [11, 12].

Losartan potassium is an orally active non-peptide angiotensin-II receptor antagonist. It is the first of a new class of drug to be introduced for clinical use in "hypertension" due to selectively blockade of AT₁ receptors and consequent reduced pressure effect of angiotensin II [13, 14]. It belongs to class III is soluble in acidic pH. Losartan having narrow therapeutic index, poor bioavailability (25 to 35%) and short biological half life (1.5 Hrs) [15,16].

Conventional tablets should be administered 3 to 4 times to maintain plasma drug concentration. Administration of Losartan potassium in a floating drug delivery system would be more desirable for antihypertensive effects by maintaining the Losartan plasma concentration well above the minimum effective concentration. Developing a sustained release drug delivery system like floating tablet for Losartan potassium is desirable for an effective treatment of hypertension and is useful to reduce the dosage frequency to improve patient compliance [17]. The aim of the present work is to develop hydrodynamically balanced system or floating drug delivery system for Losartan potassium, which increases the gastric residence time, minimizes the problems associated with oral sustained release dosage forms.

MATERIAL AND METHODS

Materials

Losartan potassium was a gift sample from Aurobindo Pharma Ltd, Hyderabad. HPMC K4M, HPMC K15M, HPMC K100M, HPMC E15, Carbopol and other polymers were received as gift sample from Cadila pharma, India. Talc and magnesium Stearate from S.D. fine chemicals Pvt. Ltd. Microcrystal line cellulose was procured from Signet Chemicals. All other ingredients used were of analytical grade.

Methods

Losartan potassium floating tablets preparation

Losartan potassium floating tablets were formulated by direct compression method. The formulation composition of different batch is shown in Table 1. All the powders passed through 40 mesh sieve. The required quantity of Losartan potassium, various polymers and fillers were mixed thoroughly. Magnesium stearate and talc were finally added as a lubricant and glidant respectively. The blend is directly compressed (8 mm diameter, circular flat faced punches) on a sixteen station rotary tablet punching machine (Cad mach Machinery Ltd., Ahmedabad, India). Each tablet contained 50 mg of Losartan potassium. All the tablets were stored in airtight containers for further study.

Table 1: Composition of Losartan potassium floating tablets

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16	F17	F18
Losartan potassium	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50	50
HPMC K4	40																	
HPMC K15		40																
HPMC K100			40							50	70	90						
HPMC E15				40														
Xanthan Gum					40								50	70	90			
Gum Acacia						40												
Sodium alginate							40											
Gur Gum								40										
Carbopol									40									
Sodium bicarbonate										20	20	20	20	20	20	20	20	20
MCC PH 200	104	104	104	104	104	104	104	104	104	74	54	34	74	54	34	74	54	34
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Talc	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4	4
Total weight	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation of floating tablets

Thickness

Ten randomly selected Losartan potassium floating tablets from each batch were used for thickness determination. Thickness of each tablet was measured by using digital Vernier Caliper (Mitutoyo dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of ten readings, with standard deviations.

Tablet Hardness

The Losartan potassium floating tablets hardness was measured by using Monsanto hardness tester. From each batch the crushing strength of ten floating tablets with known weights were recorded in kg/cm² and average was calculated and presented with standard deviation [18].

Friability

Previously weighed 10 tablets from each batch were taken in Roche friabilator (Roche friabilator, Pharma labs, Ahmedabad, India). After 100 revolutions of friabilator tablets were recovered. The tablets were then made free from dust and the total remaining weight was recorded. Friability was calculated from the following formula.

$$\text{Percentage friability} = \frac{(\text{Initial weight} - \text{Final weight}) \times 100}{\text{Initial weight}}$$

Weight variation test

All formulated Losartan potassium floating tablets were evaluated for weight variation as per USP monograph. Twenty tablets were weighed collectively and individually using an electronic balance. The average weight was calculated and percent variation of each tablet was calculated [19].

Drug content

Twenty tablets were taken and powdered; powder equivalent to one tablet was taken and dissolved in 100 ml of 0.1N HCl buffer. The solution was filtered, suitably diluted and the Losartan potassium content was measured by using UV Spectrophotometer (Elico, India) at 250 nm. Each measurement was carried out in triplicate and the average drug content in the floating tablet was calculated [20].

In-Vitro Drug Release

In vitro drug release studies were carried out using USP XXII dissolution apparatus type II (Electro lab, Mumbai, India) at 37 ± 0.5°C. The study was performed with rotation speed of 50 rpm using 900ml dissolution medium of 0.1N HCl buffer. The samples were withdrawn at predetermined intervals and replaced with an equal volume of buffer. The Losartan potassium release at different time

intervals was measured using an ultraviolet visible spectrophotometer (Elico, Ahmedabad, India) at 250 nm after suitable dilution. The study was performed in triplicate [21, 22].

Release kinetic studies

To find out the mechanism of drug release from Losartan potassium floating tablets, the *in vitro* release data was treated with different kinetic models, namely zero order, first order, Higuchi and Korsemeyer-Peppas. A criterion for selecting the most appropriate model was based on goodness of fit, high regression coefficient value [23, 24].

In Vitro Buoyancy Test

The prepared floating tablets were subjected to *in vitro* buoyancy test by placing them in 250 ml beaker containing 200ml 0.1N HCl (pH 1.2, temp. 37±0.5°C). The time required for the tablet to rise to the surface for floating was determined as the floating lag time and floating duration of all tablets was determined by visual observation [25].

Swelling index study

The extent of swelling was measured in terms of percentage weight gain by the tablet. The swelling index of all formulation was studied. One tablet from each batch was kept in a petridish containing 0.1N HCl buffer. The tablet was removed every two hour interval up to 12 hour and excess water blotted carefully using filter paper. The swollen tablets were re-weighed (W₂). The swelling index (SI) of each tablet was calculated according to the following equation [26].

$$S.I. = \{(W_t - W_0) / W_0\} \times 100$$

Where- W₀ = initial weight, W_t = final weight

DSC Studies

The DSC analysis of Losartan potassium, Drug + HPMC K100M, Drug + Xanthan gum, Drug + Carbopol 940, were carried out using a Shimadzu DSC 60, (Japan) to evaluate any possible polymer drug interaction. Exactly weighed 5 to 6 mg samples were hermetically sealed in aluminium crucible and heated at constant rate of 10°C/min over a temperature range of 40 to 300°C. Inert atmosphere was maintained by purging nitrogen gas at a flow rate of 50ml/min.

Tablets for *in vivo* radiographic studies

Tablets of 3.25±0.07mm thickness and of 200.3±0.81mg mass were prepared. To make the tablet X-ray opaque, incorporation of BaSO₄ was necessary. For this purpose, 25 mg of the Losartan was replaced with BaSO₄ (25 mg BaSO₄ + 25 mg Losartan potassium) and all other ingredients were kept constant. The floating tablets were characterized for hardness, floating lag time and floating duration.

In vivo radiographic studies

The protocol of radiographic studies on healthy human volunteers was approved by the Human Ethical Committee, KLR Pharmacy College, Paloncha, India. The study was conducted on three male healthy volunteers, weighing between 50 to 55 kg and in the age group of 23 ± 2 years. The tablets prepared for radiography (F11) were administered orally with a glass of water. During the study, the subjects were not allowed to eat but water was available *ad libitum*. After ingestion of F11 floating tablets containing barium sulphate, the human volunteers were exposed to X ray photography in the abdominal region. The X ray photographs were taken at 5min, 30min, 2hours, 4hours and 8hours after administration of the tablets. The mean gastric residence time was calculated. The institute's human ethical committee approved the protocol for the study and the protocol number was KLRPC/IHEC/2010-2011/003 [27].

Stability studies

The stability was carried out according to ICH guidelines. The optimized formulation was subjected to stability study at 4 ± 2°C and 75 ± 5 % RH for 90 days. The samples were evaluated for hardness, friability and drug content during stability studies [28, 29].

RESULTS AND DISCUSSION

The physical attributes of the tablet were found to be satisfactory. Typical tablet defects, such as capping, chipping and picking, were not observed. The physicochemical characterizations of different batches of Losartan floating tablets are given in (Table 2). The thickness of the tablets were ranged between 3.17±0.62 to 3.30±0.25 mm. All the batches showed uniform thickness. Weight variations for different formulations were found to be 199±0.92 to 201.6±2.17mg. The average percentage deviation of all tablet formulations was found to be within the limit, and hence all formulations passed the test for uniformity of weight as per official requirement. The hardness of all the Losartan floating tablets formulations were ranged from 4.5±0.3 to 6.5±0.44 kg/cm². The percentage friability of all the formulations was ranged from 0.25% to 0.60 %. In the present study, the percentage friability for all formulations was within the prescribed limits. The percentage of drug content for F1 to F18 was found to be in between 97.22±1.28 to 100.69±0.52 of Losartan which indicates that by direct compression we can get a good quality of Losartan floating tablets.

Table 2: Physico chemical properties of Losartan potassium floating tablets

Formulation code	Hardness (kg/cm ²)	Thickness (mm)	Friability	Weight variation	Drug content	Floating lag time (sec)	Floating time (hrs)
F1	6.5±0.44	3.28±0.08	0.36	200.1±0.88	98.52±1.26	--	--
F2	6.5±0.38	3.26±0.02	0.6	199.5±1.72	97.22±1.28	--	--
F3	6.2±0.40	3.18±0.05	0.52	200.2±1.99	98.58±0.59	--	--
F4	6.4±0.52	3.20±0.04	0.27	201.1±1.85	99.5±0.42	--	--
F5	6.3±0.5	3.24±0.34	0.48	200.2±1.55	97.6±0.71	--	--
F6	6.5±0.3	3.27±0.45	0.42	200±1.94	98.31±1.24	--	--
F7	6.4±0.21	3.28±0.2	0.53	200.8±1.91	99.69±0.88	--	--
F8	6.5±0.52	3.17±0.62	0.49	200.8±2.1	98.31±1.24	--	--
F9	6.2±0.3	3.26±0.59	0.39	199.7±1.49	98.25±1.8	--	--
F10	4.5±0.5	3.36±0.05	0.26	200.6±1.71	97.3±2.31	62	>12
F11	5.0±0.5	3.22±0.08	0.32	201.6±2.17	97.6±0.51	47	>12
F12	4.5±0.5	3.40±0.05	0.25	199±0.92	98.2±1.8	31	>12
F13	5.0±0.32	3.23±0.05	0.51	200±0.91	98.14±1.1	112	>12
F14	5.0±0.5	3.22±0.04	0.42	201±0.92	98.19±0.95	89	>12
F15	4.5±0.5	3.25±0.09	0.34	199±0.92	98.92±0.5	68	>12
F16	4.5±0.3	3.40±0.25	0.39	200.3±2.31	99.11±0.46	120	>12
F17	5.0±0.71	3.26±0.2	0.49	201.3±2.58	100.69±0.52	98	>12
F18	4.5±0.5	3.28±0.02	0.36	200.3±1.49	99.95±1.45	75	>12

All the batches of floating tablets were found to exhibit short floating lag times due to presence of gas generating agent, sodium bicarbonate. The buoyancy properties of various Losartan potassium floating tablets were given in Table 2. The floating lag time of all formulations was less than 2 minutes and floating duration was more than 12 hours. In order to evaluate different hydrophilic matrix polymers used to prepare Losartan potassium floating matrix tablets, nine different polymers viz., HPMC K4M, HPMC K15M, HPMC K100M, HPMC E15, sodium alginate, Carbopol, Xanthan gum, guar gum and gum acacia were selected and dosage forms were prepared and their individual drug release profiles were evaluated. It was observed that the type of polymer influences the drug release pattern as shown in Fig. 1.1-1.5.A significantly higher

rate and extent of drug release was observed from the batches F1, F2 and F4 compared with F3 batch and similarly a highest rate of drug release was observed with F6, F7 and F8 compared with F5 and F9 batches. HPMC K4M, HPMC K15M, HPMC E15, guar gum and gum acacia polymers were thus found to be unsuitable for desired floating matrix tablets of Losartan.

However, that the formulation F3, F5 and F9 (containing HPMC K100M, xanthan gum and carbopol) was found to be good for floating matrix tablets. It was finally decided to evaluate formulation containing HPMC K100, xanthan gum and carbopol to examine the effect of floating aid (NaHCO₃) on different concentrations of above polymers.

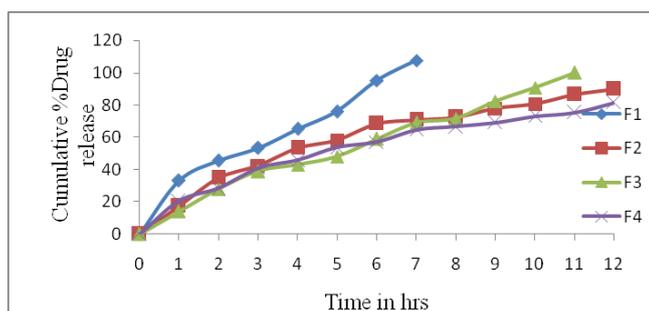


Fig. 1.1: Comparative release profile of formulation F1 to F4

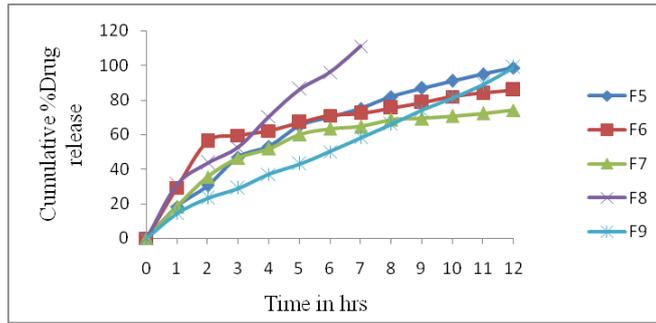


Fig. 1.2: Comparative release profile of formulation F5 to F9

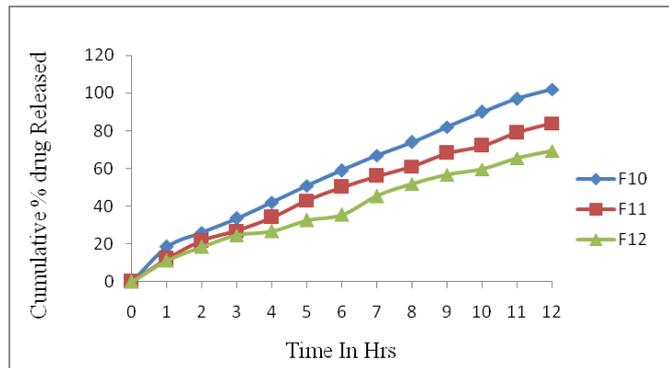


Fig. 1.3: Comparative release profile of formulation F10 to F12

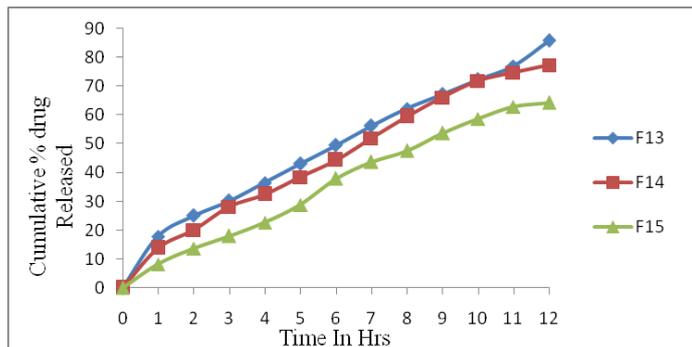


Fig. 1.4: Comparative release profile of formulation F13 to F15

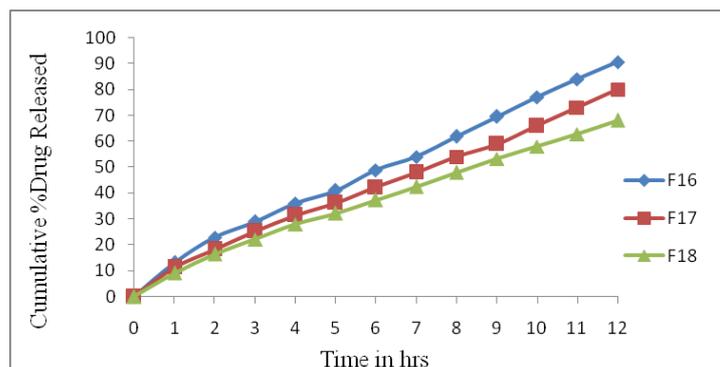


Fig. 1.5: Comparative release profile of formulation F16 to F18

The *in vitro* dissolution data were fitted in different kinetic models viz. zero order, first order, Higuchi and Korsmeyer-Peppas equation (Table.3). The zero-order plots were found to be fairly linear as indicated by their high regression values for

F11 formulation. The release exponent *n* was between 0.357 to 0.860 ($0.5 < n < 0.89$), which appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion.

Table 3: Kinetic parameter of Losartan potassium floating tablets

Formulation code	Zero order	First order	Higuchi	Korsmeyer peppas (n)
F1	0.969	0.812	0.960	0.601
F2	0.912	0.808	0.982	0.610
F3	0.987	0.766	0.955	0.747
F4	0.917	0.948	0.993	0.548
F5	0.935	0.881	0.988	0.660
F6	0.748	0.791	0.932	0.357
F7	0.808	0.752	0.958	0.513
F8	0.981	0.875	0.962	0.670
F9	0.996	0.757	0.939	0.760
F10	0.991	0.817	0.960	0.704
F11	0.988	0.671	0.950	0.727
F12	0.989	0.731	0.963	0.770
F13	0.983	0.723	0.971	0.628
F14	0.986	0.713	0.959	0.713
F15	0.991	0.666	0.936	0.860
F16	0.994	0.731	0.948	0.747
F17	0.995	0.686	0.947	0.766
F18	0.994	0.661	0.766	0.782

Swelling study was performed on all the batches (F10 to F18) for 12 hours. The result of swelling index was shown in fig 2. Formulation containing carbopol polymer showed higher swelling in dices as compared with other formulation containing HPMC K100 and xanthan gum.

The direct relationship was observed between swelling index and polymer concentration and type, and as polymer concentration increases in floating matrix tablets, swelling index was found to increase.

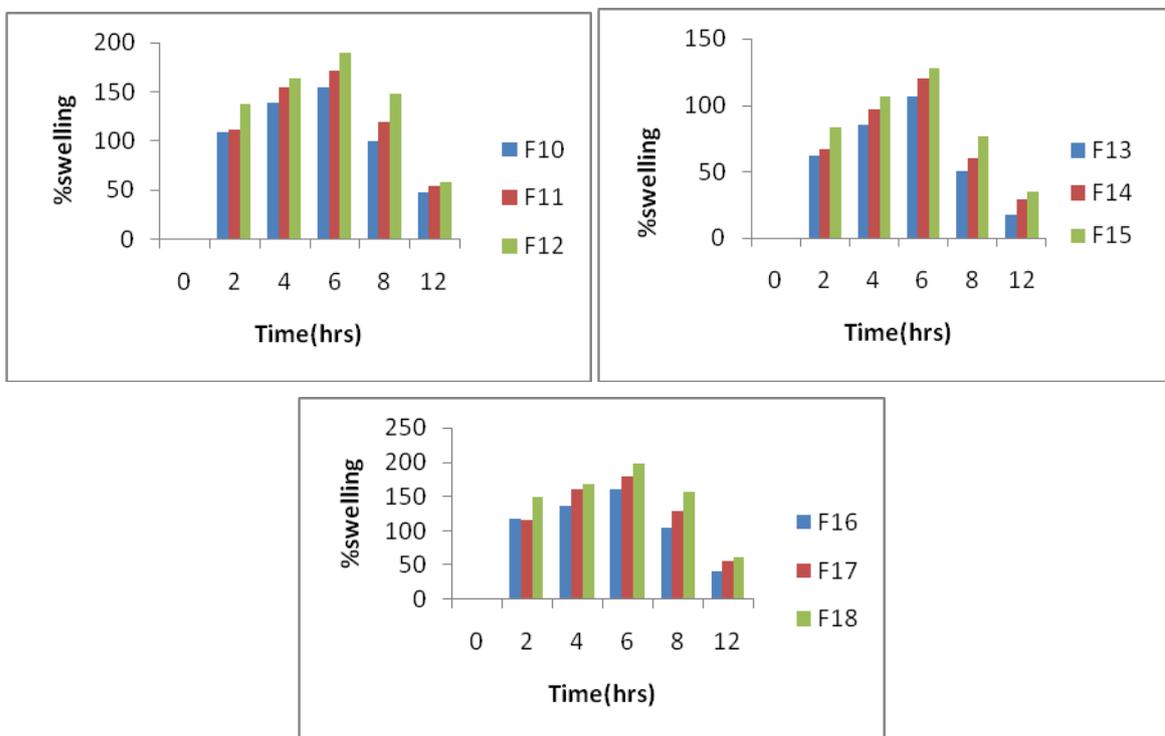


Fig. 2: Percentage swelling of formulations with HPMC K100M, Xanthan gum and Carbopol

DSC study was conducted on the selected formulations. DSC thermogram of pure Losartan shows sharp endothermic peak at 183.44 °C. Similar endothermic peaks were obtained at 179.3°C for the formulations prepared with HPMC K100 M, at 181.9°C for the formulation prepared with carbopol and 188°C for the formulation prepared with xanthan gum. Presence of all peaks indicates that all ingredients are compatible with Losartan potassium and there is no incompatibility between the selected

ingredients. Thermogram of different formulations and drug are shown in figure 3.

The BaSO₄-containing floating tablets showed a floating lag time of 121 ± 4sec, hardness of 4.5±0.5 kg cm², thickness of 3.25±0.07mm and of 200.3±0.81mg. The X-ray images shows the tablet residence in stomach for about 8hours clearly indicating the good floating property. The figures 4 shown below describe the X-ray images showing the floating tablet at different time intervals in the stomach.

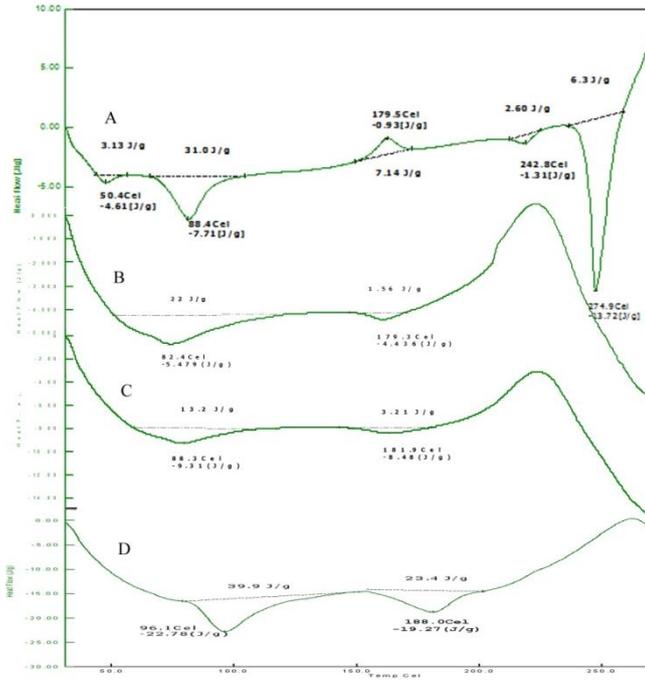


Fig. 3: DSC Thermograms of A. Pure Drug B. Formulation containing HPMC K100 C. Formulation containing Xanthan gum D. Formulation containing Carbopol

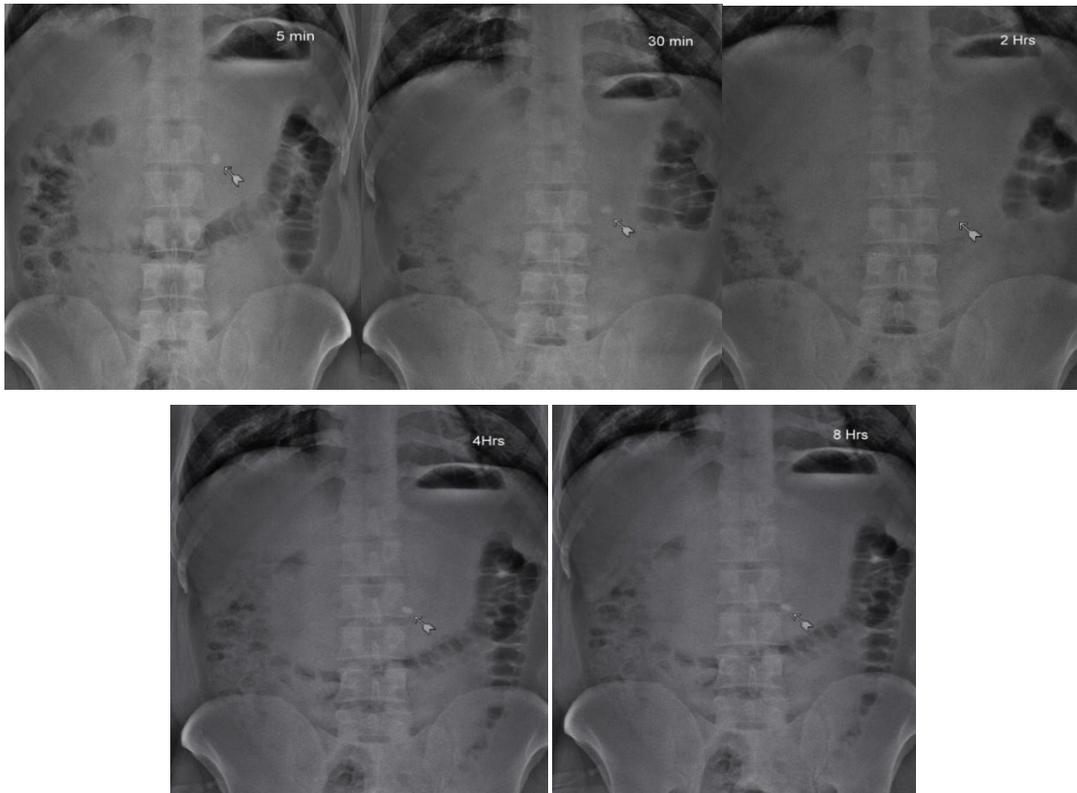


Fig. 4: Radiographic images showing the floating tablet in the stomach at different time periods (the tablet is indicated with an arrow). Images were taken after: a) 5 min, b) 0.5 h, c) 2 h, d) 4 h, and e) 8h after tablet administration

F11 formulation was selected for the stability studies. The results of stability study were shown in Table 4. The Losartan potassium floating tablets did not show any significant change in physicochemical parameters and other tests. Thus, it was found that the floating tablets of Losartan (F11) were stable under short term storage conditions for at least 3 months.

Table 4: Stability study results of formulation F11

Formulation code	Stability period	Hardness (Kg/cm ²)	Friability	Drug content %
F11	0	5.0 ± 0.5	0.32	100.4 ± 0.51
	30 Days	4.9 ± 0.4	0.41	99.24 ± 0.74
	60 Days	6.7 ± 0.7	0.49	98.16 ± 0.61
	90 Days	4.5 ± 0.5	0.58	97.23 ± 0.54

Mean ± SD; n = 3

F-11 formulation was selected for the stability studies. The results of stability study were shown in Table 5. The Losartan floating tablets did not show any significant change in physicochemical parameters (Table 5). Thus, it was found that the floating tablets of Losartan potassium (F11) were stable under short term storage conditions for at least 3 months.

CONCLUSION

The present work was to study the effect of various low density polymers on *in vitro* release rate from floating tablet of Losartan. The floating drug delivery was a promising approach to achieve a prolongation of gastric residence time of drug. Different types of low density matrix forming polymers HPMC K4M, HPMC K15M, HPMC K100M, HPMC E15, Carbopol, Xanthan gum, Gur gum, Sodium alginate and Gum acacia were studied. Sodium bicarbonate was added as a gas generating agent to improve the floating capacity of tablet. Formulation F11 containing HPMC K100 showed controlled drug release for 12h (84%) emerging as best formulation. The cumulative percentage drug was decreased by increase in polymer concentration. Mechanism of drug release of optimized formulation F-11 found to be zero order non-Fickian diffusion. DSC studies proved that no chemical interaction in Losartan potassium and polymer of the developed floating tablets. The stability studies were carried out according to ICH guideline and selected F11 formulation were stable at 40°C/75% RH up to 3 months. *In vivo* radiographic studies revealed that F11 tablets remained in the stomach for 480 min, which indicated that GRT was increased by the floating principle and was considered desirable for improving bioavailability of the absorption window drugs. Thus, 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 for patients suffering from hypertension.

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