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Formulation and In-Vitro Evaluation of Gastro Retentive Floating Drug Delivery System of Losartan Potassium.

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ABSTRACT

The objective of the study was to formulate and evaluate gastro retentive floating drug delivery tablets of Losartan potassium. It is an orally active non-peptide angiotensin -II receptor antagonist, used in the treatment of hypertension due to mainly blockade of AT1 receptors. The main reason for low therapeutic effectiveness of Losartan potassium is its narrow therapeutic index, poor bioavailability (25-35%), and short biological half life (1.5-2h). Conventional tablets should be administered 3-4 times to maintain plasma drug concentration. So, to increase therapeutic efficacy, reduce frequency of administration sustained release floating matrix tablets of Losartan potassium were prepared. Present study demonstrates the formulation of sustained release floating matrix tablets of Losartan potassium with various grades of hydroxyl propyl methylcellulose to restrict the drug release preferably in upper part of intestine and to improve its bioavailability and to provide constant drug plasma levels thereby improving the patient compliance. Losartan potassium showed maximum absorbance at 256 nm so absorbance was measured at the same wavelength and found to obey Beer lamberts law in the concentration range of 10-40 mcg/ml. In the pre formulation study of IR spectra of pure drug with the different polymers showed no interaction, Differential scanning calorimetry experiments were carried out to find out the presence of any interaction among drug and the excipients. Pure drug and individual polymers were subjected to the study and no interactions were observed .12 formulation of sustained release of Losartan potassium were prepared and they were examined for physical properties and appearance like hardness, thickness, weight variation, thickness, hardness, friability uniformity of drug content floating lag time floating duration time and *in-vitro* drug release studies . I n the study all the powder blends showed good flow ability angle of repose below 25.98±0.07°- 31.724±0.15°, compressibility index was found in the range of 12.5±0.16- 16.92±1.9 g/cm^3 Weight variation 297.2±1.19-301.52±2.73mg, hardness 5.9±0.2-7±0.2kg/cm^{2,} thickness 4.506±0.04-4.86±0.03, friability 0.91-0.41, floating time <12hrs in *vitro* release for all formulations were found to be 61.18 -99.02.

Keywords: Losartan Potassium, Gastroretentive dosage forms and HPMC K4M.

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INTRODUCTION

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

Drug exhibiting absorption from only a particular portion of GI tract or showing difference in absorption from various regions of GI tract are said to have regional variability in intestinal absorption. Such drugs show absorption window which signifies the regions of GI tract from where absorption primarily occurs. Drug released from the CRDDS after the absorption window has been crossed goes waste with no or negligible absorption occurring. This phenomenon drastically decreases the available drug for absorption, after release of drug from CRDDS. The CRDDS possessing the ability of being retained in the stomach are called GRDDS and they can help in optimizing the oral controlled delivery of drugs having absorption window by continuously releasing drug prior to absorption window, for prolonged period of time thus ensuring optimal bioavailability.

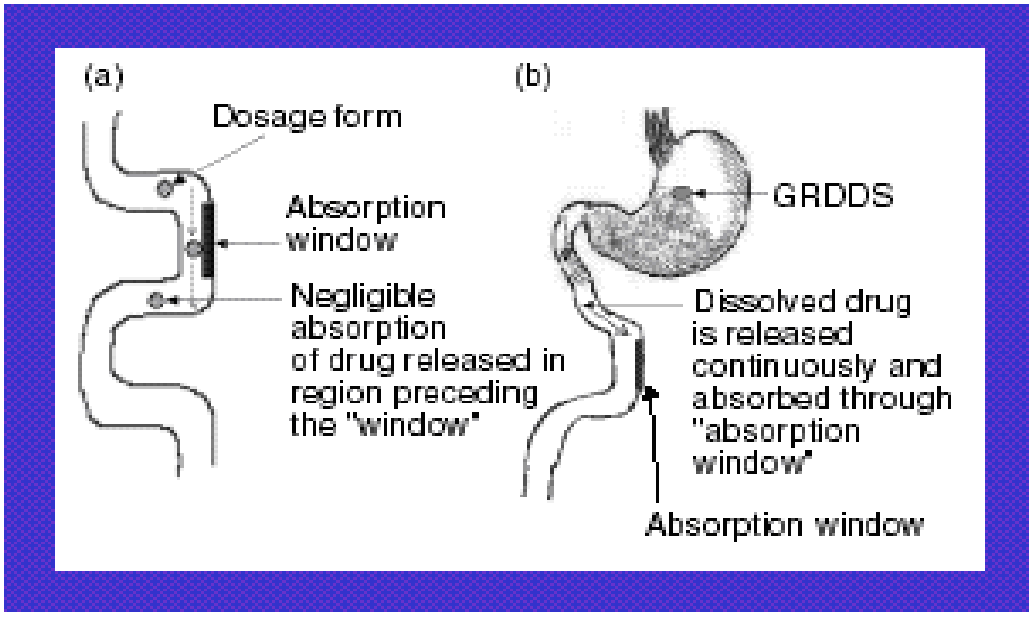

Figure 1: GI tract showing difference in absorption from various regions.

The time a dosage form takes to traverse the stomach is usually termed the 'emptying rate'. Gastric emptying of pharmaceuticals is highly variable and is dependent on dosage form. The process of gastric emptying occurs during fasting as well as fed states. However, the pattern of motility is distinct in the 2 states. In the fasting state, it is characterized by an inter digestive series of electrical events that cycle both through stomach and small intestine every 2 to 3 hours. This activity is called the inter digestive myoelectric cycle or migrating myoelectric cycle (MMC).

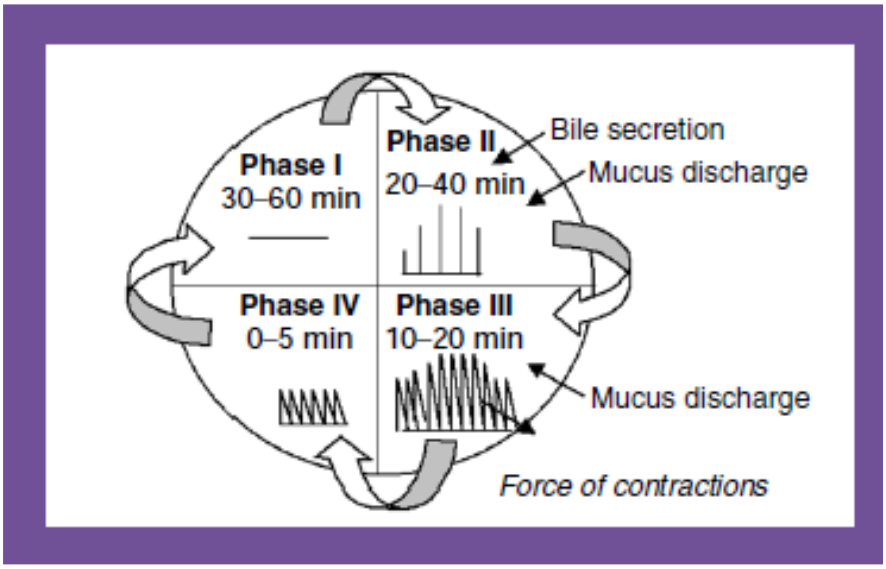

Figure 2: Motility patterns of the GIT in the fasted state

Phase I (Basal phase) lasts from 30 to 60 minutes with rare contractions.

Phase II (Preburst phase) lasts for 20 to 40 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.

Phase III (Burst phase) lasts for 10 to 20 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.

Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

The motor activity in the fed state is induced 5-10 min after ingestion of a meal and persists as long as food remains in the stomach. It consists of regular and frequent contractions. These contractions are not as severe as those in the third phase of the fasted motility pattern. The G.I. Transit times of dosage forms in the various segments of the G.I.

MATERIALS AND METHOD

Microcrystalline cellulose and Losartan potassium were obtained from Dr. Reddy's Lab's, Hyderabad HPMC K4M, HPMC K15M and HPMC K100M was obtained from Colorcon Asia Pvt. Limited and sodium bicarbonate from Merck specialties Pvt. Limited

PREPARATION OF FLOATING MATRIX TABLETS OF LOSARTAN POTASSIUM

Accurately weighed quantities of polymer and MCC were taken in a mortar and mixed geometrically, to this required quantity of Losartan potassium was added and mixed slightly with pestle. Accurately weighed quantity of Sodium bicarbonate was taken separately in a mortar and powdered with pestle. The powder is passed through sieve no 40 and mixed with the drug blend which is also passed through sieve no 40. The whole mixture was collected in a plastic bag and mixed for 3 minutes. To this Magnesium stearate was added and mixed for 5 minutes, later Talc was added and mixed for 2 minutes. The mixture equivalent to 400mg was compressed into tablets with 10 mm round concave punches at a hardness of 6 kg/cm^2.

Table 1: Composition of floating matrix tablets of Losartan potassium

Ingredients (weight in mg)	Formulations F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Losartan Potassium	50	50	50	50	50	50	50	50	50	50	50	50
Methocel K4M	63	75	88	100	-	-	-	-	-	-	-	-
Methocel K15M	-	-	-	-	63	75	88	100	-	-	-	-
Methocel K100M	-	-	-	-	-	-	-	-	63	75	88	100
Sodium bicarbonate	27	27	27	27	27	27	27	27	27	27	27	27
Avicel pH 102	150	138	125	113	150	138	125	113	150	138	125	113
Talc	5	5	5	5	5	5	5	5	5	5	5	5
Magnesium Stearate	5	5	5	5	5	5	5	5	5	5	5	5

Standard graph of Losartan Potassium in 0.1N HCl

Stock solution of the Losartan potassium was prepared by transferring an accurately weighed amount of 100mg of into 100 ml volumetric flask, containing 0.1N HCl to dissolve. Then, the volume was made up to the mark with 0.1N HCl. From this stock solution, necessary dilutions were made to give concentration ranging from 0-15 µg/ml. The absorbance of each test solution was measured at λ_{max} of i.e. 256 nm using UV/ Visible spectrophotometer against 0.1 N HCl as blank and plotted graphically to give the standard graphs Losartan potassium.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared (FTIR) Spectroscopy

The Fourier transform infrared (FTIR) spectra of samples were obtained using FTIR spectrophotometer (Perkin Elmer). Pure drug, individual polymers and optimised formulations were subjected to FTIR study. About 2–3 mg of sample was mixed with dried potassium bromide of equal weight and compressed to form a KBr disk. The samples were scanned from 400 to 4000 cm^{-1}.

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) experiments were carried out to find out the presence of

any interaction among drug and the excipients. Pure drug, individual polymers and optimised formulations were subjected to the study. Five to ten milligrams was taken in the pierced DSC aluminum pan and scanned in the temperature range of 25–220 °C. The heating rate was 10°C/min; nitrogen served as purged gas and the system was cooled down by liquid nitrogen. The differential thermal analyzer (DSC 822, Mettler Toledo, Switzerland) was used for this purpose.

Pre-compression parameters

Angle of Repose: The angle of repose is the constant, three-dimension angle (relative to horizontal base) assumed by a cone like pile of material formed by any of several different methods. When the angle of repose exceeds 50degrees, the flow is rarely accepted for manufacturing purpose.

Bulk Density: The bulk density was determined by transferring the accurately weighed sample of powder to the graduate cylinder. The initial volume and weight was noted. Ratio of weight of the sample was calculated by using the following formula.

Bulk Density =Mass /Bulk volume.

Tapped Density: Weighed powder sample was transferring to a graduated cylinder and was placed on the tap density apparatus, was operated for fixed number of taps(100).The tapped density was determined by the following formula.

Tapped Density =Mass/Tapped volume.

Percentage compressibility: Based on the apparent bulk density and tapped density,the percentage compressibility of the bulk drug was determined by the following formula

% Compressibility=Tapped density-Bulk density×100/ Tapped density.

Hauser's Ratio: It is measured by the tapped density to bulk density.

Hauser's Ratio= Tapped density/Bulk density

POST COMPRESSION PARAMETERS

Tablet thickness:

Randomly 5 tablets were taken from each formulation trial batch and their thickness was determined by using screw gauge.

Weight variation test:

20 tablets were randomly selected from each formulation trial batch and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight.

Measurement of tablet hardness:

Hardness of 10 tablets was found using Monsanto hardness tester, mean and standard deviation were computed and reported. It is expressed in kg/cm ^{2}.

Friability:

10 tablets were weighed and placed in Roche friabilator where the tablets were exposed to rolling and repeated shocks resulting from free falls within the apparatus. The Friabilator was operated at 25 rpm for 4 mins. After 100 revolutions, tablets are removed, deducted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

***In vitro* buoyancy studies**

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al*. The tablets were placed in a 100 ml beaker containing 0.1N hydrochloric acid. The time required for the tablet to rise to the surface and float was determined as ***floating lag time***. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the ***total floating time***.

***In vitro* Drug Release Studies**

The *in vitro* drug release study was performed for the single and multiple-unit tablets using USP Type II dissolution apparatus using 900ml of 01.N HCl medium 50 rpm 37±0.5ºC sampling volume 5ml and sampling time0.5, 1, 2, 3, 4, 6, 8, 10, 12 hours .At predetermined time intervals samples (5 ml) were collected and replenished with same volume of fresh media. The drug content in the samples was estimated using UV-spectrophotometer at 256 nm.

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly (assuming that area does not change and no equilibrium conditions are obtained) can be represented by the following equation.

$$W_0 - W_t = K_0 t$$

Where W_0 is the initial amount of drug in the pharmaceutical dosage form, W_t is the amount of drug in the pharmaceutical dosage form at time t and k is proportionality constant.

First order kinetics

This type of model to analyse drug dissolution study was first proposed by Gibaldi and Feldman and later by Wagner. The relation expressing this model:

$$\text{Log } Q_t = \text{Log } Q_0 + K_1 t/2.303$$

Where Q_t is the amount of drug released in time t, Q_0 is initial amount of drug in the solution and K_1 is the first order release rate constant.

Korsmeyer Peppas model

Korsmeyer developed a simple semi empirical model, relating exponentially the drug release to the elapsed time (t).

$$Q_t/Q_\alpha = K_k t^n$$

Where K_k is a constant incorporating structural and geometric characteristic of the drug dosage form and n is the release exponent, indicative of the drug release mechanism.

Table 2: kinetic model

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

Higuchi Model

This is the most widely used model to describe drug release from pharmaceutical matrices. A linear relationship between the square root of time versus concentration indicates that the drug release follows strict Fickian diffusion.

$$Q_t = K_H t^{1/2}$$

Where Q_t = the amount of drug released at time t and

K_H = the Higuchi release rate

RESULTS AND DISCUSSION

Calibration Curves of Losartan Potassium

An UV- Spectrophotometric method was used for estimation of Losartan potassium. A solution of Losartan potassium (10µg/ml) was scanned in the wavelength range of 200-300 nm and found to have maximum absorption (λ_{max}) at 256 nm. The standard plot of Losartan Potassium was prepared in 0.1 N HCl (pH 1.2). The standard graph showed good linearity with R^2 value 0.9942.

DRUG-EXCIPIENT COMPATIBILITY STUDIES

Fourier Transform Infrared (FTIR) Spectroscopy

Potential chemical interaction between drug and polymer may change the therapeutic efficacy of the drug. To investigate the possibility of chemical interaction between drug and polymer FTIR spectra of pure Losartan potassium and polymers used in formulations were analysed over the range 400–4000 cm^{-1}. The IR spectrum of pure Losartan Potassium showed strong absorption bands at wave numbers of 3434 cm^{-1}, 2956 cm^{-1}, 1577 cm^{-1}, 1460 cm^{-1} and 997 cm^{-1} attributable to Cyclic amines, C-H stretching, C=O stretching, O-H bending and Chlorine respectively. FTIR spectra of the pure drug and polymers formulations displayed all the characteristic bands, without any significant spectral shift. This suggested that there was no potential chemical interaction between the components of the formulations.

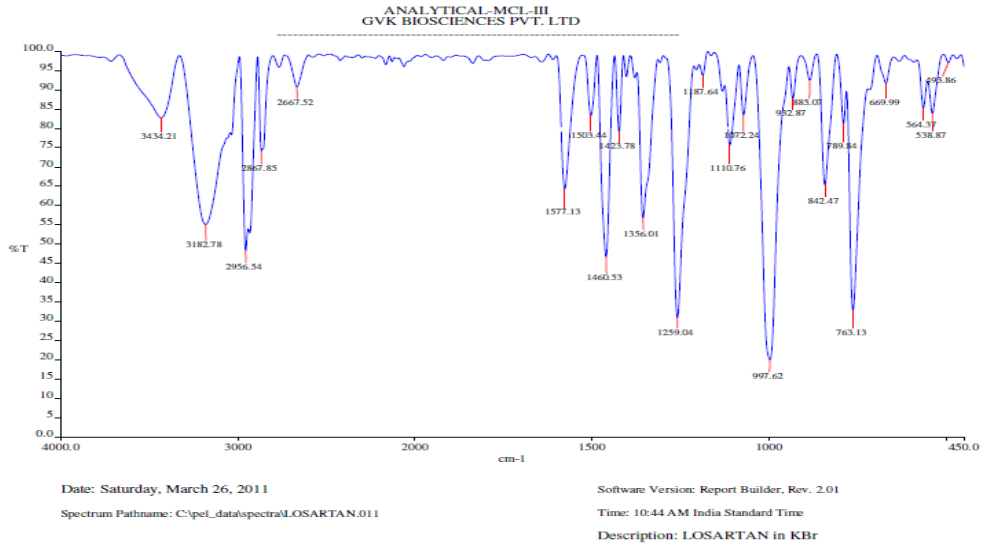

Figure 3: FTIR spectra of pure drug.

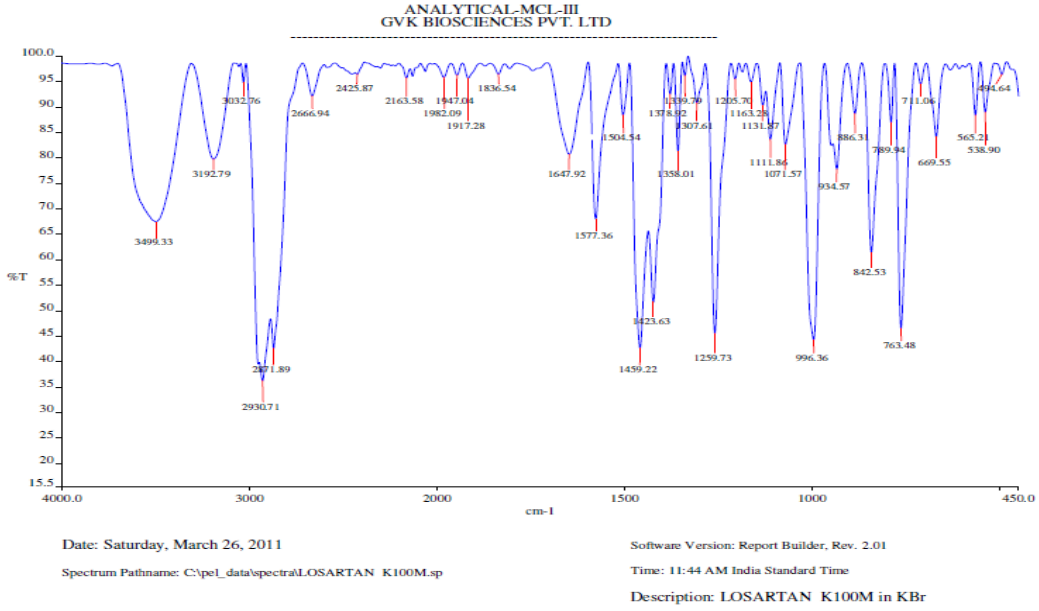

Figure 4: FTIR spectra of pure drug and polymers used in formulations.

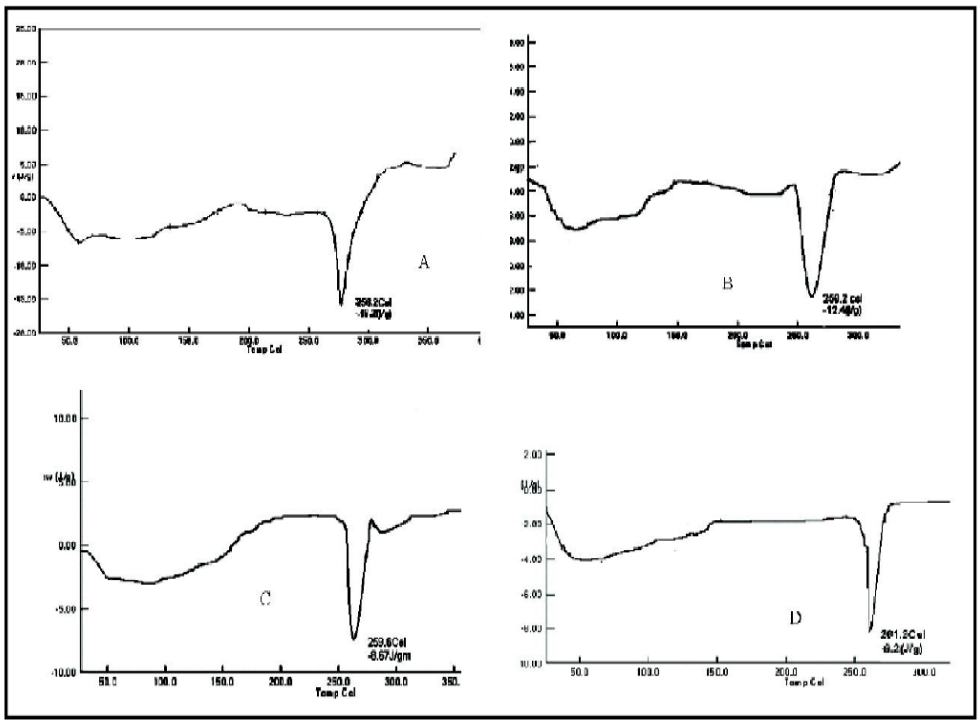

Figure 5: DSC thermograms of pure drug and polymers used in the formulations.

A) Losartan potassium, B) Losartan potassium with HPMC K4, C) Losartan potassium with HPMC K15, D) Losartan potassium with HPMC K 100.

Table 3: Micrometric properties.

Formulation code	Angle of repose () ± SD	Bulk density(gm/ml)± SD	Tapped density(gm/ml)± SD	Carr's Index(%) ± SD	Hausner's ratio ± SD
F1	26.54 ± 0.05	0.56±0.01	0.64±0.01	12.5±0.16	1.14±0.03
F2	28.42±0.04	0.55±0.03	0.66±0.04	16.66± 0.25	1.2±0.05
F3	26.89±0.05	0.54±0.01	0.65±0.04	16.92±1.9	1.2±0.02
F4	25.98±0.06	0.54±0.02	0.64±0.06	15.62±0.53	1.18±0.004
F5	27.45±0.04	0.58±0.03	0.67±0.04	13.43±0.18	1.15±0.01
F6	25.42±0.13	0.53±0.04	0.63±0.04	15.87± 0.24	1.18±0.05
F7	30.51±1.33	0.53±0.02	0.64±0.05	17.18±0.012	1.2±0.002
F8	28.18±0.07	0.55±0.02	0.66±0.06	16.66± 1.12	1.2±0.004
F9	25.98±0.07	0.54±0.03	0.65±0.04	16.92± 0.62	1.2±1.13
F10	31.72± 0.15	0.56±0.02	0.65±0.03	13.84±0.42	1.16±0.03
F11	28.67±0.03	0.54±0.01	0.65±0.03	16.92±0.45	1.2±0.004
F12	27.12±0.06	0.53±0.02	0.62±0.02	14.51±0.08	1.16±0.005

Table 4: Physical parameters of floating matrix tablets of Losartan Potassium

Formulation code	Weight variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Assay (%)
F1	298.38±3.84	6.5±0.3	4.84±0.05	0.32	98.23
F2	301.52±2.87	6.6±0.5	4.76±0.06	0.19	99.65
F3	299.23±2.73	6.8±0.4	4.86±0.03	0.26	99.12
F4	302.6±2.13	6±0.5	4.76±0.04	0.33	98.44
F5	300.19±3.48	7±0.2	4.63±0.06	0.29	99.23

F6	301.71±2.3	6.8±0.4	4.65 ±0.06	0.22	98.63
F7	297.2±1.19	6.8±0.5	4.68±0.05	0.37	99.65
F8	299.46±2.27	5.9±0.2	4.55±0.25	0.23	98.65
F9	300.67±3.84	6.8±0.5	4.506±0.04	0.29	98.45
F10	298.38±3.84	6.5±0.3	4.62±0.07	0.37	99.64
F11	300.52±2.87	6.8±0.5	4.78±0.02	0.41	98.12
F12	298.23±2.73	6.7±0.2	4.60±0.04	0.24	99.72

Table 5: Floating properties of floating matrix tablets

Formulation code	Floating Lag time(sec)	Total floating time (hrs)
F1	95	>12
F2	103	>12
F3	87	>12
F4	97	>12
F5	89	>12
F6	99	>12
F7	101	>12
F8	98	>12
F9	94	>12
F10	79	>12
F11	84	>12
F12	89	>12

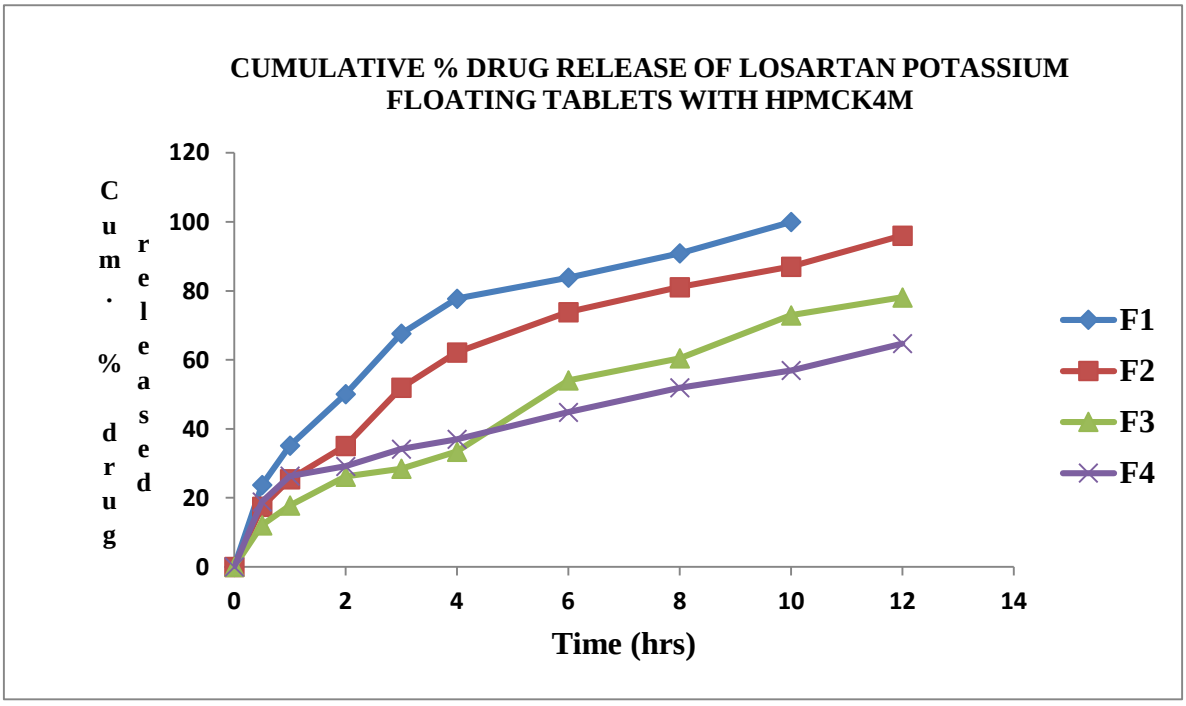

Figure 6: Cumulative drug release of Losartan potassium floating tablets with HPMCK4M

Table 6: Regression coefficient (R^2) values of floating matrix tablets for different kinetic models

Formulation	Zero-order	First-order	Higuchi model	Korsmeyer Peppas	
				R^2	N
F1	0.8341	0.4187	0.975	0.6021	0.354
F2	0.8966	0.4875	0.9886	0.5516	0.41
F3	0.9677	0.5741	0.9733	0.4216	0.413
F4	0.8865	0.4161	0.9827	0.2377	0.218
F5	0.9282	0.465	0.997	0.563	0.37
F6	0.9105	0.4563	0.9972	0.5122	0.357
F7	0.9592	0.5653	0.9834	0.431	0.4163
F8	0.8742	0.4099	0.9745	0.213	0.206
F9	0.914	0.4317	0.9972	0.5072	0.319
F10	0.9107	0.4531	0.989	0.4248	0.3257
F11	0.9502	0.539	0.9938	0.4422	0.4065
F12	0.8986	0.4885	0.9938	0.3205	0.322

CONCLUSION

Sustained release floating matrix tablets of Losartan potassium were successfully prepared with hydrophilic polymers like HPMC K4M, HPMC K15M and HPMC K100M by simple direct compression method. FTIR and DSC studies showed no incompatibility between drug, polymer and various excipients used in the formulations. The DSC curve of Losartan Potassium showed a single endothermic peak at 176.11°C corresponding to its melting point (MP 172–174°C). The DSC curves of all the formulations showed the sharp endothermic peak of the drug at 179.17°C (FS4), 174.69°C (FS8), 180.17°C (FS12), 175.81°C (FM5), 176.92°C (FM10), 174.93°C (FM15), 177.57°C (FH6), 178.46°C (FH8) and 175.84°C (FH12). In all formulations, endothermic peak of drug was well preserved with slight changes in terms of broadening or shifting towards the lower or higher temperature. It has been reported that the quantity of material used, especially in drug–excipient mixtures, affects the peak shape and enthalpy. Thus, these minor changes in the melting endotherm of drug could be due to the mixing of drug and excipient, which lowers the purity of each component in the mixture and may not necessarily indicate potential incompatibility. Thus, it was concluded that Losartan Potassium was compatible with all the excipients used in the formulation. Formulated tablets gave satisfactory results for various evaluation parameters like tablet dimensions, hardness, weight variation, friability, content uniformity, *in vitro* buoyancy properties and *in vitro* drug release. The tablets of formulations F2, F6 and F9 gave better controlled drug release and floating properties in comparison to the other formulations. The drugs release from all tablets was sufficiently sustained and fickian transport of drugs from tablets was

confirmed as the release exponent value was less than 0.5. The release from all the formulation was followed diffusion controlled release followed by zero order which was confirmed by higher correlation coefficient values for Higuchi and release exponent values of Korsemeyer Peppas equations. All the formulations followed Higuchi profiles with R^2 values more than 0.9, followed by Zero order which account for the diffusion-controlled release from the formulations. Formulation F2 was considered as best formulation among all the formulations as it showed good buoyancy properties (floating lag time: 103 sec and floating time >12 hrs) and sustained the drug release for desired period of time (12 hrs).

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