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FORMULATION AND *IN VITRO* EVALUATION OF LOSARTAN POTASSIUM FLOATING TABLETS

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ABSTRACT

The purpose of this investigation was to prepare a gastroretentive drug delivery system of Losartan Potassium. Floating tablets of Losartan Potassium were prepared employing three different grades of HPMC K100, HPMC K15M and HPMC K4M by effervescent technique. Sodium bicarbonate was incorporated as a gas-generating agent. Drug-exipient compatibility studies were conducted using DSC curves and FTIR spectra. The floating tablets were evaluated for physical characteristics viz. uniformity of weight, hardness, friability, drug content, swelling index, *in vitro* buoyancy. Further, tablets were evaluated for *in vitro* release characteristics. 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. HPMC K100 based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited prolonged drug release profiles while floating over the dissolution medium. *In vitro* release mechanism was evaluated by subjecting the dissolution data to various kinetic models and the drug release was found to best fit both the Higuchi model and the Fickian transport, followed by first order kinetics.

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Key Words

Losartan Potassium,
Gastroretentive dosage forms,
Swelling index, *In vitro* buoyancy,
HPMC

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. The transit of a drug (formulation) through the gastrointestinal (GI) tract will determine how long a compound will be in contact with its preferred absorptive site. In humans, the small intestine transit time is reasonably constant: at around three hours for a drug formulation (or a meal) to pass from the stomach to the ileo-caecal junction ^[1]. Transit through the colon is much longer and can be 20 hours or more. Hence, the time a drug will have in its absorption window can be relatively short, more so if the drug is preferentially absorbed in the proximal small intestine (e.g. jejunum) rather than the small bowel. Consequently, the bioavailability of a drug, which is largely or exclusively absorbed from the upper GI tract, will be affected by factors that change GI tract. Rapid gastrointestinal transit could result in incomplete drug release from the device above the absorption zone leading to diminished efficacy of the administered dose ^[2].

Gastroretentive systems can remain in the gastric region for several hours and hence significantly prolong the overall gastrointestinal transit time of drugs. Prolonged gastric retention improves bioavailability, reduces drug waste, and improves solubility for drugs that are less soluble in a high pH environment. It has applications also for local drug delivery to the stomach and proximal small intestines. Gastroretention helps to provide better availability of new products with new therapeutic possibilities and substantial benefits for patients ^[3]. Therefore, different approaches have been proposed to retain the dosage form in the stomach including bioadhesive systems ^[4], swelling and expanding systems ^[5,6] floating systems ^[7,8] and delayed gastric emptying devices ^[9]. The principle of buoyant preparation offers a simple and practical approach to achieve increased gastric residence time for the dosage form and sustained drug release.

Losartan potassium 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.

MATERIALS AND METHODS

Losartan Potassium was obtained as a gift sample from Dr.Reddy's Laboratories (Hyderabad, India). Hydrophilic polymers HPMC K4M, HPMC K15M and HPMC K100M were obtained from Colorcon Asia Pvt. Limited (Goa, India). Microcrystalline cellulose (MCC) was obtained from Dr. Reddy's Laboratories (Hyderabad, India). All the polymers received were of pharmaceutical grade and were used as received. Other materials used were of analytical grade or better.

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 and optimized 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 and optimized 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 25–256 °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 (Mettler Toledo) was used for this purpose.

Flow properties of precompression blend

The flow properties of powder blends (before compression) were characterized in terms of angle of repose, Carr index and Hausner ratio. For determination of angle of repose (θ), the powder blend was poured through the walls of a funnel, which was fixed at a position such that its lower tip was at a height of exactly 2.0cm above hard surface. The powder was poured till the time when upper tip of the pile surface touched the lower tip of the funnel. The \tan^{-1} of the (height of the pile / radius of its base) gave the angle of repose.

Powder was poured gently through a glass funnel into a graduated cylinder cut exactly to 10 ml mark. Excess powder was removed using a spatula and the weight of the cylinder with powder required for filling the cylinder volume was calculated. The cylinder was then tapped from a height of 2.0cm until the time when there was no more decrease in the volume. Bulk density (ρ_b) and tapped density (ρ_t) were calculated. Hausner ratio (HR) and Carr index (IC) were calculated according to the two equations given below:

$$\text{Hausner ratio, HR} = \rho_t / \rho_b$$

$$\text{Carr index, IC} = 100 (\rho_t - \rho_b) / \rho$$

Fabrication of floating matrix tablets

Drug (Losartan Potassium) and polymer were passed through sieve no. 40 separately. The drug was then mixed with the polymer and other ingredients, in the weight proportion mentioned in **Table 1**. Magnesium stearate and talc were uniformly mixed with the above mixture, and compressed on a multiple punch tableting machine (Cadmach Machinery Ltd., Ahmedabad, India.

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

Total tablet weight: 300mg

EVALUATION OF FORMULATIONS

Physical characterization

The fabricated tablets were characterized for weight variation (n=20), hardness (n=10) (Pfizer hardness tester), friability (n=20) (Roche friabilator) and thickness (n=10) using a screw-gauge.

Drug content of tablets

Six tablets from each batch were weighed and powdered. Powder equivalent to the average weight of the tablet was accurately weighed and transferred into a 100-mL volumetric flask and dissolved in a suitable quantity of 0.1N HCl. The solution was made up to the mark and mixed well. A portion of the sample was filtered and analyzed by a UV/ Visible Spectrophotometer (Shimadzu UV-2561, Japan) at 254 nm.

In vitro buoyancy studies

The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa *et al* [12]. 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 (FLT)**. The duration of time for which the dosage form constantly remained on the surface of medium was determined as the **total floating time (TFT)**.

Determination of swelling index

The swelling index of tablets was determined in 0.1N HCl (pH 1.2) at room temperature. The swollen weight of the tablet was determined at predefined time intervals. The swelling index was calculated by the following equation:

$$\text{Swelling index} = (W_t - W_0) / W_0$$

Where, W_0 is the initial weight of tablet, and W_t is the weight of tablet at time t.

In vitro drug release studies

Dissolution tests were conducted in triplicate for all the batches using USP dissolution test apparatus (type II). The release studies were performed at 50 rpm in 900 ml 0.1N HCl (pH 1.2) at $37 \pm 0.5^\circ\text{C}$. Five ml aliquots were withdrawn at

predefined intervals, and the volume of the dissolution medium was maintained by adding the same volume of fresh prewarmed dissolution medium. The absorbance of the withdrawn samples was measured spectrophotometrically at 254 nm. Experimental results were expressed as mean \pm SD (standard deviation).

Kinetic modeling of drug release

The suitability of several equations, which are reported in the literature to identify the mechanism for the release of drug, was tested with respect to the release data. The dissolution profile of all the batches was fitted to various models such as zero-order, first-order [13], Higuchi [14] and Korsmeyer-Peppas [15,16] models to ascertain the kinetic modeling of drug release. The data were evaluated according to the following equations:

First order model:

$$\ln M_t = \ln M_0 + K_1 t$$

Zero-order model:

$$M_t = M_0 + K_0 t$$

Higuchi model:

$$M_t = M_0 + K_H t^{0.5}$$

Korsmeyer–Peppas

model:

$$M_t = M_0 + K_k t^n$$

Where M_t is the amount of drug released in time t, M_0 the initial amount of drug, K is respective release constant and n is the release exponent, which characterizes the mechanism of drug release. The magnitude of the exponent 'n' indicates the release mechanism as Fickian diffusion, as case II transport, or as anomalous transport. In the present study (cylindrical shape) the limits considered were n=0.5 (indicates a classical Fickian diffusion-controlled drug release) and n=0.9 (indicates a case II relaxational release transport: polymer relaxation controls drug delivery). Values of n between 0.5 and 0.9 can be regarded as indicators of both phenomena (transport corresponding to coupled drug diffusion in the hydrated matrix and polymer relaxation) commonly called anomalous non-Fickian transport. Values of n greater than 0.89 indicates a

super case II transport, in which a pronounced acceleration in solute release by a film occurs toward the latter stages of release experiments, resulting in a more rapid relaxation-controlled transport.

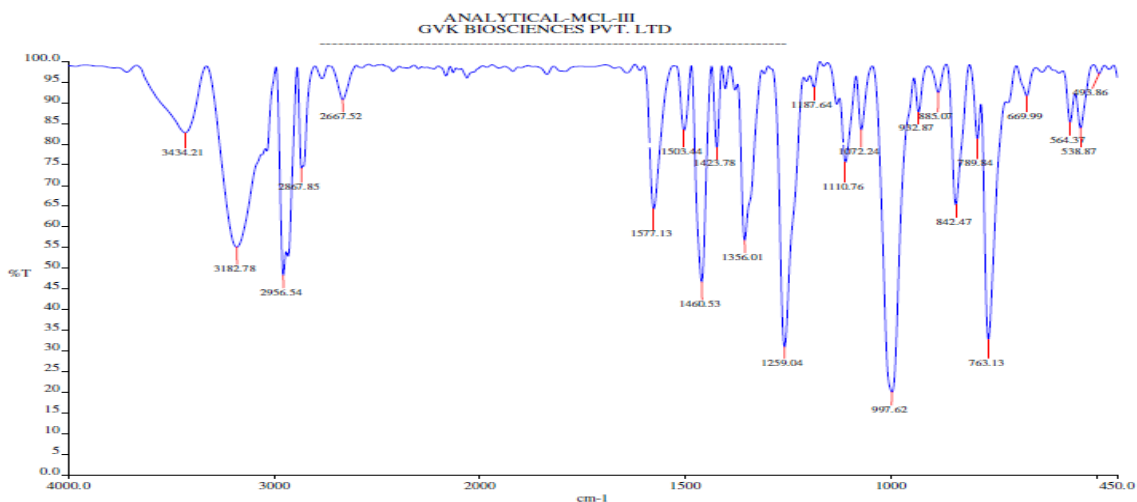
RESULTS AND DISCUSSION

Drug-exipient 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 optimised formulations were analyzed over the range 400–4000 cm^{-1} . The IR spectrum of pure Losartan Potassium (**Figure 2**) showed strong absorption bands at wave numbers of 3434 cm^{-1} , 2956 cm^{-1} , 1577 cm^{-1} , 1460 cm^{-1} and 997 cm^{-1} corresponding to Cyclic amines, C-H stretching, C=O stretching, O-H bending and Chlorine respectively. FTIR spectra of the optimised formulations displayed all the characteristic bands of both drug and excipients, without any significant spectral shift. This suggested that there was no potential chemical interaction between the components of the formulations.



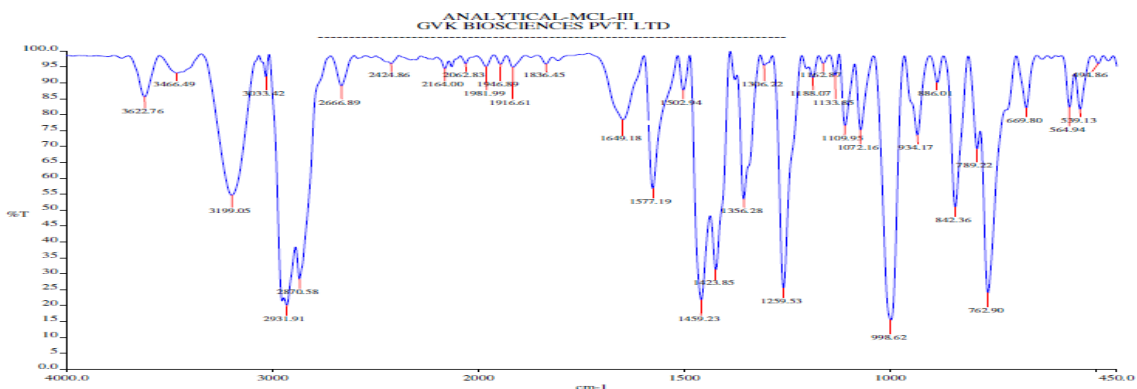
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Description: LOSARTAN in KBr



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Description: LOSARTAN K4 in KBr

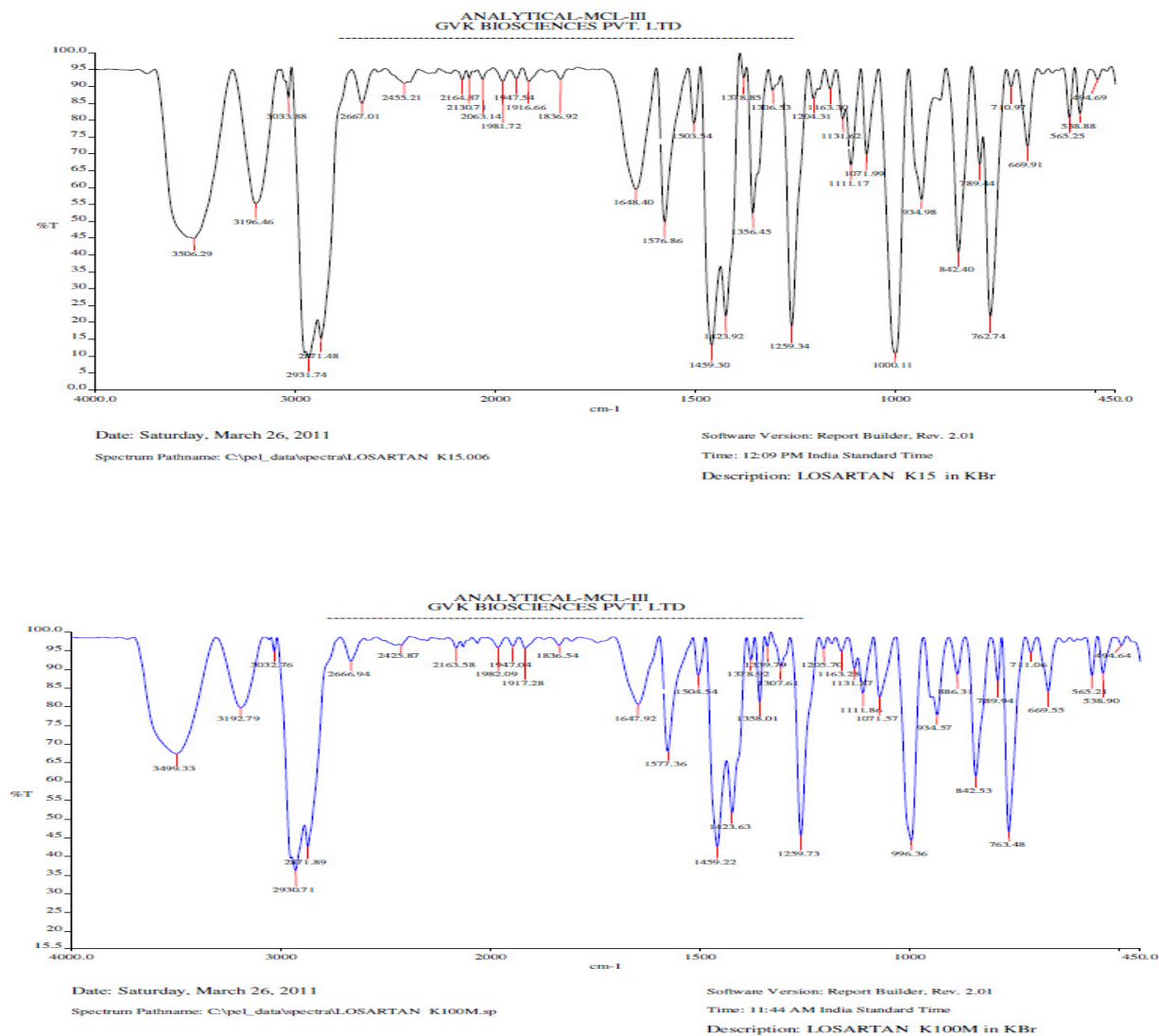


Figure 2: FTIR spectra of pure drug and optimized formulations. LOSARTAN POTASSIUM- pure drug and F3, F7 and F11 are optimized formulations.

Differential Scanning Calorimetry (DSC)

The thermal properties of the drug and the mixture of drug and excipients are of important interest since this can help to assess the interaction among different components of the formulations. The DSC curve of Losartan Potassium (**Figure 3**) showed a single endothermic peak at 176.11°C corresponding to its melting point (MP 172-174°C). The DSC curves of optimised formulations showed the sharp endothermic peak of the drug at 179.17°C (F3), 174.69°C (F7) and 180.17°C (F11). In optimised formulations, endothermic peak of drug was well

preserved with slight changes in terms of broadening or shifting towards the lower 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 is compatible with all the excipients used in the formulation.

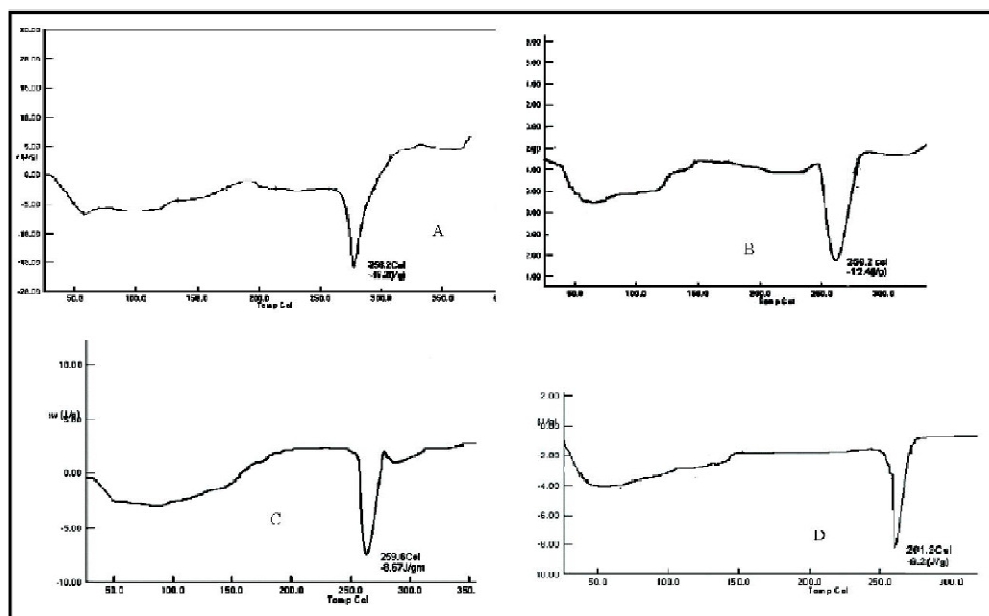


Figure 3: DSC curves of pure drug and optimized formulations. Losartan Potassium- pure drug and optimized formulations.

Flow Properties of Precompressed powder

The powder blends prepared for compression of floating tablets were evaluated for their flow properties (**Table 2**). Angle of repose was in the range of 23.6° to 28.2° . Bulk density ranged between 0.351 to 0.462 gm/cm^3 .

Tapped density ranged from 0.409 to 0.543 gm/cm^3 . Carr index was found to be 12.55 to 15.49 and Hausner ratio ranged from 1.143 to 1.181 . These values indicate that the prepared powder blends exhibited good flow properties.

Table 2: Flow properties of powder blends of floating matrix tablet formulations

Formulation	Angle repose of	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Hausner's Ratio	Carr's Index (%)
F1	23.8°	0.352	0.416	1.181	15.49
F2	27.5°	0.423	0.49	1.158	13.55
F3	24.5°	0.373	0.431	1.155	13.43
F4	25.4°	0.384	0.446	1.161	13.84
F5	25.5°	0.401	0.462	1.152	12.9
F6	27.4°	0.421	0.49	1.163	13.55
F7	25.4°	0.365	0.431	1.18	14.7
F8	26.9°	0.351	0.409	1.165	13.04
F9	28.2°	0.416	0.48	1.153	13.33
F10	27.1°	0.446	0.51	1.143	12.5

F11	23.6°	0.462	0.543	1.175	14.81
F12	25.7°	0.431	0.503	1.167	14.3

Physical characterization

Various physical parameters of prepared tablets were given in **Table 3**. The weight of the tablet varied between 397.2 mg to 401.71 mg for different formulations with low standard deviation values, indicating uniformity of weight. The variation in weight was within the range of $\pm 5\%$ complying with pharmacopoeial specifications. The hardness for different formulations was found to be between 5 and 5.9 kg/cm² indicating satisfactory mechanical strength. The friability was below 1% for all the formulations, which is an indication of good mechanical resistance of the tablet. The % drug content (assay) varied from 99.23% to 99.83% for

different formulations, indicating content uniformity in the prepared batches.

In vitro buoyancy studies

All the batches of tablets were found to exhibit short floating lag times due to presence of gas generating agent, sodium bicarbonate. Trials were carried out to optimize the concentration of sodium bicarbonate and tablets containing 9 % of sodium bicarbonate with respect to tablet weight were found to exhibit good floating properties and this concentration of sodium bicarbonate was used in all the formulations. The buoyancy properties of various formulations were given in **Table 3**. The floating lag time of all formulations was less than 2 minutes and floating duration was more than 12 hours.

Table 3: Physical parameters and *in vitro* buoyancy properties of various formulations of floating matrix tablets of LOSARTAN POTASSIUM

Formulation	Weight variation (mg)	Hardness (kg/cm ²)	Friability (%)	Assay (%)	FLT (Sec)	TFT (hrs)
F1	398.38±3.84	5.5±0.3	0.32	98.23	95	10
F2	401.52±2.87	5.6±0.5	0.19	99.65	103	>12
F3	399.23±2.73	5.8±0.4	0.26	99.12	87	>12
F4	402.6±2.13	5±0.5	0.33	98.44	97	>12
F5	400.19±3.48	5.9±0.2	0.29	99.23	89	11
F6	401.71±2.3	5.8±0.4	0.22	98.63	99	>12
F7	397.2±1.19	5.8±0.5	0.37	99.83	101	>12
F8	399.46±2.27	5.9±0.2	0.23	98.65	98	>12
F9	400.67±3.84	5.8±0.5	0.29	98.45	94	8
F10	398.38±3.84	5.5±0.3	0.37	99.64	79	>12
F11	400.52±2.87	5.8±0.5	0.41	98.12	84	>12
F12	398.23±2.73	5.7±0.2	0.24	99.72	89	>12

Swelling index

The percentage swelling obtained from the water uptake studies of the formulations is shown in **Figure 4**. The formulations with HPMC K4M, HPMC K15M and K100M showed the swelling and retained tablet integrity. Complete swelling was achieved at the end of 8 h, then diffusion and erosion takes place. The

formulation F12 containing K100M (12% w/w that of drug) shows the higher swelling compared to that of the formulations containing K4M, K15M. The swelling index of the tablets increased with an increase in the polymer viscosity grades. Maximum swelling for all the polymers, at different concentrations occurred at about 8 hrs.

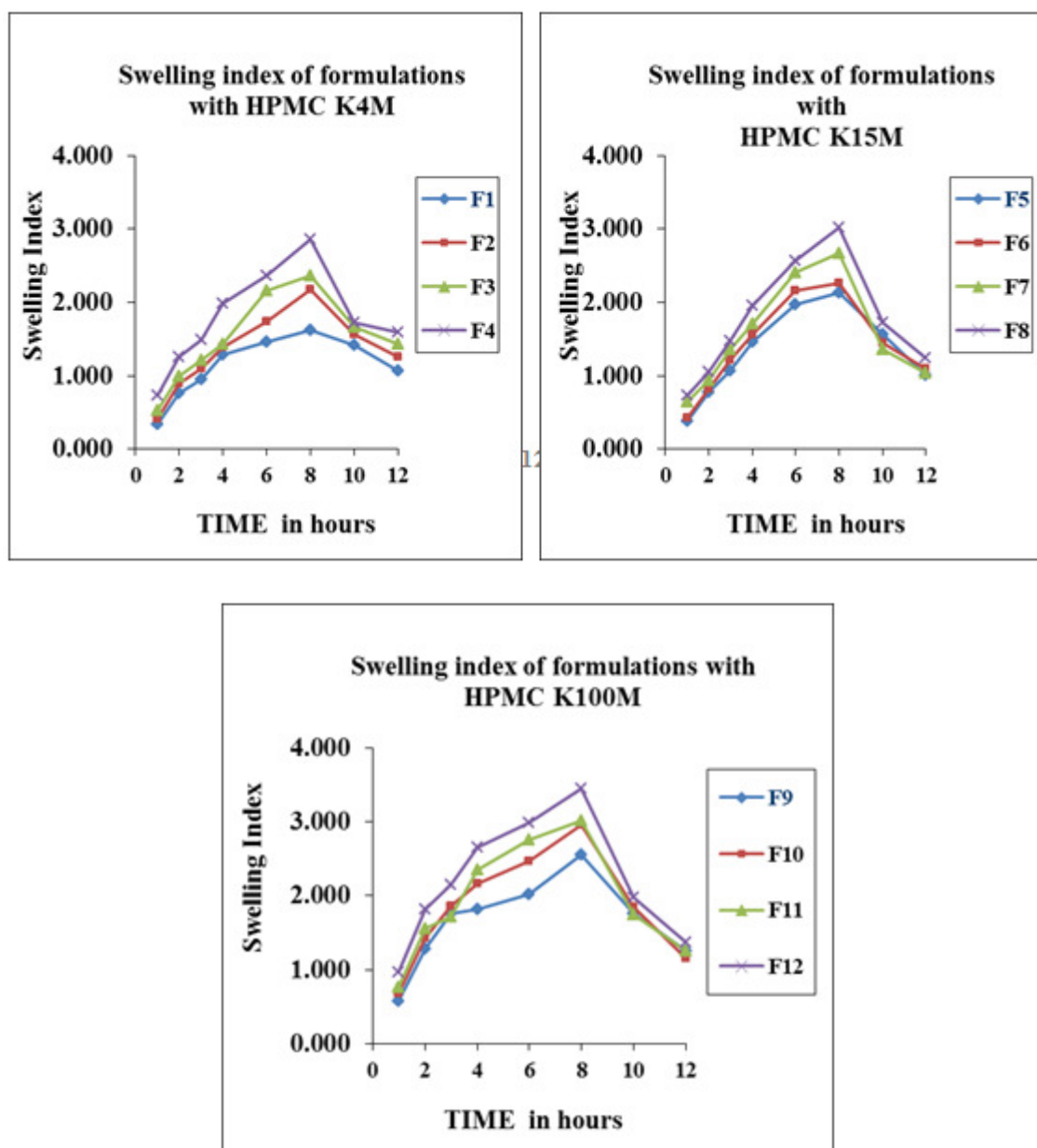


Figure 4: Results of Swelling Index Studies of Losartan Potassium floating matrix tablets in 0.1N HCl

***In vitro* drug release studies**

Three different grades of HPMC polymer were used to prepare floating matrix tablets. It was observed that the grade of polymer influences the drug release pattern. A significantly higher rate of drug release was observed from the formulations based on HPMC K100M when compared to HPMC K15M and HPMC K4M. The release profiles of prepared tablets were given in **Figure 5**.

Formulations F1, F2, F5, F6, F9 and F10 were unable to sustain the drug release for the desired period of time

(up to 12 hours), all these formulations released the total drug within 8-10 hours. Formulations F3, F7 and F11 were sustained the drug release up to 12 hours and were selected as optimized formulations. Formulations F4, F8 and F12 released 81.74%, 82.84% and 77.99% of drug within 12 hours. The difference in the drug release profiles of various formulations was due to the presence of different concentrations of polymer.

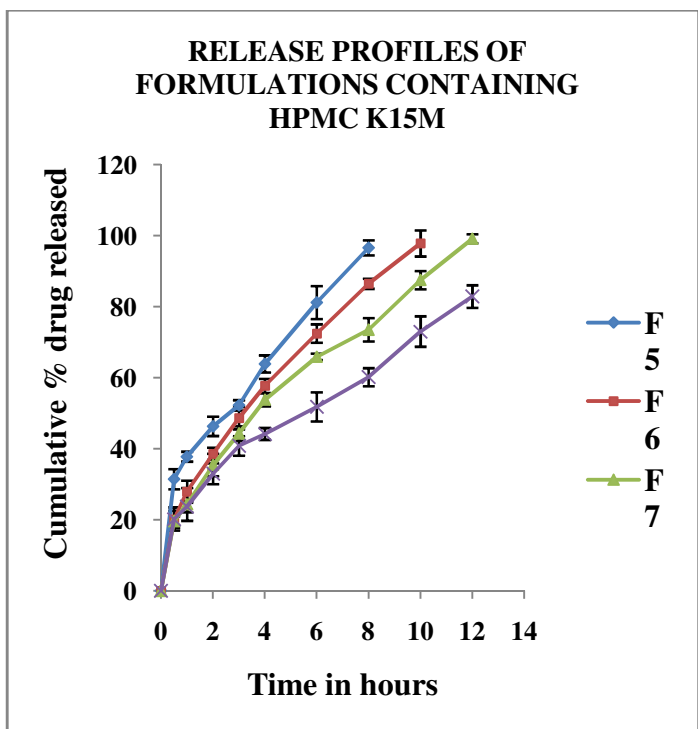
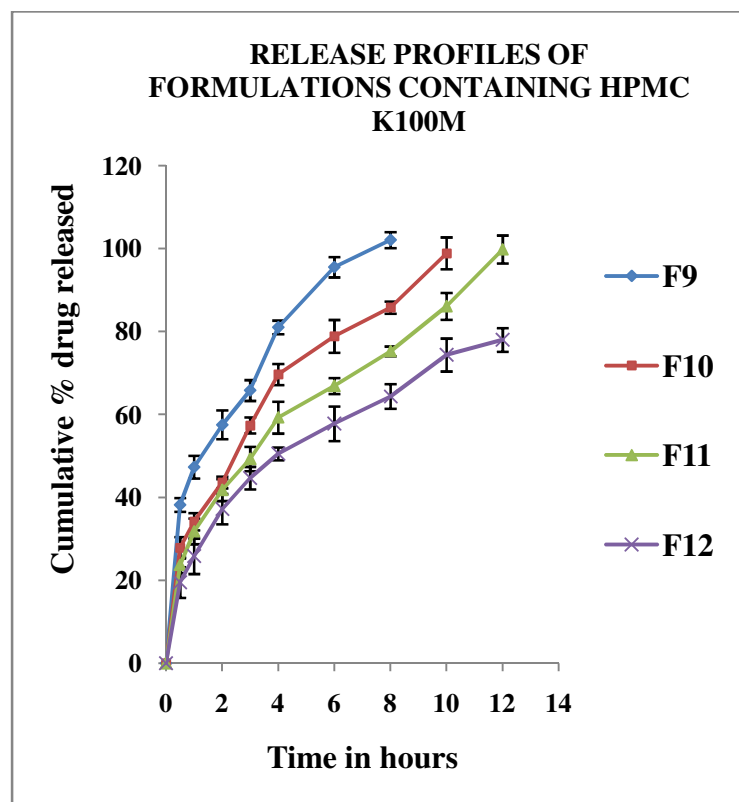
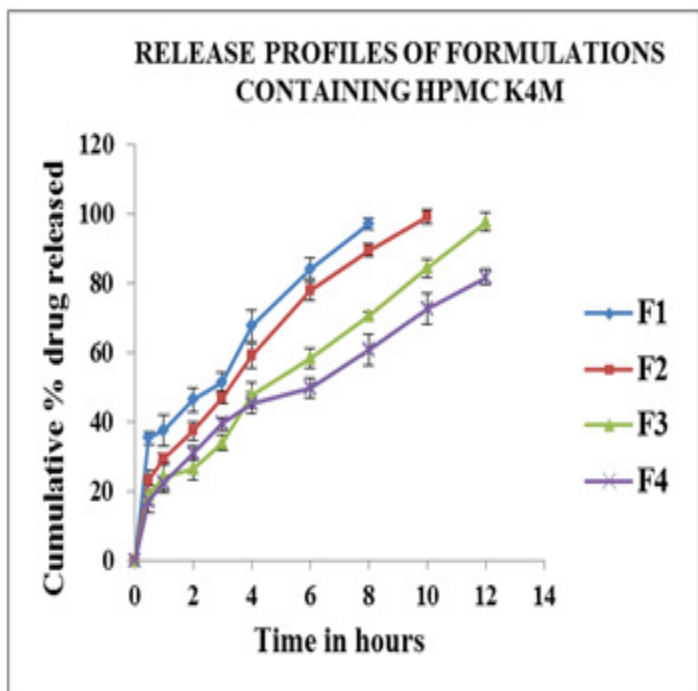


Figure 5: *In vitro* drug release profiles of various formulations (mean \pm SD)

Kinetic modeling of drug release

The data obtained from *in vitro* dissolution studies was fitted in different models viz. zero order, first order, Higuchi model and Korsmeyer's equation (Table 4). The correlation coefficient value (r^2) was used as indicator of the best fitting, for the models considered. The zero order plots were found to be fairly linear as indicated by their high regression values ($r^2 = 0.972$ to 0.998). The results reveal that all formulations of FDDS were best fitted in the Higuchi model. The mechanism of drug release from the formulations was found to be diffusion controlled as seen from r^2 values of Higuchi model. To confirm the exact mechanism of drug release from these tablets, the data were fitted according to Korsmeyer's equation. The 'n' values for all the formulations were less than 0.5 which suggest that the drug release from floating tablets followed Fickian transport mechanism.

Formulation	zero-order (r ²)	First-order (r ²)	Higuchi model (r ²)	Korsmeyer Peppas (n)
F1	0.984	0.491	0.991	0.394
F2	0.972	0.478	0.993	0.328
F3	0.998	0.441	0.99	0.292
F4	0.989	0.533	0.97	0.379
F5	0.986	0.497	0.973	0.41
F6	0.985	0.449	0.992	0.289
F7	0.995	0.454	0.995	0.313
F8	0.994	0.483	0.996	0.37
F9	0.989	0.455	0.994	0.334
F10	0.977	0.429	0.992	0.301
F11	0.997	0.394	0.982	0.247
F12	0.973	0.429	0.993	0.316

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