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Design and Evaluation of Floating Matrix Tablets of Lisinopril Dihydrate

Prasantha kumari Mantada*[1], CH. Kalyani[2]
1.A.S.N.Pharmacy College, Tenali, Guntur (Dt), Andhra Pradesh, India-522201.
2.Kakinada Institute of Technology & Science, Divili, East Godavari (Dt), Andhra Pradesh, India.

ABSTRACT

Lisinopril dihydrate (LSP) primarily used in the treatment of hypertension, congestive heart failure and heart attack. Floating matrix tablets of LSP prepared with a view of prolonging gastric residence time with a controlled release mechanism to achieve improved patient compliance, least side effects, better drug therapy and all aspects of an ideal drug delivery system. Floating matrix tablets were prepared by wet granulation technique using varying concentrations of different grades of gel forming polymers like HPMC K100, HPMC K15, HPMC K4M with sodium bicarbonate as gas generating agent and evaluated for the physico-chemical parameters, floating lag time, total floating time, in vitro dissolution study and swelling studies. The physico-chemical properties of all the formulations were found to be within the prescribed official limits. FTIR study reveals that there was no interaction between drug and excipients. The amount of drug released from various FDDS formulations was found to be in the order of HPMC K100M > HPMC K15M > HPMC K4M. From among all the formulations, the formulation LF-9 with 30% HPMC K15M showed the best result in terms of the required lag time (82±5 sec) and floating duration of 12 h and releasing 99.5% of the drug in 12 h and is considered as the ideal formulation. The dosage form can control the release, avoid dose dumping and extend the duration of action of a drug with prolonged floating time.

Keywords: Lisinopril Dihydrate, Floating matrix tablet, HPMC K100, HPMC K15, HPMC K4M

*Corresponding Author Email: prasanthi.mantada@gmail.com
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INTRODUCTION

Gastro retentive dosage forms have the potential use as controlled release systems. For prolonged gastric retention, floating drug delivery is of particular interest, for drugs which, act locally in the stomach, primarily absorbed in the stomach or upper intestine, poorly soluble at alkaline pH, have a narrow window of absorption, and are unstable in the intestinal pH. A number of techniques are designed to prolong the gastric residence time. These systems have been classified according to the basis of the principle of gastric retention [1].The concept of Floating Drug Delivery System (FDDS) was described in the literature as early as 1968[2]. FDDS have a bulk density less than gastric fluids and so remain buoyant in the stomach without affecting the gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system. After release of drug, the residual system is emptied from the stomach. This results in an increased gastric residence time and a better control of fluctuations in plasma drug concentration [3].

Buoyant delivery systems are prepared with swellable polymers or polysaccharides e.g. HPMC and effervescent components, e.g. sodium bicarbonate and citric or tartaric acid [4] or matrices containing chambers of liquid that gasify at body temperature[5]. The matrices are fabricated so that upon contact with gastric fluid, carbon dioxide is liberated by the acidity of gastric contents and is entrapped in the matrix of hydrocolloid. This produces an upward motion of the dosage form and maintains its buoyancy.

Lisinopril, a synthetic peptide derivative, is chemically described as (S)-1-N_2-(1-Carboxy-3-phenylpropyl)-L-lysyl-L-proline dihydrate. Lisinopril is a potent, competitive inhibitor of angiotensin-converting enzyme (ACE) and is used to treat hypertension, heart failure and to improve survival after heart attack and also preventing renal and retinal complications of diabetes. Reducing angiotensin II formation lead to arterial and venous dilation in turn reduces arterial and venous pressure. By reducing the effects of angiotensin II on the kidney, ACE inhibitors causes natriuresis and diuresis, which decreases blood volume and cardiac output, thereby lowering arterial pressure. Lisinopril has a half-life of 12 hrs. This drug belongs to BCS Class III, having good water solubility. Lisinopril is slowly and incompletely absorbed after oral administration with a bioavailability of 25–30%. The objective of the present study was to formulate effervescent floating matrix tablets of Lisinopril dihydrate by wet granulation technique using varying concentrations of different grades of gel forming polymers like HPMC K100, HPMC K15 and HPMC K4M to improve gastric retention, so consequently, the bioavailability of the drug.

MATERIALS AND METHOD

Materials

Lisinopril dihydrate is a gift sample from Covalent Laboratories, Hyderabad, India. HPMC K100M, HPMC K15M & HPMC K4M were procured from Sigma Aldrich, Mumbai. Sodium bicarbonate and magnesium stearate were purchased from S.D. Fine-Chem. Ltd., India. All other chemicals used were of analytical grade.

Methods

Calibration curve of Lisinopril dihydrate

The standard curve of Lisinopril was prepared using UV-VIS double beam spectrophotometer (Elico-161, India). Lisinopril (100 mg) was dissolved in 100 ml of 0.1 N HCl to make a 1000 µg/ml solution (A). A 10 ml volume of A was diluted with 100 ml 0.1 N HCl to make 100 µg/ml solution (B). A 30 ml volume of B was diluted with 100 ml 0.1 N HCl to make a stock solution of 30 µg/ml (C). Aliquots of C were pipette and diluted with 10 ml 0.1 N HCl to obtain the desired concentration of Lisinopril ranging from 2-20 µg/ml. The calibration curve shown in Figure 1.

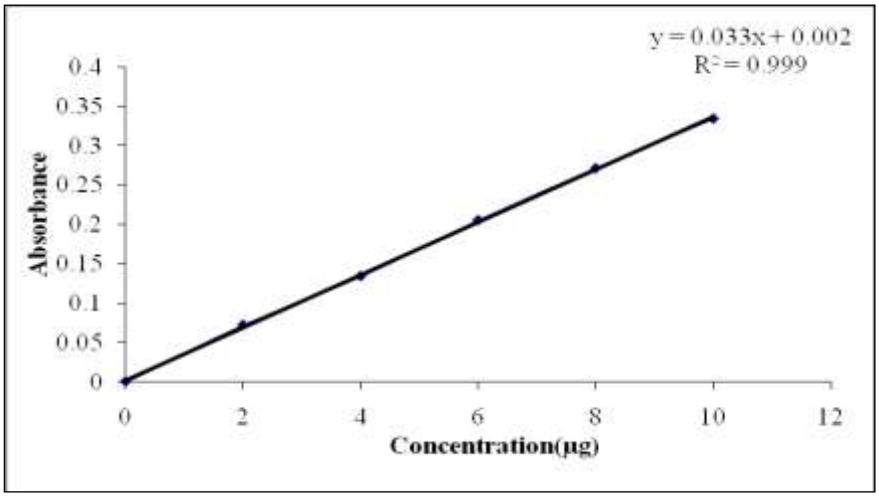

Figure 1: Calibration curve of Lisinopril Dihydrate in 0.1N HCl.

Development of floating matrix tablets

Floating matrix tablets containing LSP were prepared by wet granulation technique [6] using varying concentrations of different viscosity K-grade HPMC polymers such as K4M (4000 cps), K15M (15,000 cps) and K100M (1,00,000 cps) with sodium bicarbonate as gas generating agent. Preliminary formulations (FL1-FL4) were studied to optimize the effervescent concentration. Then, floating tablets were prepared with an optimized concentration of effervescent sodium bicarbonate composition. Quantitative composition of LSP floating matrix tablets is shown is Table 1.

Table 1: Formulation of Lisinopril floating matrix tablets

Formulation	Lisinopril dihydrate mg/tablet	HPMC K4M	HPMC K15M	HPMC K100 M	PVP K 30	Sodium bicarbonate	Lactose
LF1	20	-	50	-	8.75	5.0	87.75
LF2	20	-	50	--	8.75	13.125	79.625
LF3	20	-	50	-	8.75	17.5	75.25
LF4	20	-	50	-	8.75	26.25	66.5
LF5	20	-	-	26.25	8.75	17.5	99.0
LF6	20	-	-	52.5	8.75	17.5	72.75
LF7	20	-	-	78.75	8.75	17.5	46.5
LF8	20	-	26.25	-	8.75	17.5	99.0
LF9	20	-	52.5	-	8.75	17.5	72.75
LF10	20	-	78.75	-	8.75	17.5	46.5
LF11	20	26.25	-	-	8.75	17.5	99.0
LF12	20	52.5	-	-	8.75	17.5	72.75
LF13	20	78.75	-	-	8.75	17.5	46.5

All the Tablets contain 1.75 mg of talc and 1.75mg of magnesium stearate.

HPMC-Hydroxy propyl methylcellulose

PVP- Polyvinyl pyrrolidene

Accurately weighed quantities of LSP, various concentrations of respective retardant material (HPMC grades i.e. HPMC K4M, HPMC K15 M, HPMC K100M), diluent (lactose), sodium bi carbonate were screened through a # 30 mesh sieve (size: 350µm).The mixture was placed in a polyethylene bag and further mixed for 5 to 10 minutes to ensure a homogeneous mass and transferred to a mortar and granulated using PVP K30 binder solution. The wet mass was passed through # 22 mesh sieve (size: 700 µm). The granules were dried at 45 ± 5^0C for half an hour and dried granules were sieved through # 25 mesh (size 600 µm). The dried granules were blended with lubricant mixture (1% magnesium stearate and 1% talc). The lubricated granules were compressed on a 16-station rotary tablet punching machine (Cadmach, India) using 12.5 mm circular standard flat faced punches.

Physical characterization of compressed tablets [7]

Compressed tablets were characterized to assess the physicochemical properties and release characteristics. Weight variation of (20 tablets) from each batch was carried out using a digital balance (Shimadzu, Japan) and thickness (10 tablets) was measured by Vernier calipers (in millimeters). Crushing strength (6 tablets) was measured with a Monsanto tester (Campbell Electronics, India), and friability (20 tablets) was determined (Roche type friabilator, Germany).

The drug content in each formulation was determined by triturating 10 tablets and powder equivalent to the average mass of one tablet was added in 100 mL of 0.1N HCl, followed by

sonicating for 2 h. The drug content was estimated by recording absorbance at 210 nm using a UV-Visible spectrophotometer (Elico-161, India).

Buoyancy / Floating Test

The floatation was accomplished by incorporating gas generating salt, Sodium bicarbonate into a swellable hydrophilic polymer. As the dissolution medium was imbibed into the matrix, the interaction of acidic fluid with sodium bicarbonate resulted in the formation and entrapment of carbon dioxide gas within the swollen gel thus causing floatation, as the matrix volume expanded and its density decreased below one. It was reported that 10-20 % of sodium bicarbonate was essential to achieve optimum *in vitro* buoyancy [8]. The *in vitro* buoyancy was determined by floating lag time, as per the method described by Rosa et al., 1994 [9]. The tablets were placed in a 100-ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and to float was determined as floating lag time and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

***In vitro* Drug Release**

The *in vitro* dissolution studies were performed for the formulated effervescent floating tablets of Lisinopril dihydrate over a period of 12 hours, using USP type II (paddle) dissolution apparatus (Electro Lab, India , TDT – 082) [10] at a rotation speed of 50 rpm. The dissolution medium consists of 900 ml of 0.1 N HCl (pH 1.2) and temperature was maintained at 37 $\pm$ 0.5^{0}C a minimum of 3 tablets per each batch was tested. The tablets were placed inside the dissolution vessel. An aliquots of 5mL were collected at predetermined intervals of 0.5, 1, 2, 3 ,4 ,5 ,6 ,7, 8 ,9, 10, 11 and 12 hours and replenished with an equivalent volume of pre-warmed fresh dissolution medium. After filtration, the amount of drug release was measured by UV- Visible double beam spectrophotometer (Thermo Scientific, Mumbai, India) at 210 nm against blank. The drug concentration was calculated using standard calibration curve.

Fourier transform infrared spectroscopy

The physicochemical compatibilities of the drug and the used excipients were tested by the Fourier transform infrared spectroscopy (FTIR). Lisnopril dihydrate pure drug, physical mixture of drug and excipients FTIR spectrums were recorded between 400 to 4000cm^{-1}. The IR spectra for the test samples were obtained using KBr disk method using an FTIR spectrometer.

Drug release kinetics

The rate and mechanism of drug release was analyzed by fitting the dissolution data into several mathematical models [11] such as zero-order, first-order, Higuchi [12] and Peppas [13, 14].

RESULTS AND DISCUSSION

Physical characterization of tablets

Physical characteristics of the formulated matrix were shown in Table.2. To avoid processing variables, all batches were produced under similar conditions. The mean hardness of the tablets was 5.0 ± 0.5 kg/cm^2, average weight variation was 175 ± 1.7 mg, mean thickness was 2.86 ± 0.5 mm and friability ranged from 0.25 to 0.48 %. The content uniformity of the tablets was 99.5 ± 5.0 %.

Fourier transform infrared spectroscopy

FTIR study reveals that there was no interaction between drug and excipients. The spectra's of Lisinopril with HPMC K100M, HPMC K15 M, HPMC K4M shown in Figure 2, 3, 4 respectively.

Fourier Transform Infrared spectroscopic studies (FTIR) of:

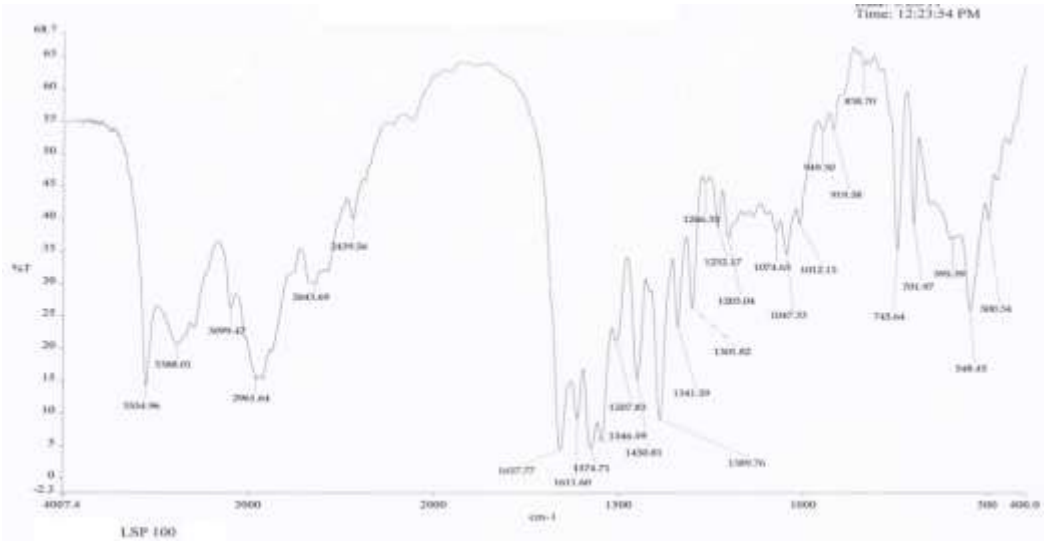

Figure 2: (Lisinopril + HPMC K100) (1:1)

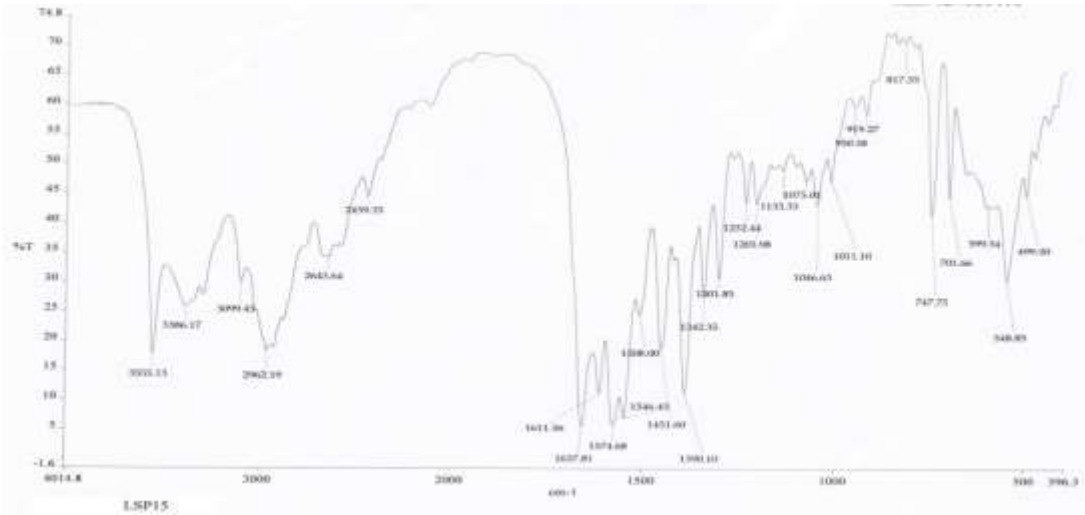

Figure 3: (Lisinopril + HPMC K15) (1:1)

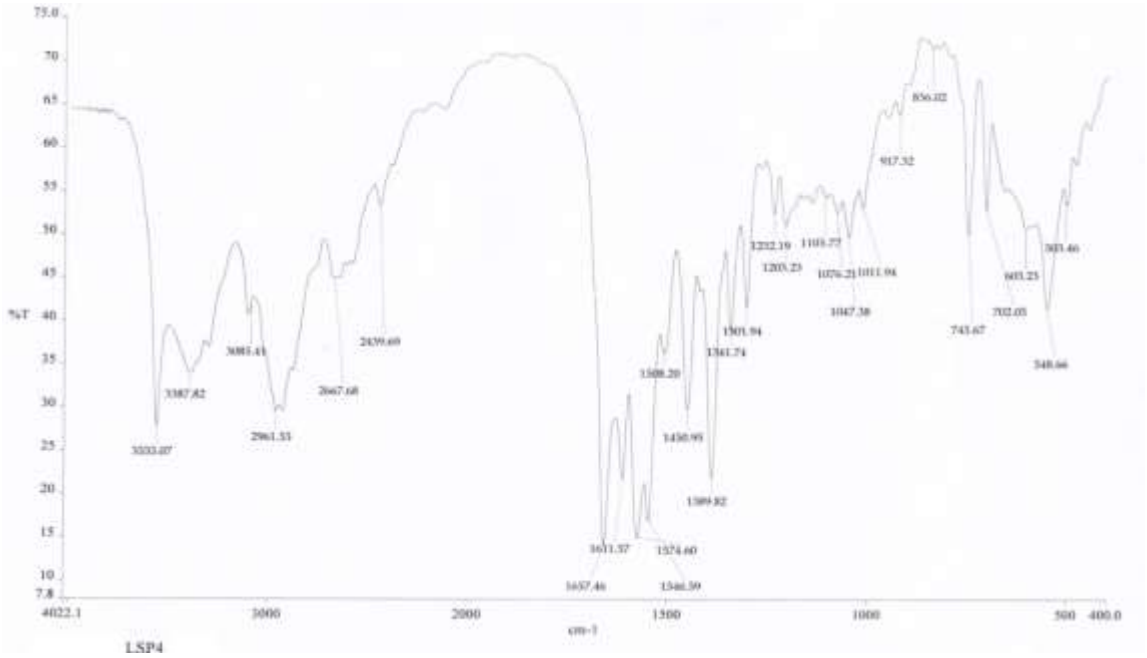

Figure 4: (Lisinopril + HPMC K4M) (1:1)

***In vitro* buoyancy**

For determination of optimum *in vitro* buoyancy and floating lag time, formulations (LF1-LF4) were prepared with different concentrations of sodium bicarbonate (5, 7.5, 10 & 15). Whitehead [15] had demonstrated good correlation between *in vitro* and *in vivo* buoyancy of floating dosage forms. Their results shown in Table 3. Increasing the concentration of sodium bicarbonate decreased the floating lag time. At 10 % sodium bicarbonate concentration tablets remained rigid and buoyant for 12 h with a lag time of 90 to 105 seconds, whereas the tablets with 15 % $NaHCO_3$ showed shorter lag time and the tablet integrity was lost during the study after 6 to 8 h (results not shown). In this study, penetration of water into tablets with low viscosity HPMC K4M was slow, causing delayed gel formation and subsequent increase in the floating lag time and decreased total floating duration (< 8 h) compared to the tablets prepared with K15M and K100M. LF-11 showed the best floating lag time of 90 ± 5 s. With the exception of formulations LF-11 to LF-13, all the formulated tablets were buoyant for more than 12h.The photographs of *in-vitro* Buoyancy study of Optimized formulation of Lisinopril dehydrate shown in Figure.8

Table 3: Effect of sodium bicarbonate concentration on floating lag time

NaHCO3 (mg)	Conc (%)	Floating lag time (sec)
8.75	5.0	148 -157
13.125	7.5	125 -140
17.5	10.0	90 - 105
26.25	15.0	88-95

Mean±SD, n=3

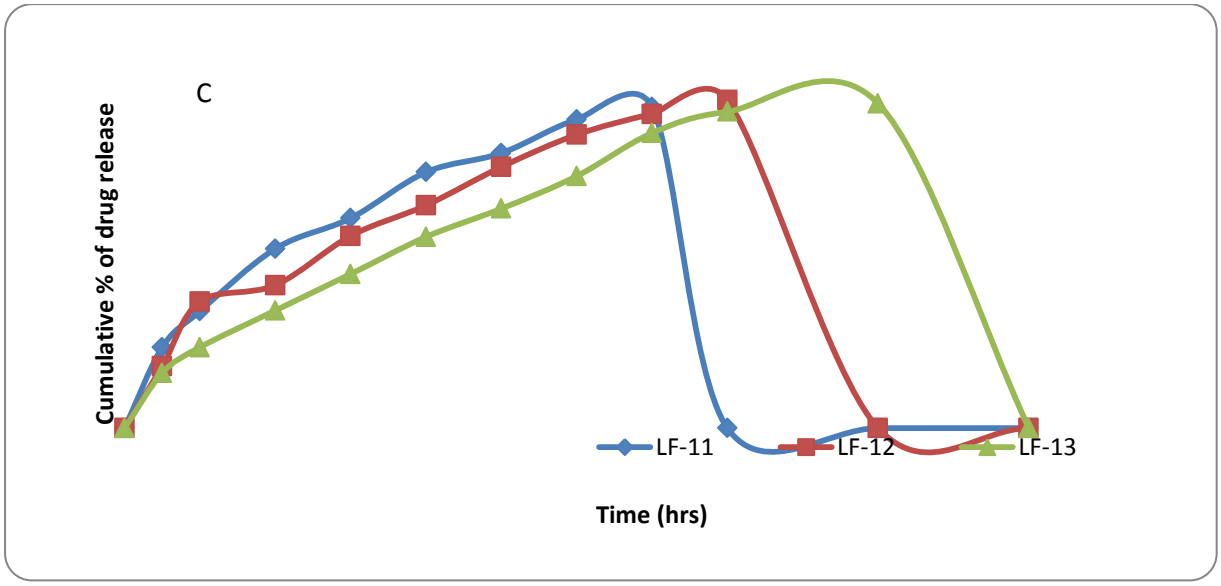

Figure.5: Drug release profiles of Lisinopril dihydrate floating tablets prepared with HPMC K4M

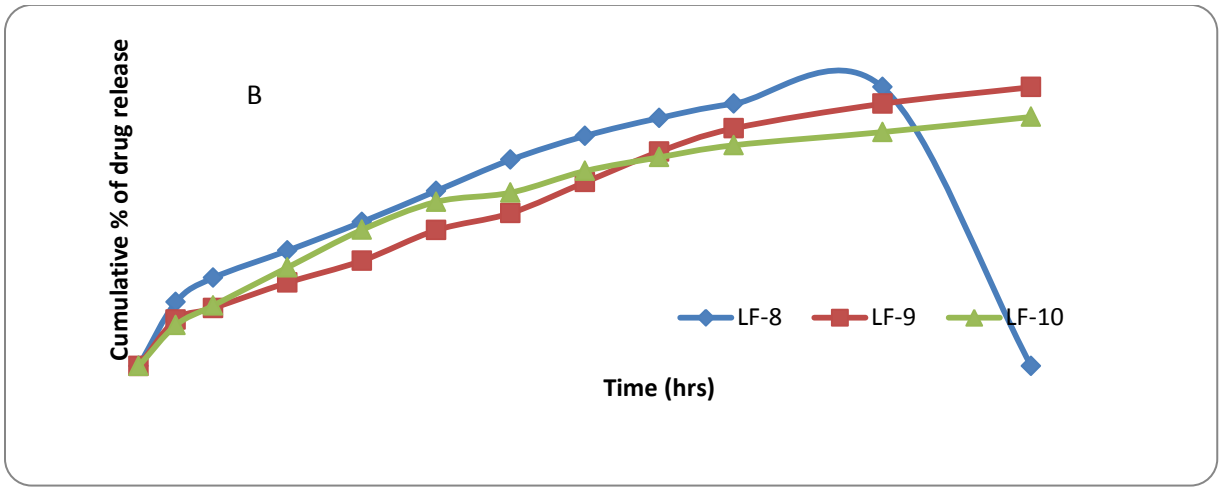

Figure 6: Drug release profiles of Lisinopril dihydrate floating tablets prepared with HPMC K15M

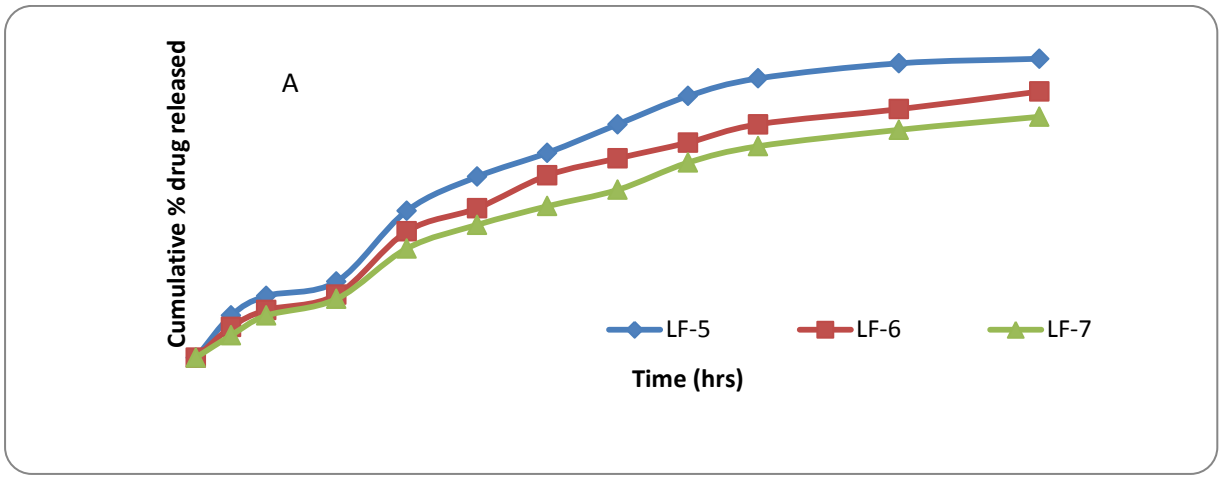

Figure.7: Drug release profiles of Lisinopril dihydrate floating tablets prepared with HPMC K100M

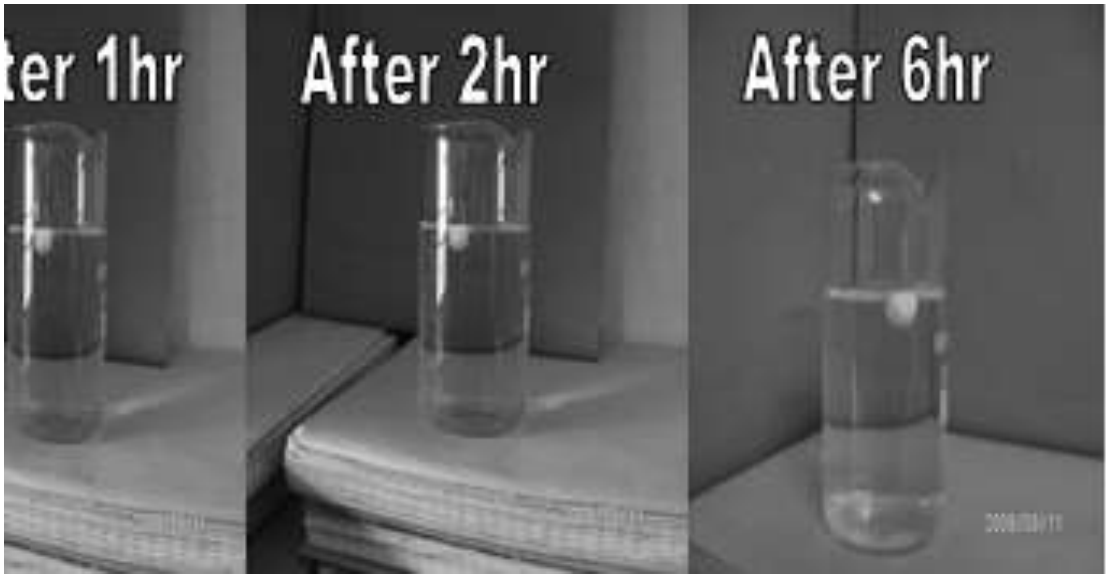

Figure.8. Images showing photographs of in-vitro Buoyancy study of Optimized formulation of Lisinopril dehydrate

Table 2: Physicochemical evaluation parameters

F CODE	Wt. variation (mg)	Hardness (kg/cm^2)	Thickness (mm)	Diameter (mm)	Friability %	Drug Content (%)
LF-5	175±2.10	5±0.5	2.86±0.5	6.5±0.03	0.34	96.2
LF-6	175±1.99	5±0.5	2.86±0.5	6.5±0.03	0.45	94.3
LF-7	175±1.74	5±0.5	2.86±0.5	6.5±0.03	0.25	96.5
LF-8	175±2.63	5±0.5	2.86±0.5	6.5±0.03	0.28	98.9
LF-9	175±2.26	5±0.5	2.86±0.5	6.5±0.03	0.39	94.0
LF-10	175±2.33	5±0.5	2.86±0.5	6.5±0.03	0.48	96.1
LF-11	175±1.80	5±0.5	2.86±0.5	6.5±0.03	0.45	105.2
LF-12	175±1.67	5±0.5	2.86±0.5	6.5±0.03	0.31	96.3
LF-13	175±1.71	5±0.5	2.86±0.5	6.5±0.03	0.29	98.3

***In vitro* dissolution studies**

An effective drug plasma concentration was maintained when the sustained release formulation released the required quantity of drug with predetermined kinetics. To achieve this, floating tablets should be formulated. So that they release the drug in a predetermined and reproducible manner. The release of Lisnopril dihydrate from effervescent floating tablets was analyzed by plotting the cumulative percent drug release against time.

The *in vitro* drug release studies revealed that formulations LF-11,LF-12 & LF-13 (Figure.5) containing 15, 30 and 45% concentration of HPMC K4M, respectively, were able to sustain the drug release for 7, 8 and 10 hrs, respectively. Floating lag time was 235 seconds; total buoyancy was 8 to 10 h and tablet integrity was poor for HPMC K4M formulations.

Drug release profiles of formulations LF-8 to LF-10 containing 15, 30 and 45% concentration of HPMC K15 M, respectively, were shown in (Figure.6). For LF8, 99.5 % of the drug was released after 10 hours. 99.5 and 88.9 % of drug was released from formulations LF-9 and LF-10 respectively, after 12 h. Formulation LF8 underwent swelling and erosion, resulting in faster drug release. In LF-9, 30 % of HPMC K15M was sufficient to sustain the drug release for 12 h. On increasing the quantity of HPMC K15M up to 45 %, the release of the drug was too slow and only 88.9 % of the drug was released. It was observed that when the polymer concentration was increased, the drug release rate decreased.

Drug release profiles of formulations LF-5 to LF-7 composed of HPMC K100M, were shown in (Figure.7).The percentage of drug released from these formulations was 91.2, 81.2 and 73.5 %, respectively, after 12h. This variation was considered to be due to different polymer concentrations. Release of the drug was faster with lower viscosity grades of HPMC (K4M) due to lower gel strength, less entanglement and smaller diffusion path length compared to higher viscosity grades of HPMCs. In all the formulations, polymer concentration greatly affected the release of the drug. Formulation LF-9 showed floating lag time of 95 s and drug releases showed 99.5% for 12 hrs. For these reasons, LF9 was considered the best among all the formulations.

The amount of drug released from various FDDS formulations was found to be in the order of HPMC K100M > HPMC K15M > HPMC K4M

Drug release kinetics

The results of kinetic models for Lisnopriil dihydrate release from floating matrix tablets are shown in Table 4. The coefficient of determination (R^2) was used as indicator of the best fitting for each of the models considered. The results revealed that all formulations of floating matrix tablets fitted best the Higuchi and first-order models. To explore the mechanism of drug release, the

results of *in vitro* data were fitted into the Korsmeyer and Peppas equation characterizing the transport mechanism. The value of *n* was 0.56–0.72, indicating release governed by the non-Fickian diffusion mechanism.

Table 4: Correlation coefficient (R2) and release exponent (n) values for different kinetic models

Formulation	Zero order	First Order	Higuchi's	n
LF-5	0.905	0.968	0.935	0.58
LF-6	0.919	0.962	0.948	0.61
LF-7	0.937	0.952	0.942	0.59
LF-8	0.929	0.956	0.935	0.62
LF-9	0.965	0.977	0.952	0.72
LF-10	0.884	0.977	0.926	0.56
LF-11	0.921	0.969	0.936	0.61
LF-12	0.939	0.918	0.919	0.67
LF-13	0.954	0.952	0.916	0.62

CONCLUSION

The effervescent based FDDS is a promising approach to achieve *in vitro* buoyancy by using gel forming polymer HPMC K4M, HPMC K15M and HPMC K100 and gas generating agent sodium bicarbonate. Through suitable combination of HPMC K15M and lactose, the desired dissolution profile could be achieved. Among the various FDDS formulations studied, the formulation containing LF-9 with 30% HPMC K15M showed the best result in terms of the required lag time (82±5 sec) and floating duration of 12 h and releasing 99.5% of the drug in 12 h and is considered as the ideal formulation. The dosage form can control the release, avoid dose dumping and extend the duration of action of a drug with prolonged floating time.

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