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FORMULATION AND IN-VITRO EVALUATION OF FLOATING PULSATILE TABLET OF LISINOPRIL

Durga Bhavani K.* and Poornima N. B.

Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka.

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***Corresponding Author**
Durga Bhavani K.
Rajiv Gandhi University of Health Sciences, Bangalore, Karnataka.

ABSTRACT

This study focuses on formulating and evaluating Lisinopril Floating Pulsatile Release Tablets (FPRTs) for enhanced chronomodulated therapy in hypertension treatment. The methodology involves the preparation of rapid-release core tablets (RRCTs) through direct compression, incorporating various superdisintegrants. These cores are subsequently compression-coated with hydrophilic polymers, including HPMC E5, HPMC K4M, HPMC K15M, and Xanthan gum, to achieve desired floating and pulsatile release characteristics. Objectives encompass optimizing drug release timing, minimizing dose-related side effects, and improving bioavailability. The comprehensive plan includes preformulation studies, Lisinopril standard curve preparation, pre-formulation studies of the drug and formulations, and the formulation and development of RRCTs and FPRTs. Evaluation parameters comprise physical characteristics, friability, drug content, disintegration, in-vitro release, buoyancy, swelling index, release kinetics, and stability studies following ICH guidelines. Lisinopril, an ACE inhibitor, is chosen for its relevance in treating hypertension, heart failure, nephropathy, and myocardial infarction. The selection of a floating pulsatile release tablet aligns with the need for chronopharmacotherapy, avoiding first-pass metabolism, targeting specific sites like the stomach, accommodating drugs with short half-lives, improving bioavailability, and enhancing patient compliance. Future directions involve scale-up, in-vivo studies, in vitro-in vivo correlation, and bioequivalence assessments with market products. In conclusion, Formulation FP8 demonstrates promising drug release kinetics and stability, offering a potential solution for addressing circadian variability in hypertension, thereby contributing to the progression of chronomodulated drug delivery systems.

KEYWORDS: Lisinopril, Floating Pulsatile Release Tablets, Chronomodulated Therapy, Hypertension, Drug Delivery.

1. INTRODUCTION

Hypertension, a ubiquitous cardiovascular ailment, poses a significant challenge to clinicians, its intricate pathophysiology and the circadian nature of blood pressure fluctuations making effective management elusive. In the arsenal against this condition, Lisinopril, an angiotensin-converting enzyme (ACE) inhibitor, stands as a cornerstone, proving invaluable in the treatment of hypertension, congestive heart failure, and related cardiovascular disorders. Despite its therapeutic efficacy, Lisinopril grapples with challenges inherent in its conventional dosing regimens—chiefly, a short half-life, dose-related side effects, and the perpetual quest for improved bioavailability.

As an angiotensin-converting enzyme inhibitor and antihypertensive agent, Lisinopril takes center stage in our pursuit to develop advanced therapeutic solutions. Its molecular formula (C9H15NO3S) and molecular weight (217.285) were pivotal considerations in our formulation studies. With indications ranging from essential or renovascular hypertension to congestive heart failure, post-myocardial infarction left ventricular dysfunction, and nephropathy, Lisinopril's versatility is a testament to its clinical importance. The recommended dosage spans from 12.5 to 50mg twice daily, with a typical maintenance dose of 25mg twice daily.

Navigating the intricacies of Lisinopril's pharmacokinetics, encompassing absorption, protein binding, metabolism, elimination half-life, and excretion, provided critical insights guiding our formulation design. To surmount the challenges posed by its conventional dosing, our study takes on the formidable task of crafting a novel drug delivery system specifically tailored for Lisinopril, with a focus on providing chronomodulated therapy. The overarching objective is clear—formulate Floating Pulsatile Tablets of Lisinopril that release the drug precisely when its therapeutic impact is most needed. In doing so, we aspire to enhance patient compliance, minimize side effects, and ultimately optimize the therapeutic outcome.[1-5]

The uniqueness of our approach lies in the meticulous preparation of rapid-release core tablets of Lisinopril, incorporating various superdisintegrants. These cores undergo a transformative process, as they are compression-coated with hydrophilic polymers, ensuring

the attainment of pulsatile drug release—a key feature in our quest for a more effective and patient-centric therapeutic solution. The model drug's selection is rooted in its ACE inhibitor classification and its efficacy in treating a spectrum of cardiovascular conditions. Furthermore, Lisinopril's distinctive pharmacokinetic profile, marked by a short half-life and specific absorption preferences, solidifies its role as the ideal candidate for this innovative drug delivery system.

As we embark on this scientific journey, we delve into comprehensive preformulation studies, setting the stage for the subsequent development of both Rapid Release Core Tablets (RRCTs) and Floating Pulsatile Release Tablets (FRCTs) of Lisinopril. Our manuscript unfolds as a narrative of exploration and innovation, with each section detailing the formulation strategies, evaluation parameters, and in vitro studies that collectively contribute to advancing the field of hypertension management. In an era where personalized and precision medicine herald a new frontier in healthcare, our research endeavors to pave the way for a breakthrough in optimizing the therapeutic potential of Lisinopril, aligning it more closely with the evolving landscape of patient-centered cardiovascular care.

2. MATERIALS AND METHODS

2.1. Preformulation Studies[6-10]

Preformulation studies are pivotal in understanding the physicochemical characteristics of a drug and its compatibility with various excipients employed in the formulation process. This ensures the development of a stable, safe, and effective dosage form.

In preformulation studies, drug-excipient compatibility was evaluated. Physical tests, conducted at room temperature and 40°C with 75% RH, examined mixtures for appearance changes. Chemical compatibility utilized FT-IR analysis for drug-excipient interactions. A pH 1.2 HCl solution was prepared for formulation studies. Lisinopril quantification involved creating a calibration curve by dissolving 100 mg in 0.1N HCl, pipetting aliquots, adjusting to 100 ml, and measuring absorbance at 212 nm.

2.2. Precompression Studies[6,7, 10-12]

Flow properties of powders were assessed for efficient tableting. Parameters measured included:

Bulk Density (ρb): Ratio of powder mass to bulk volume.

Tapped Density (ρt): Ratio of powder weight to tapped volume.

Angle of Repose (θ): Maximum angle between powder surface and horizontal plane.

Compressibility Index: Measure of powder flow expressed as a percentage.

Hausner's Ratio: Indirect index of powder flow ease.

2.3. Formulation Development

2.3.1 Formulation of Rapid Release core tablets (RRCT) of Lisinopril[13,14,15]

The inner core- tablets of Lisinopril were prepared by direct compression method. Different concentrations of various superdisintegrant such as sodium starch glycolate, croscarmellose sodium and crospovidone were used. The powder mixtures of Lisinopril, superdisintegrant, microcrystalline cellulose, lactose were dry blended for 20 minutes, followed by addition of magnesium stearate (fig 1). The mixtures were further blended for 10 minutes. 100 mg of the resultant powder blend was compressed using 10 station tablet compression machine (table 1).

Table 1: Formulation of rapid release core tablets.

S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	LISINOPRIL	25	25	25	25	25	25	25	25	25
2.	Croscarmellose Sodium	1	1.5	2	-	-	-	-	-	-
3.	Crospovidone	-	-	-	2	3.5	5	-	-	-
4.	Sodium starch glycolate	-	-	-	-	-	-	2	3	4
5.	Microcrystalline cellulose	25	25	25	25	25	25	25	25	25
6.	Lactose	46	45.5	45	45	43.5	42	45	44	43
7.	Magnesium stearate	3	3	3	3	3	3	3	3	3

Average weight of each tablet = 100mg

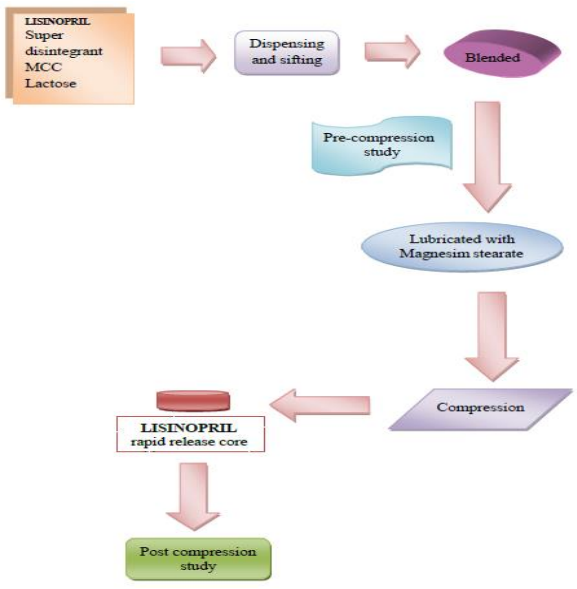

Fig. 1: Flowchart for formulation of rapid release Lisinopril tablet.

2.3.2 Formulation of Lisinopril floating pulsatile release tablet (FPRT)[13,15-17]

Floating pulsatile release tablets were prepared by press-coated method using HPMC E15, HPMC K4M, HPMC K15M, Xanthan gum (polymers) and sodium bicarbonate (gas generating agent). The compression coated tablets were prepared by firstfilling one half of the coating powder in the 10mm die cavity, then centrally positioning the tablet core on the powder bed, followed by filling the remaining half of the coating powder on top and followed by direct compression (tab 2 and fig 2).

Table 2: Formulation of Floating pulsatile release tablets.

S. No	Ingredients	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8
1.	Optimizedcore tablet	100	100	100	100	100	100	100	100
2.	HPMC E15	150	-	-	-	200	250	200	200
3.	HPMC K15M	-	150	-	-	-	-	25	-
4.	HPMC K4M	-	-	150	-	-	-	-	50
5.	Xanthan gum	-	-	-	150	-	-	-	-
6.	Sodium bicarbonate	50	50	50	50	50	50	50	50
7.	Lactose	180	180	180	180	130	80	105	80
8.	Magnesium stearate	10	10	10	10	10	10	10	10
9.	Talc	10	10	10	10	10	10	10	10

Average weight of each tablet = 500mg

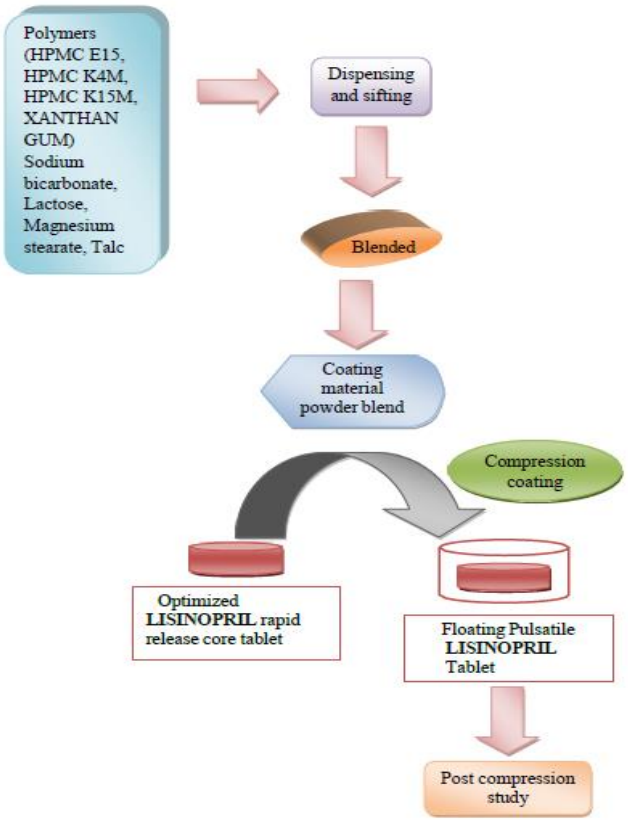

Fig. 2: Flowchart for formulation of Lisinopril floating pulsatile tablet.

2.4. POST COMPRESSION STUDIES[10]

2.4.1. PHYSICAL PARAMETERS[7,13,18]

Post-compression studies evaluated formulated tablet physical parameters. Visual inspection assessed shape and color. Weight uniformity was determined for twenty tablets, comparing average weight with standard specifications. Thickness and diameter were measured for size consistency. Hardness, indicating breakage force, was measured using a Monsanto Hardness Tester. Friability, a durability indicator, was assessed using a Rochelle Friabilator, calculating percentage friability after 100 revolutions (table 3).

Table 3: Uniformity of weight.

S No.	Average weight of Tablet	% Deviation
1	80 mg or less	10
2	80 to 250 mg	7.5
3	More than 250 mg	5

2.4.1.1. Disintegration test for Lisinopril Core Tablets[7]

Tablet disintegration in 0.1N Hydrochloric acid (pH 1.2) at 37 °C involved placing one tablet in each basket, immersing in the acid. The assembly was raised and lowered for 30 cycles per minute, and the time for complete disintegration was recorded in triplicate.

2.4.1.2. DRUG CONTENT

2.4.1.2.1. For Rapid Release Core Tablets (RRCT)[7]

Five randomly selected tablets were weighed, ground, and a 25mg equivalent of Lisinopril powder transferred to a 100ml flask. Dissolved in a few ml of 0.1N HCl, the volume was adjusted to 100ml. After filtration, a 10ml portion of the filtrate was diluted with 0.1N HCl in a 100ml flask. The resulting solution's absorbance at 212nm was measured using a UV-Visible Spectrophotometer, and concentration was determined from the calibration graph with 0.1N HCl as a blank.

2.4.1.2.2. For Floating Pulsatile Release Tablets (FPRT)[15,16]

Five tablets, randomly selected, were weighed, ground, and 25mg Lisinopril powder was dissolved in a 100ml flask with 0.1N HCl. After filtration, a 10ml portion of the filtrate was diluted in a 100ml flask with 0.1N HCl. Absorbance at 212nm was measured using a UV-Visible Spectrophotometer, and concentration was determined from the calibration graph, with 0.1N HCl as a blank.

2.4.1.3. *IN-VITRO* STUDIES

2.4.1.3.1. *IN-VITRO* DISSOLUTION STUDIES FOR RRCT[7, 13]

Lisinopril core tablet release was assessed with USP Type II apparatus. Dissolution used 900ml of 0.1N HCl (pH 1.2) at 37°C ± 0.5°C, with the paddle at 50 rpm. At defined intervals, 5ml samples were withdrawn, replaced with fresh medium. After dilution with 0.1N HCl, absorbance at 212nm was measured using a UV Spectrophotometer.

2.4.1.3.1. *IN-VITRO* DISSOLUTION STUDIES FOR FPRT[15, 17]

Lisinopril floating pulsatile tablet release was assessed with USP Type II apparatus, using 900ml of 0.1N HCl (pH 1.2) at 37°C ± 0.5°C, with the paddle at 50 rpm. At defined intervals over 24 hrs, 10ml samples were withdrawn, replaced with fresh medium. After dilution with 0.1N HCl, absorbance at 212nm was measured using a UV Spectrophotometer.

2.4.1.3.2. *IN-VITRO* BUOYANCY DETERMINATION[15,17]

The tablet's in-vitro buoyancy was determined using USP dissolution apparatus-II in 900ml 0.1N HCl at 37°C ± 0.5°C, rotating at 50 rpm. Floating lag time and duration were observed, along with visual monitoring of tablet integrity. Lag time denoted the period between tablet placement and core tablet exposure. Swelling index was determined by weighing tablets (W1), incubating in 200ml 0.1N HCl at 37°C, removing at hourly intervals, drying excess liquid, and reweighing (W2). Swelling index (SI) was calculated using the formula SI = (W2 - W1) x 100 / W1.

2.4.1.3.3. *IN-VITRO* RELEASE KINETICS[19]

Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were plotted in various kinetic models (Zero-order, First order, Higuchi, Hixson-Crowell release model and Korsmeyer-Peppas release model) (table 4).

1. Zero order equation

The zero order release can be obtained by plotting cumulative % percentage drug release versus time. It is ideal for the formulation to have release profile of zero order to achieve pharmacological prolonged action.

$$C=K_0t$$

Where, K_0 = Zero order constantt = Time in hours

2. First order equation

The graph was plotted as log % cumulative drug remaining Vs time in hours.

$$\textbf{Log C= log } C_0 \textbf{ - Kt/2.303}$$

Where, C_0 = Initial concentration of drugK = First order

t = Time in hours

3. Higuchi kinetics

The graph was plotted with % cumulative drug released vs. square root of time

$$Q = Kt^{½}$$

Where, K= constant reflecting design variable system (differential rateconstant)

t = Time in hours

4. Hixon and Crowell erosion equation

To evaluate the drug release with changes in the surface area and the diameter of particles, the data were plotted using the Hixon and Crowell rate equation. The graph was plotted by cube root of % drug remaining vs. time in hours.

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t$$

Where, Q_t = amount of drug released in time t.

Q_0 = Initial Amount of drug

K_{HC}= Rate constant for Hixon Crowell equation

5. Korsmeyer-Peppas equation

To evaluate the mechanism of drug release, it was further plotted in Peppas equation as log cumulative % of drug released Vs.log time.

$$M_t/M_\alpha = Kt^n$$

Where, M_t/M_α = Fraction of drug released at time t

t = Release time

K=Kinetics constant (Incorporating structural and geometric characteristics of the formulation)

n = Diffusional exponent indicative of the mechanism of drug release.

Table 4: Diffusion exponent and solute release mechanism for cylindrical shape.

Diffusion exponent (n)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45 < n < 0.89	Anomalous (non- Fickian) diffusion

0.89	Case II transport
n > 0.89	Super case II transport

2.6. STABILITY STUDIES[15, 20]

A short – term stability study on optimized FPRT was carried out by storing the tablets at 40°C (± 2°C) and 75% RH over a period of 90 days according to ICH guidelines. At the end of 90 days time interval, the tablets were examined for physical characteristics, drug content, *in-vitro* drug release (lag time), floating lag time, andfloating duration.

3. RESULTS AND DISCUSSION

3.1.PREFORMULATION STUDIES

3.1.1. DRUG – EXCIPIENT COMPATIBILITY STUDY

The drug-excipient compatibility study was conducted to reveal the excipient compatibility with the drug.

3.1.1.1.1. PHYSICAL COMPATIBILITY

The Physical compatibility study (table 5) was performed visually. The study showed that the drug and excipients were physically compatible with each other as there was no Physical interaction. The excipients which were compatible with the drugs were selected for formulation.

Table 5: Physical compatibility study of Drug and Excipients.

S.No.	Drug + Excipient	Description and Condition			
		Initial	Room temperature and 40°C / 75% RH in days		
			10th	20th	30th
1	Lisinopril	A white to off-white, crystalline powder	NC	NC	NC
2	SSG	White / off white powder	NC	NC	NC
3	CCS	Grayish-white powder	NC	NC	NC
4	CP	Creamy white powder	NC	NC	NC
5	Xanthan gum	Creamy white free flowing fine powder	NC	NC	NC
6	HPMC E15	White or Creamy white Powder	NC	NC	NC
7	HPMC K4M	White or Creamy white Crystalline Powder	NC	NC	NC
8	HPMC K15M	White or Creamy white Crystalline Powder	NC	NC	NC
9	Sodium bicarbonate	White, Crystalline Powder	NC	NC	NC
10	Lactose	Off white crystalline powder	NC	NC	NC
11	MCC	White, Crystalline Powder	NC	NC	NC
12	Magnesium stearate	White or Off white crystalline Powder	NC	NC	NC
13	Talc	White or Off white crystalline Powder	NC	NC	NC

14	Erythrosine	Cherry Pink Colour Powder	NC	NC	NC
15	Lisinopril + SSG	White / off white powder	NC	NC	NC
16	Lisinopril + CCS	Grayish-white powder	NC	NC	NC
17	Lisinopril + CP	Creamy white powder	NC	NC	NC
18	Lisinopril + Xanthan gum	Creamy white free flowing fine powder	NC	NC	NC
19	Lisinopril + HPMC E15	White or Creamy white Powder	NC	NC	NC
20	Lisinopril + HPMC K4M	White or Creamy white Crystalline Powder	NC	NC	NC
21	Lisinopril + HPMC K15M	White or Creamy white Crystalline Powder	NC	NC	NC
22	Lisinopril + Sodium bicarbonate	White, Crystalline Powder	NC	NC	NC
23	Lisinopril + Lactose	Off white crystalline powder	NC	NC	NC
24	Lisinopril + MCC	White, Crystalline Powder	NC	NC	NC
25	Lisinopril + Magnesium stearate	White or Off white crystalline Powder	NC	NC	NC
26	Lisinopril + Talc	White or Off white crystalline Powder	NC	NC	NC
27	Lisinopril + Erythrosine	Cherry Pinkish Colour Powder	NC	NC	NC

NC –No change.

1.1.1.1. CHEMICAL COMPATIBILITY STUDY[21]

The possible interaction between the drug and the excipients used in the formulation was studied by FTIR spectroscopy. The results are given in the below.

FTIR SPECTROSCOPY OF DRUG

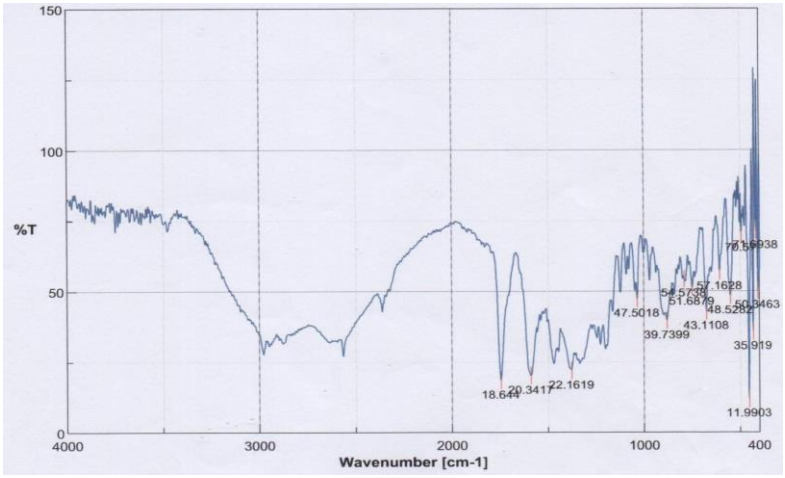

Fig. 3: FTIR of Lisinopril.

Table 6: IR Spectral interpretation of Lisinopril.

Wave number (cm^{-1})	Type of Vibration
1725	C=O
2985	C-H (aliphatic)
2580	-OH (carboxylic acid)

FTIR spectroscopy of drug Lisinopril is shown in fig 3 and table 6.

FTIR SPECTROSCOPY OF LISINOPRIL AND EXCIPIENTS

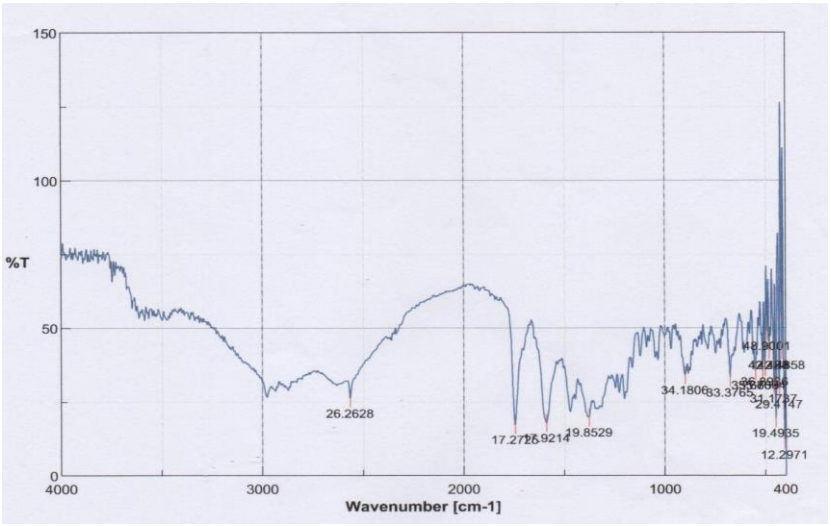

Fig. 4: FTIR of Lisinopril with croscarmellose sodium (CCS).

Table 7: IR Spectral interpretation of Lisinopril with Croscarmellose Sodium.

Wave number (cm^{-1})	Type of Vibration
1725	C=O
2985	C-H (aliphatic)
2580	-OH (carboxylic acid)

The peaks observed in the FTIR spectrum showed no shift and no disappearance of characteristic peaks of drugs. This suggests that there was no interaction between the drug and Croscarmellose sodium (fig 4 and table 7).

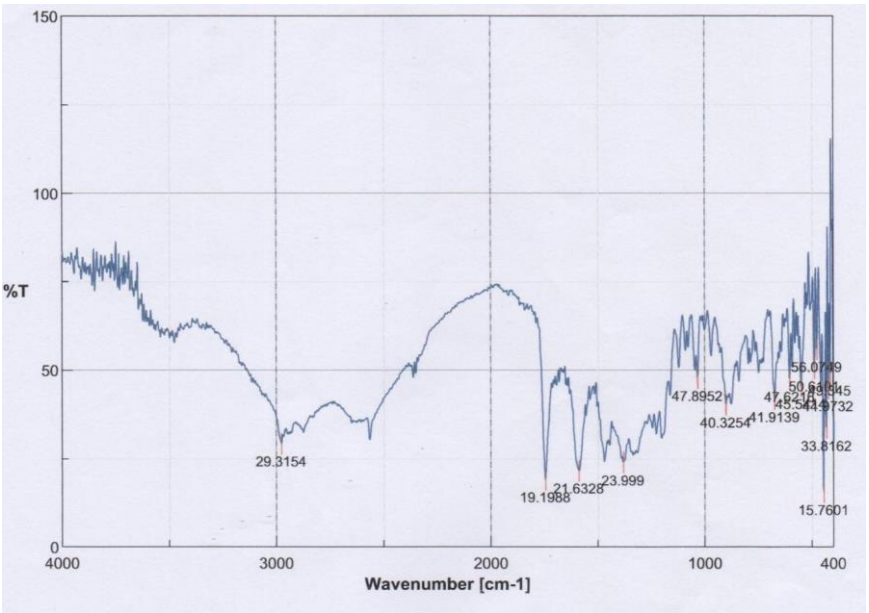

Fig. 5: FTIR of Lisinopril with crospovidone (CP).

Table 8: IR Spectral interpretation of Lisinopril with Crospovidone.

Wave number (cm^{-1})	Type of Vibration
1725	C=O
2985	C-H (aliphatic)
2580	-OH (carboxylic acid)

The peaks observed in the FTIR spectrum showed no shift and no disappearance of characteristic peaks of drugs. This suggests that there was no interaction between the drug and Crospovidone (fig 5 and table 8).

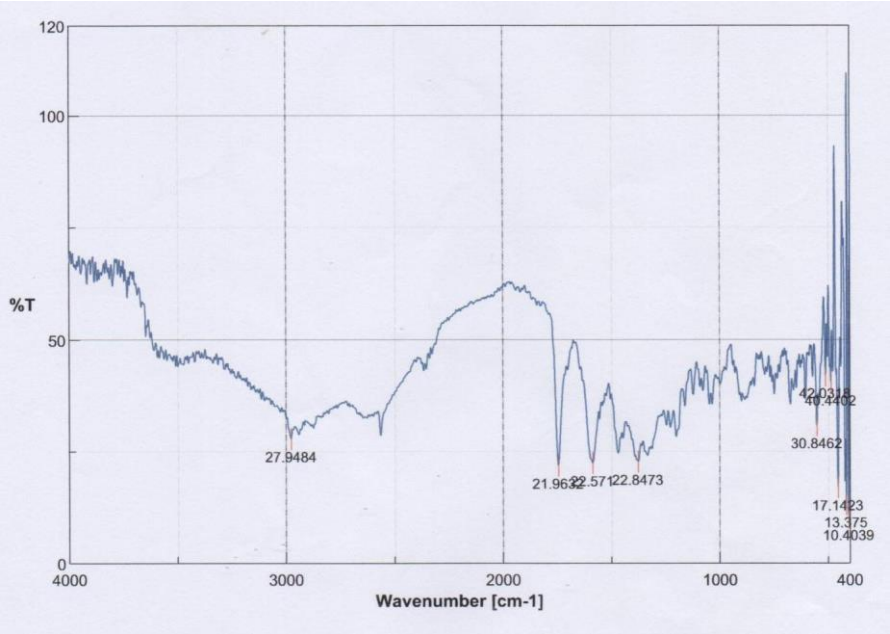

Fig. 6: FTIR of Lisinopril with sodium starch glycolate (SSG).

Table 9: IR Spectral interpretation of Lisinopril with sodium starch glycolate.

Wave number (cm^{-1})	Type of Vibration
1725	C=O
2985	C-H (aliphatic)
2580	-OH (carboxylic acid)

The peaks observed in the FTIR spectrum showed no shift and no disappearance of characteristic peaks of drugs. This suggests that there was no interaction between the drug and Sodium Starch Glycolate (fig 6 and table 9).

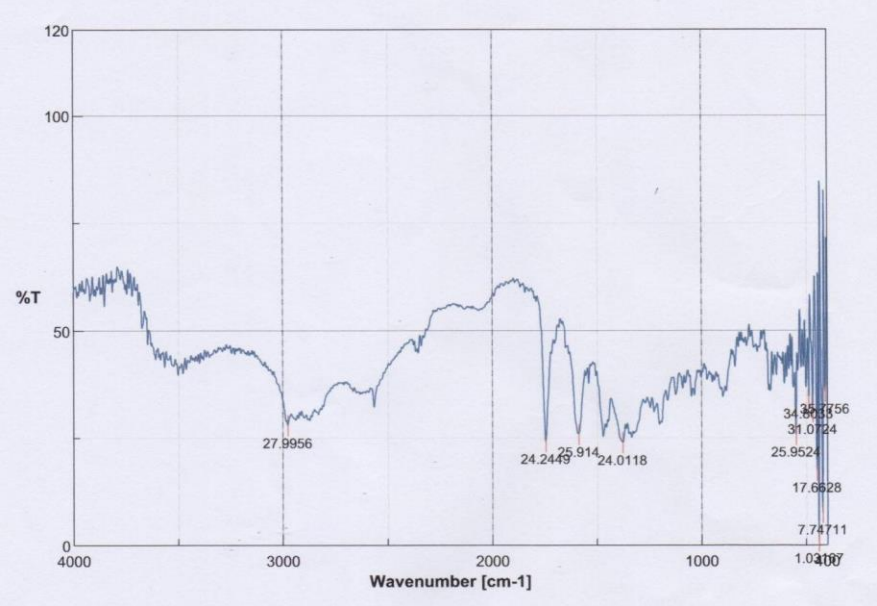

Fig. 7: FTIR of Lisinopril with HPMC E15.

Table 10: IR Spectral interpretation of Lisinopril with HPMC E15.

Wave number (cm^{-1})	Type of Vibration
1725	C=O
2985	C-H (aliphatic)
2580	-OH (carboxylic acid)

The peaks observed in the FTIR spectrum showed no shift and no disappearance of characteristic peaks of drugs. This suggests that there was no interaction between the drug and HPMC E15 (fig 7 and table 10).

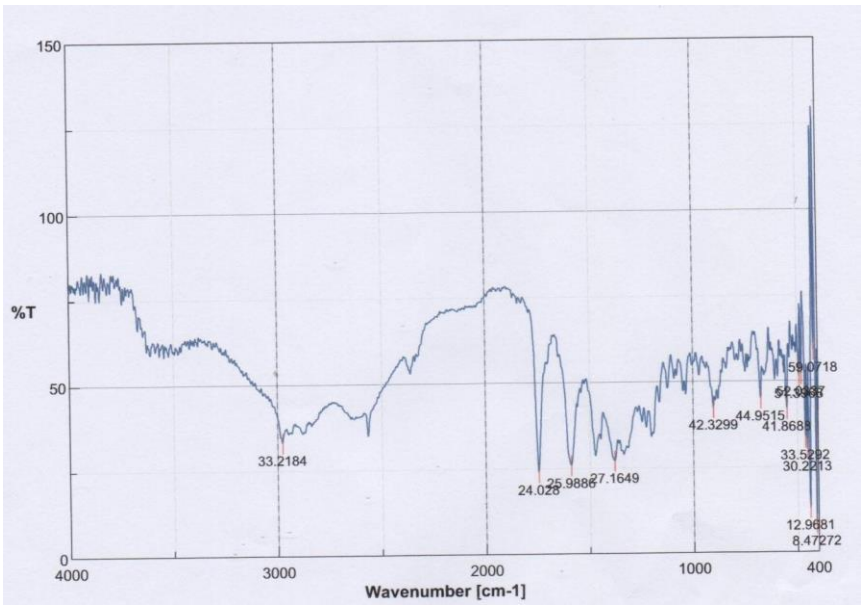

Fig. 8: FTIR of Lisinopril with HPMC K15M.

Table 11: IR Spectral interpretation of Lisinopril with HPMC K15M.

Wave number (cm^{-1})	Type of Vibration
1725	C=O
2985	C-H (aliphatic)
2580	-OH (carboxylic acid)

The peaks observed in the FTIR spectrum showed no shift and no disappearance of characteristic peaks of drugs. This suggests that there was no interactionbetween the drug and HPMC K15M (fig 8 and table 11).

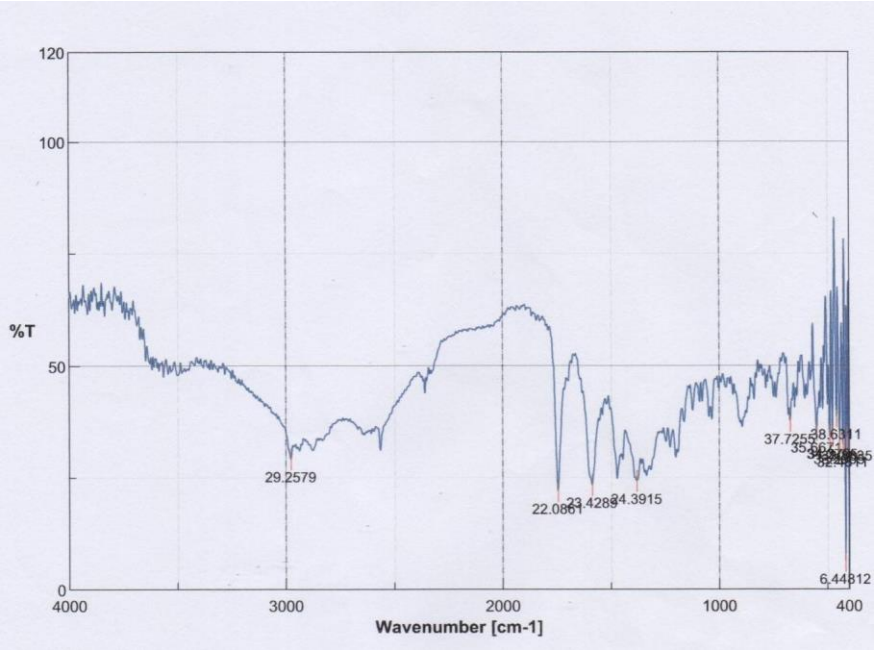

Fig. 9: FTIR of Lisinopril with HPMC K4M.

Table 12: IR Spectral interpretation of Lisinopril with HPMC K4M.

Wave number (cm^{-1})	Type of Vibration
1725	C=O
2985	C-H (aliphatic)
2580	-OH (carboxylic acid)

The peaks observed in the FTIR spectrum showed no shift and no disappearance of characteristic peaks of drugs. This suggests that there was no interactionbetween the drug and HPMC K4M (fig 9 and table 12).

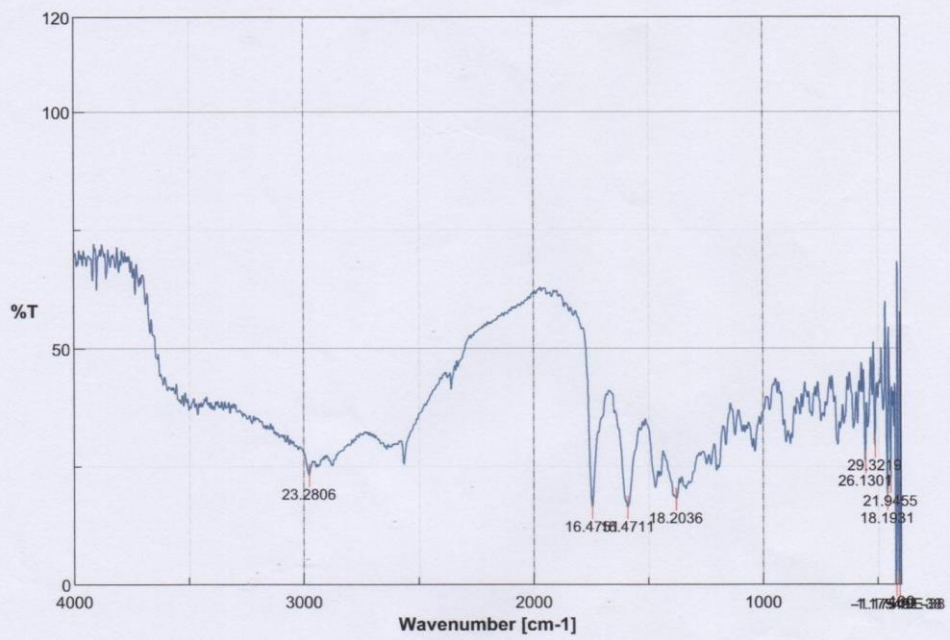

Fig. 10: FTIR of Lisinopril with Xanthan gum.

Table 13: IR Spectral interpretation of Lisinopril with Xanthan Gum.

Wave number (cm^{-1})	Type of Vibration
1725	C=O
2985	C-H (aliphatic)
2580	-OH (carboxylic acid)

The peaks observed in the FTIR spectrum showed no shift and no disappearance of characteristic peaks of drugs. This suggests that there was no interactionbetween the drug and Xanthan gum(fig 10 and table 13).

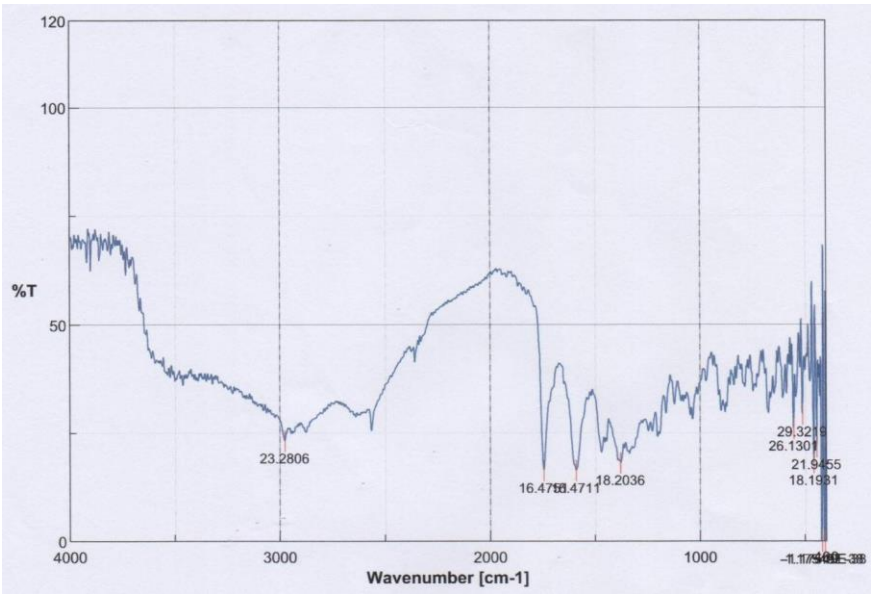

Fig. 11: FTIR of Lisinopril powder blend.

Table 14: IR Spectral interpretation of Lisinopril powder blend.

Wave number (cm^{-1})	Type of Vibration
1725	C=O
2975	C-H (aliphatic)
2580	-OH (carboxylic acid)

The peaks observed in the FTIR spectrum showed no shift and no disappearance of characteristic peaks of drugs. This suggests that there was no interaction between the drug and excipients (Powder blend). (fig 11 and table 14).

1.2. CALIBRATION CURVE OF LISINOPRIL

Table 15: Data for calibration curve of Lisinopril in 0.1N Hydrochloric acid (pH 1.2).

Concentration (µg/ml)	Absorbance*
0	0
2	0.057 ± 0.0073
4	0.109 ± 0.0055
6	0.164 ± 0.0095
8	0.222 ± 0.0082
10	0.284 ± 0.0065

*Mean ± SD (n=3)

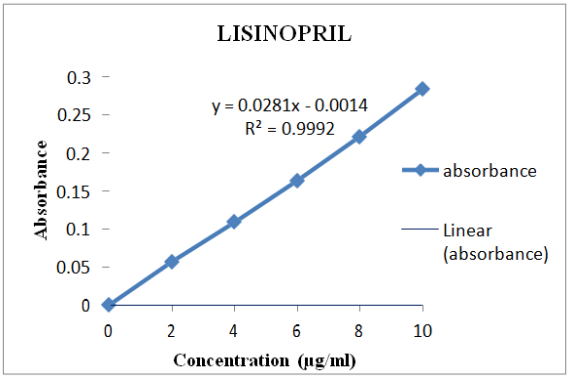

Fig. 12: Calibration curve of Lisinopril.

It was found that the solutions of Lisinopril in 0.1N Hydrochloric acid (pH 1.2) showed linearity (R^2 = 0.9996) in absorbance at concentrations of 2 to 10 µg/ml and obey Beer Lambert's Law (fig 12 and table 15).

1.3. RAPID RELEASE FORMULATION OF LISINOPRIL

1.3.1.PRECOMPRESSION STUDY

1.3.2. The drug and the formulated blends are evaluated for precompression parameters. The results are given in the table 16.

Table 16: Precompression study of drug and formulated blends.

Drug Formulation	Bulk density* (g/cm^3)	Tappeddensity* (g/cm^3)	Compressibility index* (%)	Hausner's ratio*	Angle of repose*
Lisinopril	0.5773 ± 0.015	0.6824 ± 0.022	15.35 ± 0.57	1.18 ± 0.036	31°31′ ± 1.61
F1	0.5026 ± 0.008	0.6669 ± 0.021	18.55 ± 0.48	1.25 ± 0.042	42°02′ ± 0.588
F2	0.4942 ± 0.118	0.6385 ± 0.034	19.44± 0.76	1.23 ± 0.047	45°22′ ± 0.205
F3	0.4868 ±0.011	0.6247± 0.018	20.01± 0.15	1.22 ± 0.038	45°50′ ± 0.335
F4	0.4791± 0.0001	0.5630± 0.0001	14.92± 0.001	1.17± 0.0002	44°19′ ± 0.205
F5	0.4681 ± 0.010	0.5806± 0.016	19.36± 0.443	1.23± 0.0065	43°25′ ± 0.048
F6	0.4228 ± 0.0089	0.5322 ± 0.002	20.56± 0.682	1.25± 0.023	43°40′ ± 0.420
F7	0.4710 ± 0.010	0.5521 ± 0.014	14.70± 0.30	1.16± 0.004	43°45′ ± 0.35
F8	0.479 ± 0.0001	0.598 ± 0.001	19.89± 0.0002	1.24± 0.0002	42°41′ ± 0.505
F9	0.4825 ± 0.001	0.6301 ± 0.0001	19.99± 0.0002	1.24± 0.0002	43°56′ ± 0.590

*Mean ±S.D (n=3)

The bulk density, tapped density, Carr's index, Hausner's ratio, Angle of repose of drug were found to be 0.5773, 0.6824, 15.35, 1.18, 31°31′ respectively.

The bulk density of Lisinopril blends ranged from 0.4228 to 0.5026 g/cm^3 and tapped density ranged from 0.5322 to 0.6669 g/cm^3. The compressibility index of the Lisinopril powder blend ranged from 14.70 to 20.56% and Hausner's ratio ranged from 1.16 – 1.25 which showed fair-good flow. The angle of repose of Lisinopril powder blendranged from 42°02′ to 45°50′ which showed passable flow property.

Table 17: Precompression study of formulated blends with lubricant.

Drug Formulation	Bulk density* (g/cm^3)	Tapped density* (g/cm^3)	Compressibility index* (%)	Hausner's ratio*	Angle of repose*
F1	0.5070 ± 0.012	0.6487 ± 0.020	17.82 ± 0.546	1.23 ± 0.0094	35°41′ ± 0.1518
F2	0.5472 ± 0.014	0.7118 ± 0.024	18.08 ± 0.612	1.21 ± 0.0091	40°43′ ± 0.025
F3	0.5349 ± 0.024	0.6272 ± 0.018	14.74 ± 2.13	1.17± 0.029	37°29′ ± 0.241

F4	0.5063 ± 0.0001	0.5894± 0.016	14.15± 2.57	1.16 ± 0.036	40°21′ ± 0.135
F5	0.4899 ± 0.0119	0.5559 ± 0.014	11.83 ± 2.235	1.13 ± 0.028	39°26′ ± 0.390
F6	0.4585 ± 0.0001	0.5256 ± 0.013	12.70 ± 2.24	1.14 ± 0.042	38°56′ ± 0.331
F7	0.5145 ± 0.013	0.5898 ± 0.035	12.57 ± 2.89	1.14 ± 0.028	39°17′ ± 0.145
F8	0.524 ± 0.013	0.627 ± 0.018	16.14 ± 0.419	1.19 ± 0.009	33°58′ ± 0.385
F9	0.548 ± 0.014	0.660 ± 0.018	16.99± 0.457	1.20 ± 0.004	37°23′ ± 0.518

*Mean ±S.D (n=3)

The bulk density of Lisinopril blends ranged from 0.4585 to 0.548 g/cm^3 and tapped density ranged from 0.5256 to 0.7118 g/cm^3. The compressibility index of the Lisinopril powder blend ranged from 11.83 to 18.08% and Hausner's ratio ranged from 1.13 – 1.23 which showed fair-good flow. The angle of repose of Lisinopril powder blendranged from 33°58′ to 40°43′ which showed fair-good flow property (table 17).

1.3.3. POST COMPRESSION STUDY FORMULATED RRCTs

Table 18: Post-compression characteristics of the formulated RRCTs.

Formulation	Uniformity weight* (mg)	Thickness (mm)**	Diameter (mm) **	Hardness** (kg/cm2)	Friability** (%)	Drug content** (%)
FP1	99.54	2 ± 0.0	6 ± 0.0	2.7 ± 0.244	0.476 ± 0.284	93.15 ± 0.235
FP2	99.36	2 ± 0.0	6 ± 0.0	2.3 ± 0.244	0.538 ± 0.365	93.68 ± 0.342
FP3	99.88	2 ± 0.0	6 ± 0.0	2.5 ± 0.218	0.348 ± 0.214	96.68 ± 0.215
FP4	99.50	2 ± 0.0	6 ± 0.0	2.8 ± 0.241	0.561 ± 0.341	94.71 ± 0.359
FP5	100.14	2 ± 0.0	6 ± 0.0	2.5 ± 0.244	0.648 ± 0.244	98.61 ± 0.256
FP6	100.48	2 ± 0.0	6 ± 0.0	2.3 ± 0.210	0.636 ± 0.176	100.54 ± 0.328
FP7	100.30	2 ± 0.0	6 ± 0.0	2.8 ± 0.241	0.590 ± 0.198	95.14 ± 0.268
FP8	100.61	2 ± 0.0	6 ± 0.0	2.7 ± 0.244	0.650 ± 0.289	97.60 ± 0.318

* Mean ±S.D (n=20), ** Mean ±S.D (n=5), **

The tablets comply with the test for uniformity of weight. The tablets have uniform thickness

and diameter. The hardness of the tablets was found to be between 2.3 kg/cm^2 and 2.8 kg/cm^2. All the formulated tablets showed sufficient mechanical strength to resist stress during the transportation.[26] The percentage friability of the tablets ranged from 0.348% to 0.648%. The percentage friability of all the formulation was within Pharmacopeial limits[84] (table 18).

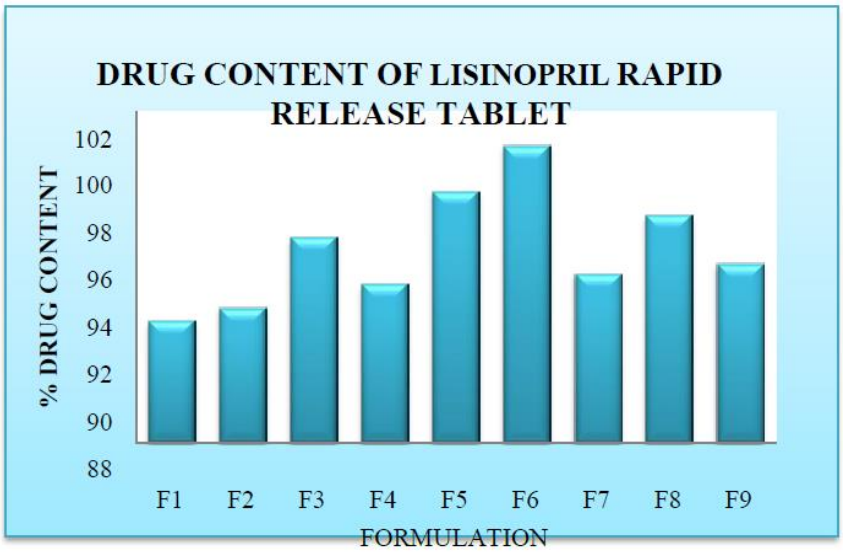

Fig. 13: Drug content of the formulated rapid release tablets.

The percentage drug content of Lisinopril in all the formulations ranged from 93.15 %w/w to 100.54 %w/w. All the formulations comply with the official standards.[4]

DISINEGRATION TIME

Table 19: Disintegration time of RRCTs.

Formulation	Disintegration time* (seconds)
F1	38 ± 0.015
F2	30 ± 0.023
F3	21 ± 0.012
F4	37 ± 0.030
F5	29 ± 0.018
F6	23 ± 0.025
F7	53 ± 0.021
F8	48 ± 0.017
F9	43 ± 0.026

*Mean ±S.D (n=3)

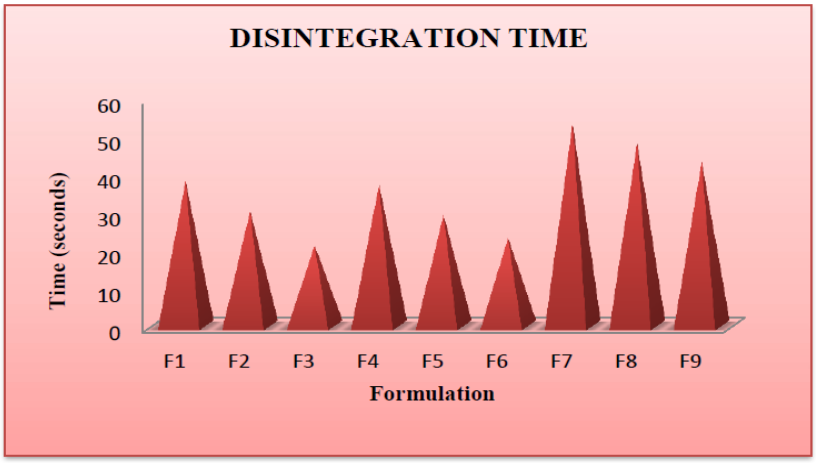

Fig. 14: Disintegration time of the formulated rapid release tablets.

The disintegration time of the Lisinopril tablets (fig 14 and table 19) ranged from 21 seconds to 53 seconds. The disintegration time of Lisinopril core tablet (F3) containing croscarmellose sodium (2%) as a super disintegrant was found to be the optimum core tablet for final tablet. All the formulations comply with the official standards.[6,10]

IN-VITRO DISSOLUTION STUDY

The *invitro* dissolution of RRCTs of Lisinopril is given in the Table 20

Table 20: *in-vitro* dissolution of rapid release formulation of Lisinopril.

Time (min)	Percentage Drug release*								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	42.21 ± 3.53	48.69 ± 2.26	**46.86 ± 2.49**	29.62 ± 2.26	32.08 ± 2.39	40.68 ± 1.13	-	-	-
2	61.65 ± 2.24	84.98 ± 3.38	**88.55 ± 2.14**	38.69 ± 2.85	44.68 ± 2.35	60.89 ± 2.26	-	-	-
3	72.07 ± 1.33	87.30 ± 3.40	**98.31 ± 2.14**	57.09 ± 1.68	60.63 ± 1.20	88.55 ± 2.14	-	-	-
4	75.22 ± 2.59	95.05 ± 2.21	**104.5 ± 1.22**	68.76 ± 1.73	76.31 ± 2.43	92.94 ± 2.80	-	-	-
5	78.37 ± 1.32	98.58 ± 2.23		72.08 ± 1.76	86.01 ± 1.20	96.05 ± 3.74	43.86 ± 1.18	45.65 ± 2.35	58.56 ± 1.63
6	87.97 ± 2.24	**106.8 ± 1.56**		86.73 ± 1.11	95.32 ± 1.13	**103.7 ± 3.14**	-	-	-
7	95.77 ± 3.45			91.08 ± 1.26	**102.8 ± 0.71**		-	-	-
8	**100.87 ± 1.29**			96.48 ± 2.36			-	-	-
9				**103.8 ± 1.78**			-	-	-

10							51.78 ± 1.08	54.83 ± 2.06	66.55 ± 1.86
15							53.81 ± 1.63	67.01 ± 2.34	74.66 ± 1.98
20							58.79 ± 1.18	70.57 ± 1.76	87.28 ± 2.13
25							71.35 ± 2.36	77.12 ± 1.58	97.09 ± 1.53
30							75.06 ± 2.32	83.69 ± 2.26	**103.98 ± 1.18**
35							-	91.74 ± 2.24	
40							80.21 ± 2.38	**99.97 ± 1.18**	
50							**101.26 ± 1.18**		

*Mean ±S.D (n=3)

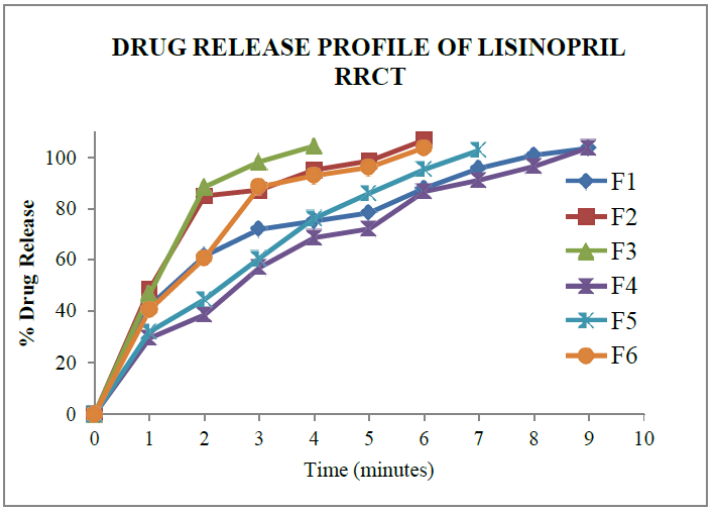

Fig. 15: *in vitro* drug release of formulated Lisinopril rapid Release Tablets.

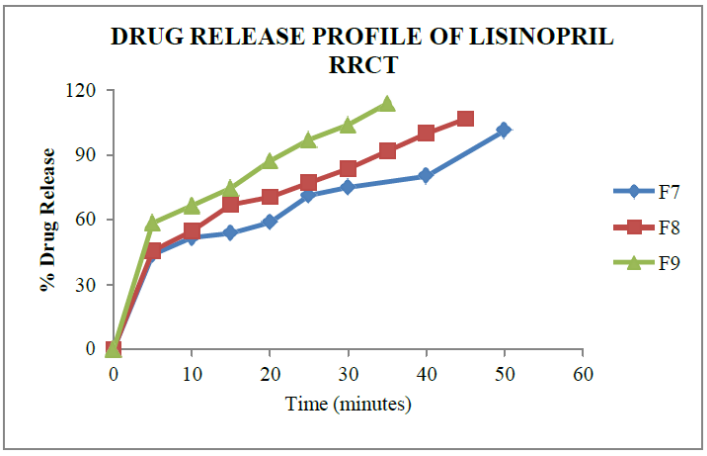

Fig. 16: *in vitro* drug release of formulated Lisinopril rapid release tablet.

From the *in-vitro* release study (fig 15 and 16), it was found that Formulation F3 containing 2% CCS showed rapid release of 98.31±2.14 at the end of 3 minutes compared to other formulations. So, F3 was optimized for final formulation.

Formulation F7 (2% SSG) showed slow release compared to other formulations.

1.4. FLOATING PULSATILE RELEASE TABLET OF LISINOPRIL

1.4.1.PRECOMPRESSION STUDY

The formulated coating material blends are evaluated for Pre-compression parameters. The results are given in the table 21.

Table 21: Precompression study of formulated blends of coating materials.

Drug Formulation	Bulk density* (g/cm^3)	Tappeddensity* (g/cm^3)	Compressibility index* (%)	Hausner's ratio*	Angle of repose*
FP1	0.6114 ± 0.0089	0.722 ± 0.012	15.31 ± 0.226	1.18 ± 0.0032	38°50′ ± 0.345
FP2	0.6509 ± 0.010	0.7581 ± 0.013	14.11 ± 1.42	1.16 ± 0.0019	29°24′ ± 0.190
FP3	0.6732 ± 0.010	0.7782 ± 0.014	13.48 ± 0.216	1.15 ± 0.0032	31°21′ ± 0.995
FP4	0.6522 ± 0.010	0.802 ± 0.015	18.67 ± 1.43	1.22 ± 0.021	35°39′ ± 0.540
FP5	0.6221 ± 0.017	0.740 ± 0.001	15.92 ± 2.42	1.18 ± 0.032	33°46′ ± 0.425
FP6	0.6115 ± 0.008	0.7147 ± 0.012	14.42 ± 1.37	1.16 ± 0.016	32°08′ ± 0.880
FP7	0.6139 ± 0.017	0.752 ± 0.025	18.37 ± 0.51	1.22 ± 0.0094	31°37′ ± 0.495
FP8	0.6657 ± 0.024	0.820 ± 0.001	18.82 ± 2.30	1.23 ± 0.047	36°54′ ± 0.445

*Mean ±S.D (n=3)

The bulk density of coating material blends ranged from 0.6114 to 0.6732 g/cm^3 and tapped density ranged from 0.7147 to 0.820 g/cm^3. The compressibility index of the coating material powder blend ranged from 13.48 to 18.80% and Hausner's ratio ranged from 1.15 – 1.23. The angle of repose of coating material powder blend ranged from 29°24′ to 38°- 50°′. The formulated coating material powder blend showed good flow property.

1.4.2. POST COMPRESSION STUDY

Table 22: Post-compression characteristics of the formulated Lisinopril Floating Pulsatile Release Tablets (FPRTs).

Formulation	Uniformity weight*	Thickness (mm)**	Diameter (mm)**	Hardness** (kg/cm2)	Friability** (%)	Drug content** (%)
FP1	(mg)	4 ± 0.0	10 ± 0.0	4.9 ± 0.374	0.741 ± 0.0351	96.56 ± 0.178
FP2	504.7	4 ± 0.0	10 ± 0.0	5.1 ± 0.374	0.649 ± 0.0265	93.71 ± 0.245
FP3	498.11	4 ± 0.0	10 ± 0.0	4.8 ± 0.244	0.572 ± 0.0376	93.00 ± 0.269
FP4	498.5	4 ± 0.0	10 ± 0.0	4.8 ± 0.244	0.560 ± 0.0278	92.01 ± 0.312
FP5	497.22	4 ± 0.0	10 ± 0.0	4.7 ± 0.244	0.736 ± 0.0198	95.99 ± 0.287
FP6	496.34	4 ± 0.0	10 ± 0.0	4.9 ± 0.210	0.589 ± 0.0267	93.71 ± 0.189
FP7	499.99	4 ± 0.0	10 ± 0.0	4.6 ± 0.244	0.638 ± 0.0356	96.13 ± 0.223
FP8	499.54	4 ± 0.0	10 ± 0.0	4.8 ± 0.210	0.654 ± 0.0263	95.29 ± 0.256

* Mean ±S.D (n=20), ** Mean ±S.D (n=5), **

The tablets comply with the test for uniformity of weight. The thickness and diameter of the formulated tablets is given in table 22. The tablets have uniform thickness and diameter. The hardness of the tablets was found to be between 4.7 kg/cm^2 and 5.1 kg/cm^2. All the formulated tablets showed sufficient mechanical strength to resist stress during the transportation.[6] The percentage friability of the tablets ranged from 0.560% to 0.741%. The percentage friability of all the formulation was within Pharmacopeial limits.[8] The percentage drug content of Lisinopril in all the formulations ranged from 93.00% w/w to 96.56 % w/w (fig 17). All the formulations comply with the official standards.[4]

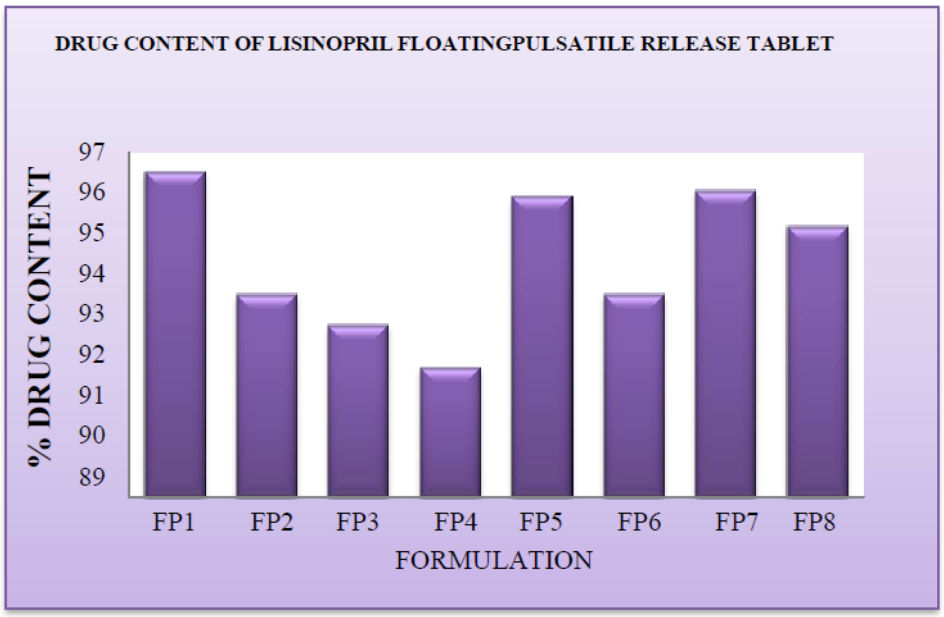

Fig. 17: Drug content of the formulated floating pulsatile release tablets.

INVITRO FLOATING STUDIES

The *invitro* floating characteristics of Lisinopril floating FPRT is given in the table 36.

Table 24: *in-vitro* floating characteristics of Lisinopril FPRT.

Formulation	Floating lag time* (minutes)	Floating duration* (hours)
FP1	15 min 30 sec	> 12hrs
FP2	2 min 50 sec	> 24hrs
FP3	2 min 05 sec	> 24hrs
FP4	14 min 08 sec	> 24hrs
FP5	8 min 17 sec	> 12hrs
FP6	9 min 15 sec	> 12hrs
FP7	8 min 32 sec	> 12hrs
FP8	7 min 30 sec	> 12hrs

*MEAN±S.D (n=3)

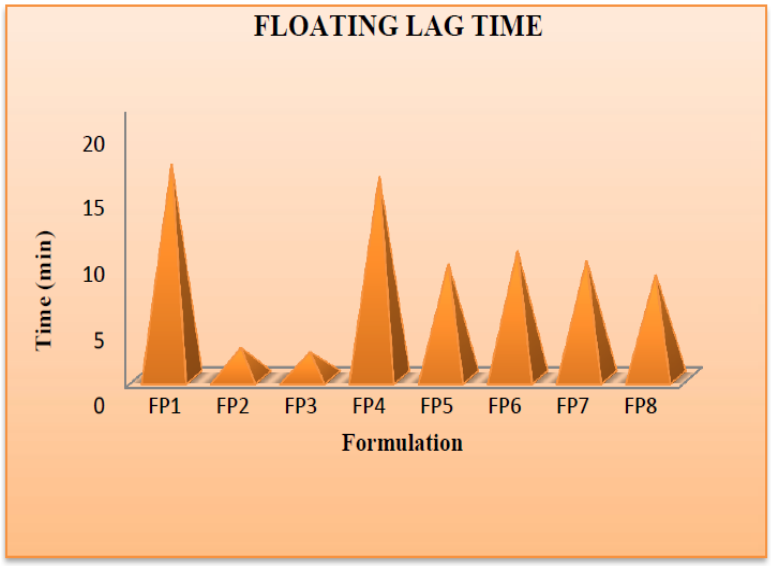

Fig. 18: Floating lag time of the formulated floating pulsatile release tablets.

The floating duration was ranged from 12 - >24 hours and the floating lag time ranged from 2 – 15 minutes.[20] The matrix integrity of the prepared floating tablets is good during the floating study. The formulation FP3 exhibits optimum floating behavior when compared with all the other formulations (fig 18).[13]

Swelling studies

Swelling study was carried out for floating pulsatile release tablets of Lisinopril. The % swelling index of the Lisinopril floating pulsatile tablets were given in the table 25 and figure 19.

Table 25: Swelling index (%) of Lisinopril FPRTs.

Time (hrs)	% Swelling index							
	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8
1	10.75	102.36	88.36	93.45	12.52	15.13	50.32	69.12
2	24.79	160.88	150.22	140.34	39.09	48.05	96.89	101.18
3	45.65	198.78	180.98	169.24	58.93	69.32	131.66	142.50
4	36.67	220.99	205.67	199.90	69.56	76.90	152.65	169.54
5	20.19	249.89	238.78	239.72	52.67	56.12	121.54	135.87
6	11.63	275.56	259.54	269.82	36.71	43.28	106.75	112.98
7	0.56	298.32	289.31	290.94	19.01	31.13	82.15	89.76
8		330.34	305.14	315.06	8.05	20.46	59.15	68.43
9		368.21	349.91	359.35	1.23	12.07	42.56	51.98
10		354.43	332.13	342.86		3.08	31.57	39.13

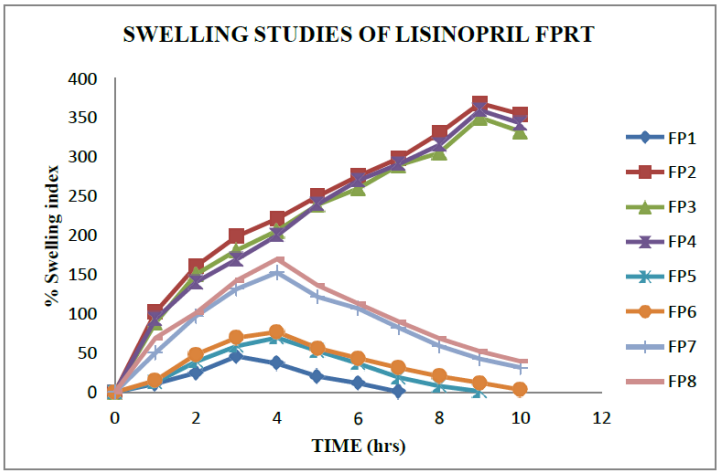

Fig. 19: Swelling index of Lisinopril FPRTs.

The swelling behavior of FPRT containing HPMC E15, HPMC K15M, HPMC K4M, Xanthan gum individually and in combination was compared. The obtained results showed that the swelling front erodes faster for HPMC E15 (150 mg) and the swelling front erosion was comparably slower in FPRTs with increased concentration of HPMC E15 and HPMC E15 in combination.[20]

FPRT containing HPMC K15M showed the highest swelling index as comparedto HPMC K4M, HPMC E15, and Xanthan gum. HPMC K4M, Xanthan gum and HPMC K15M showed a constant increase in the swelling index up to 9 hrs, after this there was a decrease due to the start of tablet erosion.[13]

IN-VITRO DISSOLUTION STUDY

The *invitro* dissolution of floating pulsatile formulations of Lisinopril is given in the table 26.

Table 26: *in-vitro* dissolution of floating pulsatile formulations of Lisinopril.

Time (hr)	Percentage Drug release							
	FP1	**FP2**	**FP3**	**FP4**	**FP5**	**FP6**	**FP7**	**FP8**
1	3.15	3.25	3.27	3.31	5.83	4.61	3.16	**4.68**
2	5.83	8.74	8.81	3.34	13.90	8.76	5.86	**4.73**
3	9.87	10.20	13.03	7.55	18.05	15.83	5.93	**6.17**
3.5	98.74	-	-	-	-	-	-	-
3.75	**103.81**	-	-	-	-	-	-	-
4	-	15.78	22.08	10.41	**100.90**	71.84	9.99	**13.17**
4.25	-	-	-	-	-	**101.31**	-	-
5	-	17.32	29.93	13.31	-	-	94.04	**17.47**
5.5	-		-	-	-	-	**103.07**	-
6	-	20.97	48.14	17.62	-	-	-	**20.38**
7	-	42.31	56.92	20.59	-	-	-	**89.17**
7.5	-	-	-	-	-	-	-	**101.23**
8	-	55.07	67.16	38.89	-	-	-	-
9	-	65.24	80.26	44.68	-	-	-	-
10	-	72.01	90.76	54.48	-	-	-	-
11	-	77.56	99.98	68.78	-	-	-	-
24	-	**89.98**	**108.66**	**88.18**	-	-	-	-

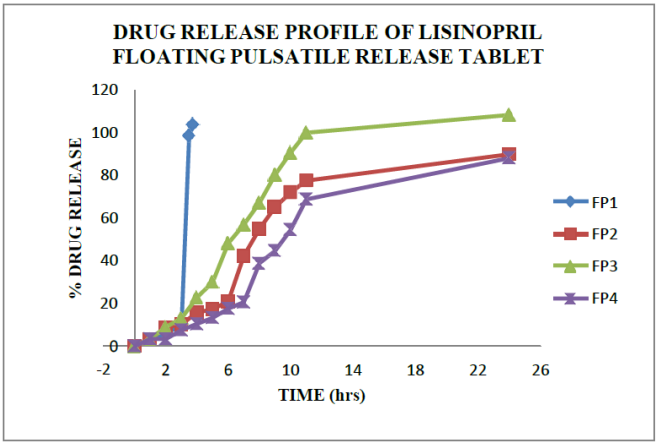

Fig. 20: *in vitro* drug release of formulated FPRT.

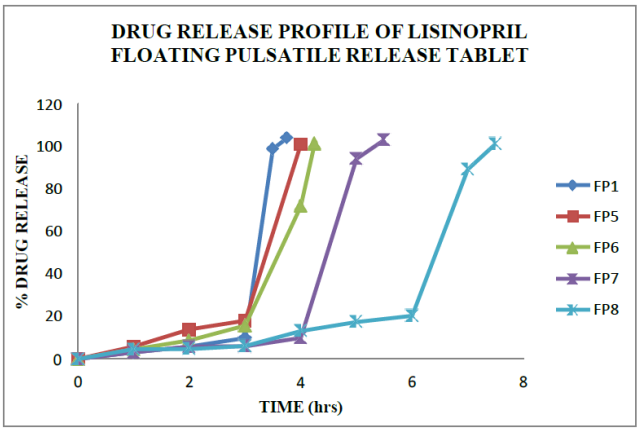

Fig. 21: *in vitro* drug release of formulated FPRT.

From the *in-vitro* release study, it was found that Formulation containing HPMC E15 individually and in combination showed a burst release after a lag time, whereas formulations containing HPMC K15M, HPMC K4M and Xanthan gum showed controlled release. Formulation FP8 showed a satisfactory drug release of 101.23% with a lag time of 6hrs (fig 20 and 21). So, the formulation was optimized for morning surge of hypertension.

1.5. *INVITRO* RELEASE KINETICS

The values obtained from invitro dissolution of Lisinopril floating pulsatile releasetablet were fitted in various kinetic models. The results are given in table 27 and figure 22, 23, 24, 25 and 26.

Table 27: *In-vitro* release kinetics of optimized FPRT.

Time (Hours)	Log time (Hours)	Sq. Root of time (Hours)	Cum % drug release	Cum % drug remaining	Log cum % drug release	Log cum % drug remaining	Cube rootof cum % drug remaining
0	∞	0	0	102.25	∞	2.009	4.676
1	0	1	3.29	98.96	0.517	1.995	4.625
2	0.301	1.414	5.17	97.08	0.713	1.987	4.595
3	0.477	1.732	6.62	95.63	0.820	1.980	4.572
4	0.602	2	12.22	90.03	1.087	1.954	4.481
5	0.698	2.236	16.99	85.26	1.230	1.930	4.401
6	0.778	2.449	21.33	80.92	1.328	1.908	4.325

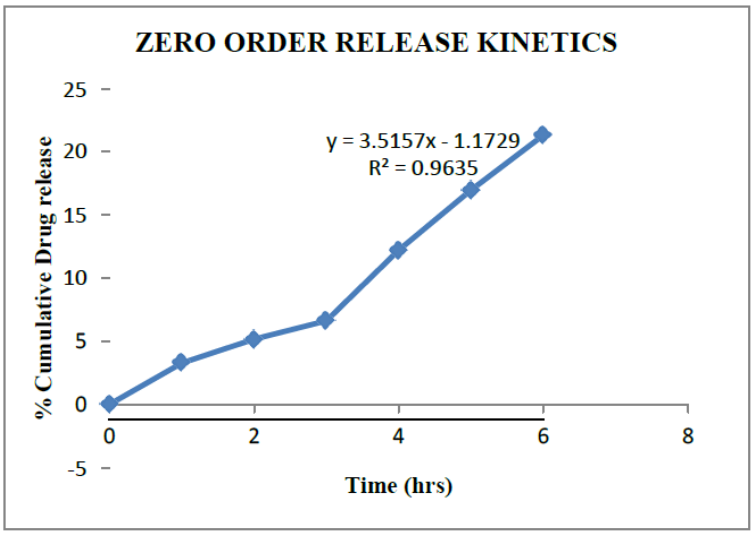

Fig. 22: Zero order kinetics.

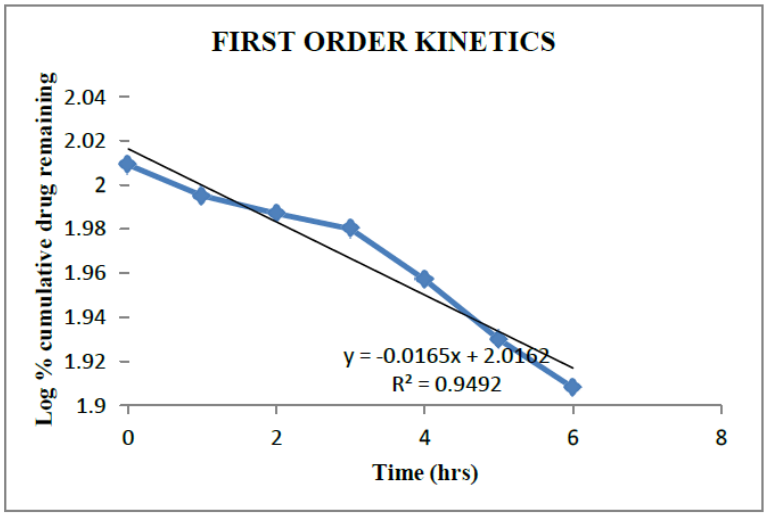

Fig. 23: First Order Kinetics.

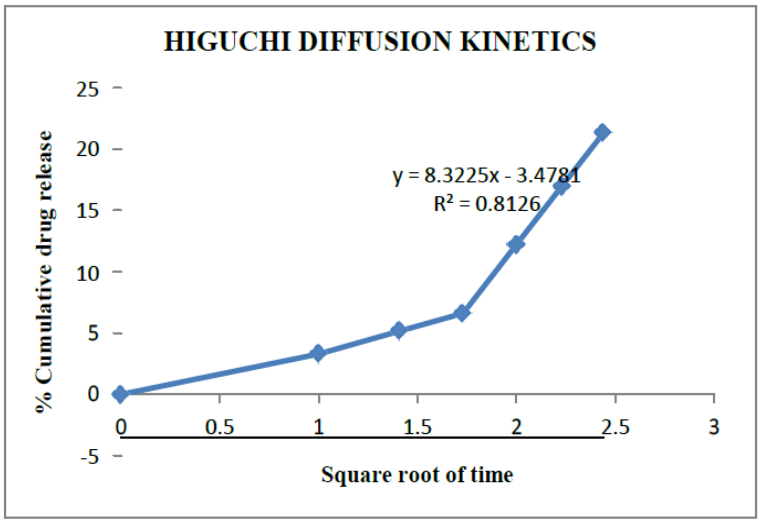

Fig. 24: Higuchi Diffusion Kinetics.

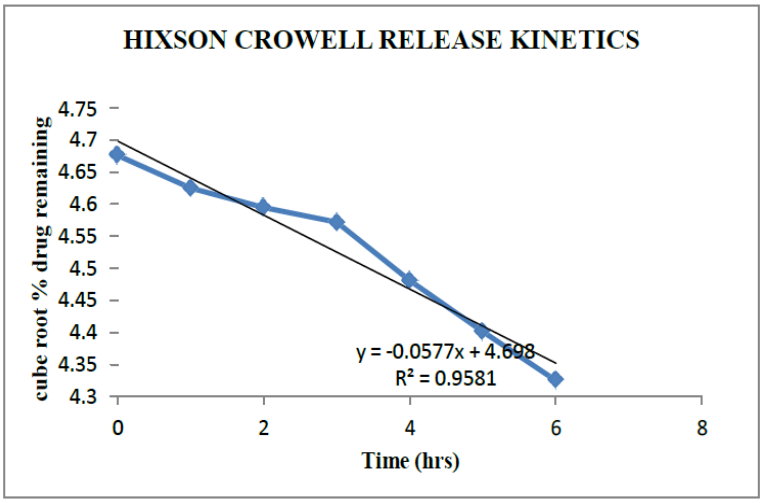

Fig. 25: Hixson crowell release kinetic.

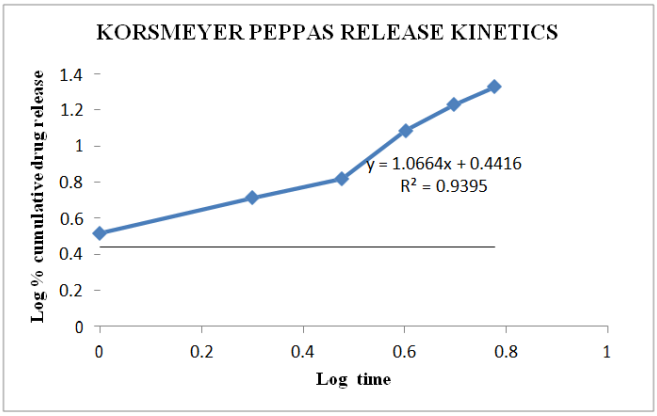

Fig. 26: Korsmeyer Peppas release kinetics.

The optimized FPRT (FP8) follows zero order kinetics up to the lag time, inwhich the regression value was 0.963. The 'n' value of Korsmeyer-peppas equation was found to be 1.066. From this it was concluded that the drug release follows non-fickian super case II transport.

1.6. STABILITY STUDIES

The stability studies of the optimized formulations are done at ambient room temperature and 40ºC ± 2ºC maintained at RH 75% ± 5% for 45 days (table 28).

Table 28: Stability study of Lisinopril FPRT– Optimized formulation.

Sample withdrawa lperiod	Drug content (in % w/w)		Percentage drug release (at the end of 7.5 hours)	
	At Ambient temperature	40ºC ± 2ºC and 75% ± 5% RH	At Ambient temperature	40ºC ± 2ºC and 75% ± 5% RH
0th day	96.54	96.21	101.13	99.65
15th day	96.87	95.80	99.91	101.50
30th day	97.35	96.54	100.67	99.79
45th day	97.15	96.98	98.70	99.32

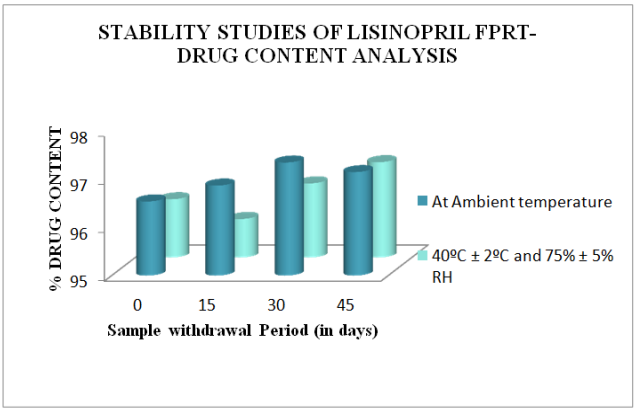

Fig. 27: Stability study of Lisinopril FPRT – Drug content analysis.

There was no significant difference in the physical appearance of the formulation (fig 27).

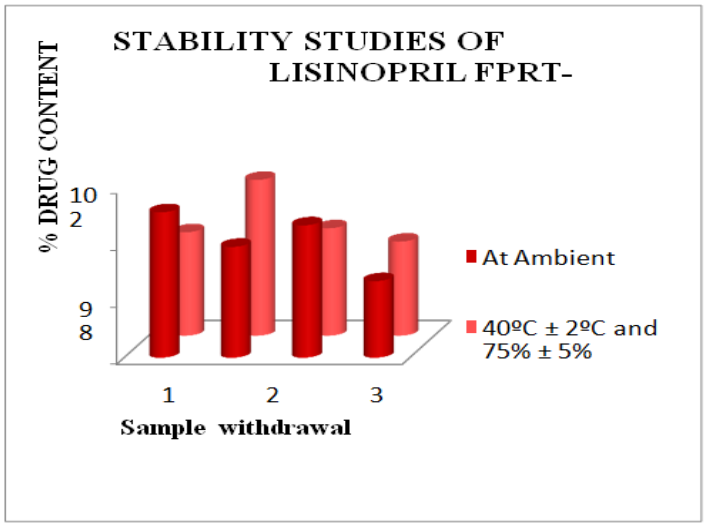

Fig. 28: Stability study of Lisinopril FPRT – Drug release study.

Short term stability studies of the optimized FPRT (FP8) indicated that there were no significant difference in the results of drug content analysis and the *in-vitro*drug release at the end of stability study (fig 28). This shows that the formulations remained stable during the process of storage.

CONCLUSION

In conclusion, the study successfully developed and evaluated Lisinopril Floating Pulsatile Release Tablets (FPRT) for mitigating the morning surge of hypertension. The formulation, comprising rapid release core tablets coated with hydrophilic polymers, demonstrated excellent pre-compression parameters and met quality standards for weight uniformity, hardness, and other key attributes. The optimized FPRT, particularly Formulation FP8, exhibited favorable drug release characteristics following zero-order kinetics and non-fickian super case II transport. The stability study over 45 days affirmed the formulation's robustness, with no significant alterations in physical attributes, drug content, or release profile. Overall, these findings underscore the potential of the Lisinopril FPRT, specifically FP8, as a stable and efficacious dosage form for addressing the circadian variability in hypertension. This manuscript explores the formulation and *in-vitro* evaluation of a floating pulsatile tablet of Lisinopril, targeting chronomodulated therapy for hypertension. By mimicking circadian rhythms, this pulsatile drug delivery system aims to enhance drug efficacy, minimize side effects, and improve patient compliance, offering a promising avenue for optimized treatment.

Recommended Future Works

Future studies could focus on scale-up processes to ensure the feasibility of large-scale production and evaluate the developed formulation's performance in in-vivo models. In vitro-in vivo correlation studies would strengthen the link between laboratory findings and clinical outcomes. Additionally, conducting bioequivalence studies against marketed products could provide valuable insights into the formulation's comparative efficacy and safety in real-world scenarios. Exploration of alternative polymers and coating techniques may further refine the floating pulsatile tablet's characteristics, contributing to the ongoing advancement of chronomodulated drug delivery systems.

REFERENCES

1. Harrisons online: Hypertensive vascular disease; chapter 24.
2. Tripathi, K D. Essentials of medical pharmacology. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd., 2008; 6: 483, 484, 488.
3. Hypertension. Available from: http://www.webmed.com/hypertension/highblood pressure/guide/high-blood-pressure
4. Indian Pharmacopoeia, Ministry of Health and Family Welfare. Ghaziabad, India:The Indian Pharmacopoeia commission, 2014; 2: 1264-1266.
5. DrugBank.ca. 'Lisinopril' Available from: **http://www.drugbank.ca/drugs/DB01197**
6. Indian Pharmacopoeia, Ministry of Health and Family Welfare. Ghaziabad, India:The Indian Pharmacopoeia commission, 2014; 1: 224-226, 251-258, 788.
7. P S Gangane, N M Mahajan, K R Danao, G N Pawde. Formulation and Evaluation of Chronomodulated Pulsatile Therapeutic System for Early Morning Surge in Blood Pressure. Int J Pharm Pharm Sci., 2015; 7(6): 337-341.
8. S. Sahu1, A Chourasia, A Toppo, A Asati. Formulation and evaluation of Lisinopril microspheres by ionic gelation technique. IJPLS, Jan. 2012; 3(1): 1377-1379.
9. Gurdeep R Chatwal and Sham K Anand. Instrumental methods of Chemical Analysis. Himalaya Publishing House, Mumbai, 2011; 2nd: 44-68.
10. United States Pharmacopoeia, 30th edition NF 25-2007. The Official Compendia of Standards, 242, 643, 674, 728.
11. Yeswanth Reddy Musukula. Design and evaluation of compression coated colon targeted tablets of Ketorolac Tromethamine using natural polymers and their combination with HPMC K100M. International Journal of Research in Pharmaceutical and Nano Sciences, 2014; 3(5): 408-417.

12. Anantha Nayaki Ravula, Bairi Agaiah Goud. A Review on - Recent Advances In Oral Pulsatile Drug Delivery. Journal of Advanced Pharmaceutical Sciences, 2011; 1(1): 132-145.
13. Swati C. Jagdale, Vishnu M. Suryawanshi, Sudhir V. Pandya, Bhanudas S. Kuchekar, Aniruddha R. Chabukswar. Development of Press-Coated, Floating-Pulsatile Drug Delivery of Lisinopril. Sci Pharm., 2014; 82: 423–440.
14. Arpit Mishra, Aadesh Kumar, Manoj Bhardwaj, Vaseem Fateh. Formulation and In Vitro Evaluation of Dry Coated Floating Pulsatile Drug Delivery Sysytem Of Enalapril Maleate. IJPSR, 2015; 6(5): 2005-2012.
15. Swati C. Jagdale, Nilesh A. Bari, Bhanudas S. Kuchekar, Aniruddha R. Chabukswar. Optimization Studies on Compression Coated Floating-Pulsatile Drug Delivery of Bisoprolol. BioMed Research International, 2013; Article ID 801769: 1-11.
16. Gagganapalli Santhoshi Reddy, Usha Yogendra Nayak, Praful Balavant Deshpande, Srinivas Mutalik. Gastroretentive Pulsatile Release Tablets of Lercanidipine HCl: Development, Statistical Optimization, and In Vitro and In Vivo Evaluation. The Scientific World Journal, 2014; 421931: 1-13.
17. Swati C. Jagdale, Chandrakala R. Pawar. Application of Design of Experiment for Polyox and Xanthan Gum Coated Floating Pulsatile Delivery of Sumatriptan Succinate in Migraine Treatment. BioMed Research International, 2014; 547212: 1-10.
18. N. Raja, S. Vijaykumar, R. Anantha kumar, C. Benedict jose. Development And Evaluation Of Floating Pulsatile Drug Delivery System Of Metoprolol Succinate. World Journal of Pharmacy and Pharmaceutical Sciences, 2015; 4(5): 549-561.
19. Suvakanda Dash, Padala Narasimha Murthy, Lilakanta Nath and Prasanta Chowdhary. Kinetic modeling on drug release from controlled drug delivery systems. Acta Poloniae Pharmaceutica. Drug research, 2010; 67(3): 217-223.
20. Anuradha K. Salunkhe, Remeth J. Dias, Kailas K. Mali, Niranjan S. Mahajan, Vishwajeet S. Ghorpade. Formulation and evaluation of floating pulsatile drug delivery system of Metoprolol tartrate. Scholars Research Library, Der Pharmacia Lettre, 2011; 3(3): 147-160.
21. Y R Sharma. Elementary Organic Spectroscopy. New Delhi: S Chand Publishing Pvt. Ltd., 2013; 5th revised edition: 91-141.