JETIR.ORG ISSN: 2349-5162 | ESTD Year : 2014 | Monthly Issue
JOURNAL OF EMERGING TECHNOLOGIES AND INNOVATIVE RESEARCH (JETIR)
An International Scholarly Open Access, Peer-reviewed, Refereed Journal

FORMULATION AND EVALUATION OF GASTRORETENTIVE FLOATING TABLET OF LISINOPRIL

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Abstract

The present work involves the design, development and in-vitro evaluation of Lisinopril floating pulsatile release tablet, in which the core tablets are rapid release formulation which is coated with hydrophilic polymers such as HPMC E15, HPMC K15M, HPMC K4M, Xanthan gum individually and in combination. FPRT was designed for the treatment of morning surge of Hypertension The rapid release core tablets of Lisinopril were formulated with various concentrations of SSG (2%, 3% and 4%), CCS (1%, 1.5% and 2%) and Crospovidone (2 %, 3.5% and 5%) by direct compression. The in-vitro dissolution studies of the formulated Lisinopril Core tablets were performed using USP type-II dissolution apparatus. From the formulated batches, the formulation F3 released the drug very quickly (within 4 minutes) when compared to other formulations. Based on the Disintegration and in-vitro release studies of Lisinopril rapid release core tablets, formulation F3 was optimized and selected for Press coating. The formulated Lisinopril FPRTs were found to be within limits with respect to Weight uniformity, Hardness, Thickness, Diameter and Friability. The drug content of the Lisinopril FPRTs were estimated and found to be within Pharmacopoeial limits. The formulated Lisinopril FPRTs were found to be within limits with respect to Weight uniformity, Hardness, Thickness, Diameter and Friability. The drug content of the Lisinopril FPRTs were estimated and found to be within Pharmacopoeial limits.

Keywords: gastroretentive, lisinopril, floating tablets.

INTRODUCTION

ORAL SOLID DOSAGE FORMS [1, 2, 3]

Oral route is the most widely used route of administration among all the routes that have been developed for systemic controlled delivery of drugs.

This is due to following reasons:

1. Oral route is most convenient and uncomplicated
2. Ease of administration and safe
3. Improved patient compliance
4. Cost-effective

Oral solid forms such as tablets and capsules has been formulated and developed nowadays since they are most effective routes of administration of a new drug. Pharmaceutical products designed for oral delivery and currently available on the prescription and over the counter markets are mostly immediate release type, which is designed for immediate release of drug for rapid absorption.

TABLET[2]

Tablet is defined as a compressed solid dosage form containing medicaments with or without excipients. Pharmaceutical tablets are solid, flat or biconvex dishes, unit dosage form, prepared by compressing a drugs or a mixture of drugs, with or without diluents. They vary in shape and different greatly in size and weight, depending on amount of medicinal substance and the intended mode of administration. It is the most popular dosage form and 70% of the total medicines are dispensed in the form of tablet.

Advantages of the tablet dosage form

- They are unit dosage form and greatest capabilities of all oral dosage form for the greatest dose precision and the least content variability.
- Cost is lower of all oral dosage form.
- Lighter and compact.
- Easiest and cheapest to package and strip.
- Easy to swallowing with least tendency for hang-up.
- Sustained release product is possible by enteric coating.
- Objectionable odor and taste can be masked by coating technique.
- Suitable for large scale production.
- Greatest chemical and microbial stability over all oral dosage for.

Disadvantages of tablet dosage form

- Elderly ill and children could have problem in swallowing the tablets.
- Some drugs resist compression into dense compacts, owing to amorphous nature, low density character.
- Drugs with poor wetting, slow dissolution properties, may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability.

IMMEDIATE RELEASE DRUG DELIVERY SYSTEM[5, 6]

DEFINITION[5]

Immediate release drug delivery system are based on single or multiple-unit reservoir or matrix system, which are designed to provide immediate drug levels in short period of time.

1.2.1 DESIRED CRITERIA FOR IMMEDIATE RELEASE DRUG DELIVERY SYSTEM

- Immediate release dosage form should dissolve or disintegrate in the stomach within a short period.
- In the case of liquid dosage form it should be compatible with taste masking.
- Be portable without fragility concern.
- Have a pleasing mouth feel.
- It should not leave minimal or no residue in the mouth after oral administration.
- Exhibit low sensitivity to environmental condition as humidity and temperature.
- Be manufactured using conventional processing and packaging equipment at low cost.

Merits of Immediate Release Drug Delivery System

- Improved compliance/added convenience
- Improved stability, bioavailability
- Suitable for controlled/sustained release actives Allows high drug loading.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Adaptable and amenable to existing processing and packaging machinery.
- Cost effective.
- Decreased disintegration and dissolution times for immediate release oral dosage forms;
- Increased solubility of Pharmaceutical composition.

Controlled Drug Delivery Systems:

Controlled drug delivery systems have been developed which are capable of controlling the rate of drug delivery, sustaining the duration of therapeutic activity and/or targeting the delivery of drug to a tissue[4].

Controlled drug delivery or modified drug delivery systems are divided into four categories.

1. Delayed release
2. Sustained release
3. Site-specific targeting
4. Receptor targeting

More precisely, controlled delivery can be defined as:-

1. Sustained drug action at a predetermined rate by maintaining a relatively constant, effective drug level in the body with concomitant minimization of undesirable side effects.
2. Localized drug action by spatial placement of a controlled release system adjacent to or in the diseased tissue.
3. Targeted drug action by using carriers or chemical derivatives to deliver drug to a particular target cell type.
4. Provide physiologically/therapeutically based drug release system. In other words, the amount and the rate of drug release are determined by the physiological/ therapeutic needs of the body.
5. A controlled drug delivery system is usually designed to deliver the drug at particular rate. Safe and effective blood levels are maintained for a period as long as the system continues to deliver the drug.
6. Controlled drug deliveries usually results in substantially constant blood levels of the active ingredient as compared to the uncontrolled fluctuations observed when multiple doses of quick releasing conventional dosage forms are administered to a patient.

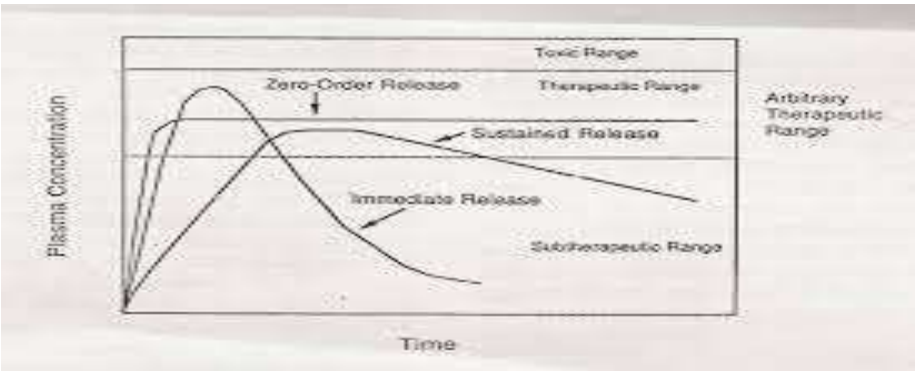


Fig. 1.1: Drug level verses time profile showing differences between zero order, controlled releases, slow first order sustained release and release from conventional tablet

Oral drug delivery systems have progressed from immediate release to site-specific delivery over a period of time. Every patient would always like to have a ideal drug delivery system possessing the two main properties that are single dose or less frequent dosing for the whole duration of treatment and the dosage form must release active drug directly at the site of action.

Floating Drug Delivery System (FDDS) [12, 13, 14]

Floating systems or hydrodynamically controlled systems are low-density systems that have sufficient buoyancy to float over the gastric contents and 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 the fluctuation in plasma drug concentration.

Advantages of FDDS[13]

- Improved drug absorption, because of increased gastric residence time and more time spent by the dosage form at its absorption site Controlled delivery of drugs.
- Delivery of drugs for local action in the stomach.
- Minimizing the mucosal irritation due to drugs, by drug releasing slowly at controlled rate.
- Treatment of gastrointestinal disorders such as gastro-esophageal reflux.
- Simple and conventional equipment for manufacture.
- Ease of administration and better patient compliance.
- Site-specific drug delivery.

Disadvantages of FDDS [14]

- Floating systems are not feasible for those drugs that have solubility or stability problems in gastric fluids.
- Gastric retention is influenced by many factors such as gastric motility, pH and presence of food. These factors are never constant and hence the buoyancy cannot be predicted.
- Drugs that cause irritation and lesion to gastric mucosa are not suitable to be formulated as floating drug delivery systems.

MODIFIED DRUG RELEASE PREPARATIONS[7, 8]

During the early 1990s, second-generation modified-release drug preparations achieved continuous and constant-rate drug delivery, in which constant or sustained drug output minimize drug concentration “peak and valley”

levels in the blood, so promoting drug efficacy and reducing adverse effects. Modified-release drug preparations are expected to provide reduced dosing frequency and improved patient compliance compared to conventional release preparations. Second generation modified-release dosage forms include slowed-release, delayed-release, prolonged-release, extended- release, repeated-release, sustained-release, and controlled-release drug preparations. Several controlled-release preparations present numerous problems such as resistance and drug tolerance, and activation of the physiological system due to long- term constant drug concentrations in the blood and tissues.

Recent studies reveal that the body's biological rhythm may affect normal physiological function, including gastrointestinal motility, gastric acid secretion, gastrointestinal blood flow, renal blood flow, hepatic blood flow, urinary pH, cardiac output, drug-protein binding, and liver enzymatic activity, and biological functions such as heart rate, blood pressure, body temperature, blood-plasma concentration, intraocular pressure, stroke volume and platelet aggregation. Most organ functions vary with the time of the day, particularly when there are rhythmic and temporal patterns in the manifestation of a given disease state. The symptoms of many diseases, such as bronchial asthma, myocardial infarction, angina pectoris, hypertension, and rheumatic disease have followed the body's biological rhythm. Day-night variation in asthmatic dyspnea and variations in the incidence of myocardial infarction occur throughout the early morning hours.

Controlled release medications deliver continuous treatment, rather than providing relief of symptoms and protection from adverse events solely when necessary, the development of a third-generation of advanced drug delivery systems (DDSs) to optimize and create new innovative DDS which provide a defined dose, at a chosen rate, at a selected time, to a targeted site is now a growing challenge.

A chronodelivery system, based on biological rhythms, is a state of the art technology for drug delivery; chrono-modulated DDSs not only increase safety and efficacy levels, but also improve overall drug performance.

Chronopharmaceutics[7, 11],

It is evident that drug delivery and therapy should be modified to achieve an efficient drug level at an optimum time, rather than merely maintaining constant drug concentrations. Thus, the time-controlled function of third-generation DDSs currently under development is finding application in new and improved disease therapeutics. Biological rhythms may be applied to pharmacotherapy by adopting a dosage form that synchronizes drug concentrations to rhythms in disease activity. During the past two decades, diseases that follow rhythmic patterns have given rise to the creation of new drug delivery dosage forms, called chronopharmaceuticals.

Chronopharmaceutics includes the fundamentals and research into various aspects of chronophysiology, chronopathology, chronogenetics, chronopharmacology, chronopharmacokinetics, chronopharmacodynamics, chronotherapeutics, and chronotoxicology. Broadly, chronopharmaceutics bring together chronobiology and pharmaceutics.

Chronobiology[11] is the study of biological rhythms and mechanisms in living systems. It assumes that the bioprocesses and functions of all living organisms exhibit predictable variability over time.

Pharmaceutics is one of the most diverse subject areas in all of pharmaceutical science and deals with both the scientific and technological aspects of the design and manufacture of dosage forms for medicines to assure their safety, effectiveness, quality, and reliability. Thus, chronopharmaceutics is defined as a branch of pharmaceutics devoted to the design and evaluation of DDSs, that release a drug at a rhythm to match the biological requirement for a given disease therapy.

It has been found out that circadian rhythm is useful for the treatment of various pathophysiological conditions of human body, but such chronopharmacological phenomena are markedly influenced by not only the pharmacodynamics but also the pharmacokinetics of drugs. Thus, the application of circadian rhythm to pharmacotherapy may be accomplished by the optimal timing of the special formulation or DDS designed to synchronize drug concentrations to rhythms in disease activity.

The new chronotropic DDS technology for delivering drugs precisely in a time-controlled fashion in accordance with circadian rhythms may be developed as a chronopharmaceuticals product to treat different human diseases, as proposed by Fig

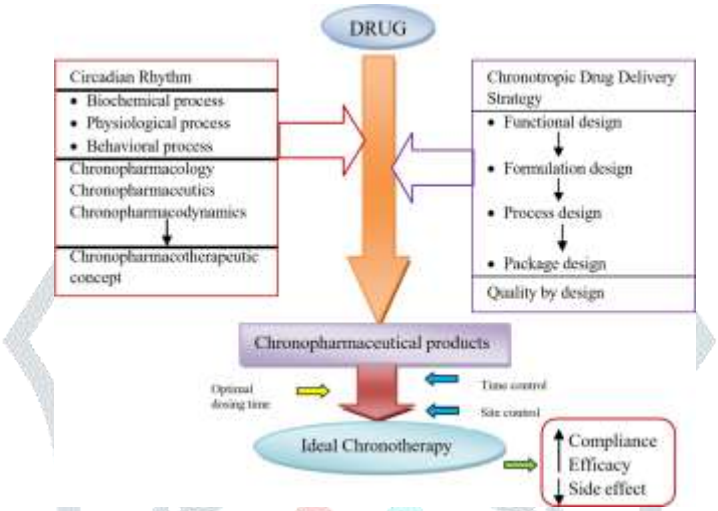


Fig: Design and development of new chronotropic DDSs in accordance with circadian rhythm of human body.

Rationale behind designing these chronotropic DDSs is to release the drug at desired time based on pathophysiological need of disease, which results in the improvement of therapeutic efficacy and patient-compliance. These systems are meant for treatment of those diseases that are caused due to circadian changes in body but the zero-order drug released products seem to have no desire.

Biological rhythms and pulsatile hormone secretion[7, 8, 11]

Biological rhythms exist in all living organisms, and may be necessary for survival under changing environmental conditions. The interval of biological rhythms can vary considerably according to the type of living organism. Some biological rhythms are very fast while others can be very slow, and many normal human biological functions exhibit predictable cyclic rhythms.

Ultradian rhythms11: Oscillations of shorter duration are termed Ultradian rhythms (more than one cycle per 24 hours) E.g. 90 minutes sleep cycle.

Infradian rhythms11: Oscillations that are longer than 24hrs are termed as Infradian rhythms (less than one cycle per 24 hours) e.g. menstrual cycle.

A biological clock exists in the brains of all mammals, and provides circadian information to all cells in the body, thereby allowing animals to adjust their physiology according to the time of day.

Circadian rhythm[7, 8]

Circadian rhythms can change the sleep-wake cycles, hormone release, body temperature, and other important bodily functions driving the alteration of various physiological, biochemical and behavioral processes

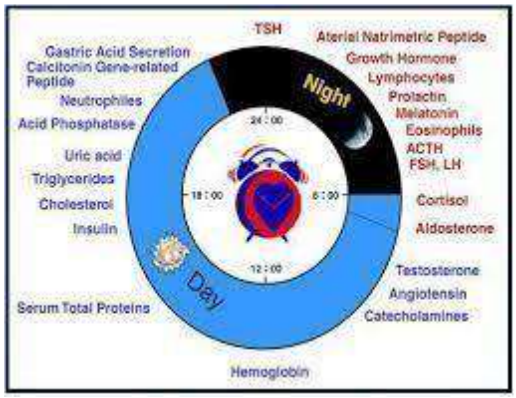


Fig.: Human circadian time structure-dependent pulsatile hormones secretion

Pulsatile hormone secretion

Many hormones in the human body are secreted in a cyclical or pulsatile manner, rather than continuously. Secretions of the anterior and posterior pituitary hormones, adrenal glucocorticoids, mineralocorticoids and catecholamine's, gonadal sex steroids, parathormone, insulin, and glucagon are pulsatile. During hormone secretion, a baseline release is combined with the pulsed release. Insulin is one good example of a pulsatile hormone release. Pulsatile release of gastrointestinal hormones, stimulated by presence of food in the gastrointestinal tract, generally causes the release of digestive enzymes from the pancreas and stomach. Many hormones including follicle stimulating hormone (FSH), luteinizing hormone (LH), luteinizing hormone releasing hormone (LHRH), estrogen, and progesterone are also regulated in the body in pulsatile manner. Numerous biological functions in the body are thus regulated by the temporal and pulsatile release of hormones.

If the hormones were continuously secreted, a hormonal imbalance may arise, which would not only induce down regulation of hormone receptors on the target cellular membranes, but might also produce undesired side-effects.

Circadian variation[7, 8, 16]

Circadian rhythm regulates several body functions such as metabolism, physiology, behavior, sleep patterns, hormone production, and so on.

The circadian rhythm not only affects most physiological functions but also influences the absorption, distribution, metabolism, and elimination (ADME) of drugs, leading to changes in drug availability and target cell responsiveness Thus, the time-dependent dynamic bioprocesses in human body are significantly dependent on circadian variations, and so constant delivery of a drug into the human body seems both unnecessary and undesirable.

Timing the administration of some medications in accordance with the body's circadian rhythm may significantly affect the drug's pharmacokinetics and pharmacodynamics.

Many common diseases also display a marked circadian variation during onset or exacerbation of symptoms.

Since the circadian rhythm influences normal biological processes, the occurrence or intensity of symptoms of these diseases is not constant throughout the day.

Several diseases, including arthritis, asthma, allergies, peptic ulcer disease, dyslipidemia and cancer exhibit predictable circadian variation. Medications and treatments given at the appropriate time according to the body's circadian rhythms will result in more favorable outcomes.

The circadian pattern of disease

Pulsatile Drug Delivery system[7,8,10,11,17]

. The pulsatile drug delivery system (PDDS) is intended to deliver a rapid, or transient, and quantified medication release after a predetermined off-release period (lag time). PDDS can deliver the correct amount of medication at the desired location at the optimal time for maximum effect against disease, thereby enhancing therapeutic efficacy and improving patient compliance.

PDDS avoids problems with degradation of drugs in the stomach or first-pass metabolism, enables the simultaneous administration of two different drugs, allows the release drugs at different sites within the gastro-intestinal tract, and can deliver a drug release burst at one or more predetermined time intervals, according to patient requirements.

The advantages of PDDS extend to drugs with chronopharmacological behaviors, where nighttime dosing is required, and for various diseases that are influenced by circadian rhythms. Since PDDS has a unique mechanism of delivery, whereby a drug releases rapidly after a lag time, various PDDSs have appeared on the markets that replace modified-release dosage forms. Various release patterns are illustrated in Fig.

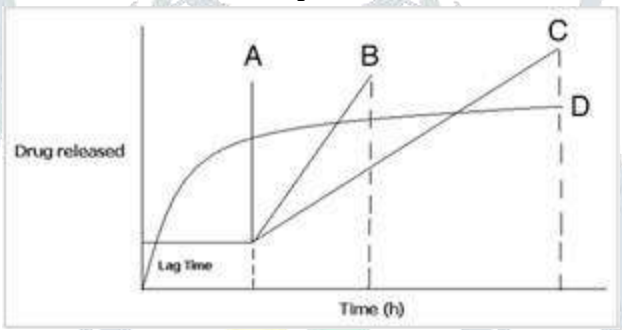


Fig. Different release patterns for various pharmaceutical dosage forms

The PDDS is formulated to release a drug after a predetermined lag time in a specific region of the gastrointestinal tract, or as a chronotherapeutic time-dependent release. Pulsatile drug release should occur independently of the environment (e.g. pH, enzymatic activity, intestinal motility) or other stimuli; lag time prior to the release of the drug is primarily determined by the formulation's design.

Advantages of PDDS [18, 20, 21]

•Nearly constant drug levels at the site of action.

•Avoidance of undesirable side effects.

•Reduced dose.

•Improved patience compliance.

•Used for drugs with chronopharmacological behavior.

•No risk of dose dumping. • Improved bioavailability, tolerability and reduces side effects.

Limitations of PDDS [18,20,21]

•Lack of manufacturing reproducibility and efficacy.

•Large number of process variables.

•Multiple formulation steps.

•Higher cost of production.

•Need of advanced technology. • Trained/ skilled personal needed for manufacturing.

Mechanism of drug release from pulsatile drug delivery system [20]

The mechanism of drug release from PDDS can be occurring in the following ways:

Diffusion

Water diffuses into the interior of the particle when particle come in contact with aqueous fluids in the gastrointestinal tract and resultant drug solutions diffuse across the release coat to the exterior.

Erosion

Some coatings designed to erode gradually with time, result in the release of drug contained within the particle.

Osmosis

An osmotic pressure can be built up within the interior of the particle when water allows entering under the right circumstances. The drug is forced out of the particle into the exterior through the coating.

Methodologies for PDDS [17, 20]

Methodologies for the PDDS can be broadly classified into four classes; I. Time Controlled Pulsatile release

A. Single unit system

B. Multi-particulate system

II. Stimuli induced

A. Thermo-Responsive Pulsatile release

B. Chemical stimuli induced pulsatile systems

III. External Stimuli Pulsatile release

A. Electro responsive pulsatile release

B. Magnetically induced pulsatile release

IV. Pulsatile release systems for vaccine and hormone products

Disease treatments requiring pulsatile drug delivery [8, 9, 16]

Normal physiological condition

The body varies greatly in physiological and biochemical status over a 24-hour period due to circadian rhythm. Variation may be expressed as sleep-wakefulness, changes in body temperature, cell division, heart rate, and other factors.

Normal lung function undergoes circadian changes that reach a low level during the early morning hours. Endocrine substances, such as growth hormones, gonadotropins, and insulin are secreted from glands and organs in a pulsatile fashion, according to circadian rhythms, which maintain the normal condition of human life. The secretion of growth hormone reaches peak rates during sleep, but the plasma levels of both testosterone and cortisol are typically greatest in the early morning.

Variation in the severity of many diseases over a 24-hour period is well known. Diseases such as bronchial asthma, myocardial infarction, angina pectoris, rheumatic disease, ulcers, diabetes, attention deficit syndrome, hypercholesterolemia and hypertension show symptomatic changes due to circadian rhythmicity.

Thus, understanding the biological basis of these changes over the day and during the night can help to enhance drug therapy, by identifying appropriate times for drug administration.

Polymers used in PDDS [15]

Commonly used polymers in PDDS are Hydroxypropyl methyl cellulose (HPMC), Ethyl cellulose, Cellulose Acetate, Phthalate, Eudragit, Hydroxypropyl cellulose (HPC), Xanthan gum.

FLOATING PULSATILE DRUG DELIVERY SYSTEM[14]

The combinations of floating and pulsatile principle are very well suitable for site and time specific oral drug delivery has recently been of greater interest in pharmaceutical field to achieve improved therapeutic efficacy.

Advantages [14]

- Prolonged retention of drug delivery system in stomach

➢ To increase drug bioavailability, predictable, reproducible and improved generally short gastric residence time, no risk of dose dumping local drug action and the flexibility to blend dosage form with different composition and release pattern.

➢ To keep the drug in floating condition in stomach to get relative better response.

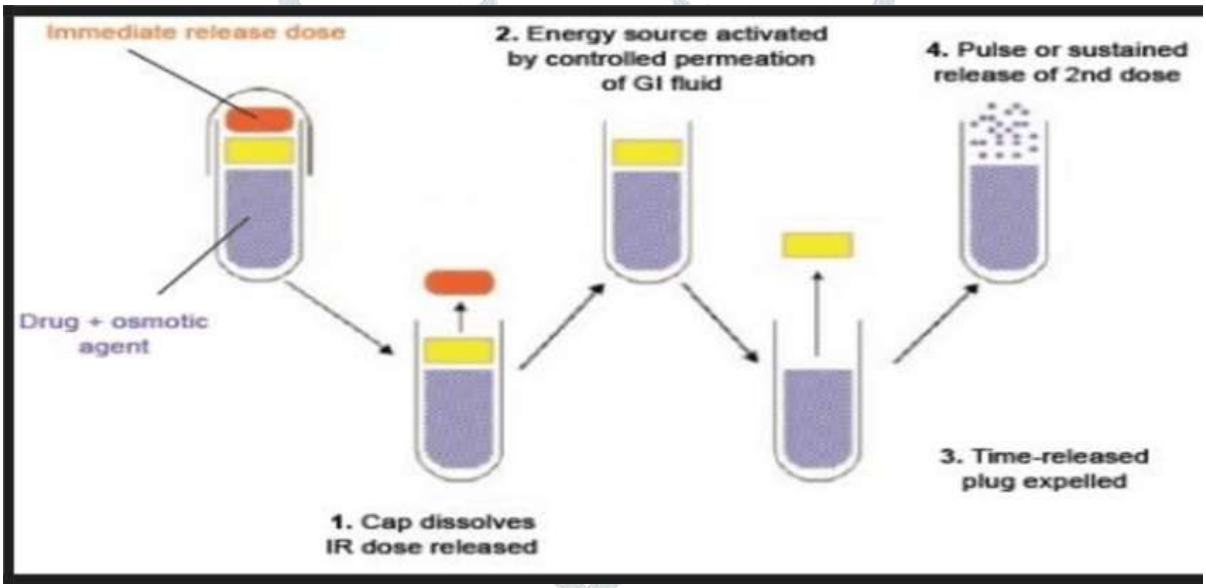
Disadvantages [14]

➢ Manufacturing of dosage form requires multiple formulation steps and higher cost of production.

➢ The dosage form should be administered with full glass of water.

➢ Drugs which are irritant to gastric mucosa is not desirable or suitable.

Design of floating pulsatile drug delivery system (FPDDS) [14]



It consists of capsule which coated with a semi permeable membrane. A mysterious drug consisting of the osmotic ally active agents and drug formulations are integrated inside the capsule. When this capsule comes in contact with dissolution fluid, the semi permeable membrane allows the entry of water, which causes increase of pressure and the insoluble plug expels after a lag time

AIM OF THE WORK

- To formulate and evaluate Floating Pulsatile tablet of Lisinopril providing chronomodulated therapy for better treatment of Hypertension
- To prepare the rapid release core tablets of Lisinopril using various superdisintegrants such as sodium starch glycolate, croscarmellose sodium, crospovidone by direct compression
- Compression coating of optimized core tablets using hydrophilic polymers such as HPMC E5, HPMC K4M, HPMC K15M and Xanthan gum by direct compression

OBJECTIVE

- To provide drug release at the time when it is needed most.
- To reduce dose related side effects.
- To enhance the bioavailability of the drug.

PLAN OF WORK

The present study was designed and planned as follows:

I. Compatibility studies

- Physical compatibility study – at room temperature and accelerated condition (40º C ± 75 RH)
- Chemical compatibility study – Fourier transform Infra-Red Spectroscopy

(FT-IR) study (identification and compatibility of drug and excipients)

II. Preparation of Standard curve for LISINOPRIL

III. Pre-formulation studies of drug and formulations

IV. Formulation and Development of Rapid release core tablet of Lisinopril

V. Evaluation of Rapid release core tablet of Lisinopril Physical characteristics

•Description

•Uniformity of weight

•Diameter and thickness

•Hardness

•Friability

•Drug content

•Disintegration study

•In-vitro release study

VI. Formulation and Development of Floating Pulsatile release tablet of Lisinopril VII. Evaluation of Compression coated (FPRT) tablets Physical characteristics

•Description

•Uniformity of weight

•Diameter and thickness

•Hardness

•Friability

•Drug content

•In-vitro release study /

•In-vitro buoyancy studies

•Swelling index determination

•Stability study of optimized formulation as per ICH guidelines

Materials and methodology

S.No	Name of the material	Manufacturer / Supplier	Use in formulation
1	Lisinopril	Unicure (India) Pvt. Ltd.,	Active Pharmaceutical Ingredient
2	Sodium Starch Glycolate	Kniss Laboratories	Super Disintegrant
3	Cros Povidone	Kniss Laboratories	Super Disintegrant
4	Cros Carmellose Sodium	Kniss Laboratories	Super Disintegrant
5	Xanthan gum	Kniss Laboratories	Hydrophilic polymer
6	HPMC K15M	Sai Mirra Innopharm Pvt. Ltd.,	Hydrophilic polymer
7	HPMC E15	Colorcon Asia Pvt. Ltd.,	Hydrophilic polymer
8	HPMC K4M	Kniss Laboratories	Hydrophilic polymer
9	Sodium bicarbonate	Indian Research products	Gas generating agent
10	Microcrystalline Cellulose	Pharma French Ltd	Diluent
11	Lactose	Kniss Laboratories	Diluent
12	Magnesium Stearate	Kniss Laboratories	Lubricant
13	Talc	Kniss Laboratories	Glidant
14	Erythrosine	Kwality pharmaceuticals	Colorant

PREFORMUALTION STUDIES

The Preformulation studies are conducted to establish the physicochemical characteristics of the drug and its compatibility with the various excipients utilized in the formulation. The Preformulation studies are necessary to formulate the drug into stable, safe and effective dosage form.

DRUG-EXCIPIENT COMPATIBILITY STUDY83

The Drug and the Excipients selected for the formulation were evaluated for physical and chemical compatibility studies.

Physical Compatibility study

The physical compatibility studies were conducted to provide valuable information to the formulator in selecting the appropriate excipients for the formulation. It was done by mixing the drug and excipients and kept at room temperature and at 40° C and 75 % RH. Any colour change of the physical mixture was observed visually.

Chemical Compatibility study

Infrared spectroscopy can be used to identify a compound and also to investigate the composition of the mixture. Pure drug and Drug-Excipient mixtures were subjected to FT-IR to investigate the Drug-Excipient interactions. The IR spectra of the test samples were obtained by Pressed Pellet Technique using Potassium bromide.

Potassium bromide pellet method

A small amount of finely ground solid sample was intimately mixed with about 100 times of its weight of powdered Potassium bromide. The finely ground mixture was then passed under high pressure in a press (at least 25,000 psig) to form a small pellet (about 1-2 mm thick and 1 cm in diameter). The resulting pellet was placed in the sample cell and the spectra were recorded.

PREPARATION OF BUFFER SOLUTION

Preparation of 0.1N Hydrochloric acid (pH 1.2) [25]

8.5 ml of conc. Hydrochloric acid was dissolved in few ml of distilled water and volume made up to 1000 ml with distilled water.

CALIBRATION CURVE[59]

100 mg of Lisinopril was dissolved in a small amount of 0.1N Hydrochloric acid and made up to 100 ml with 0.1N Hydrochloric Acid in a standard flask. 10 ml of the solution was pipetted out into a standard flask and made up to 100 ml using 0.1N Hydrochloric Acid. 2 ml, 4 ml, 6 ml, 8 ml and 10 ml of the solution were pipetted into separate standard flasks and made up to 100 ml using 0.1N Hydrochloric Acid. The absorbance of the resulting solutions was measured at 212 nm using UV Spectrophotometer. Calibration curve was plotted using Concentration in x-axis and Absorbance in y-axis.

PRECOMPRESSION STUDIES [35]

The flow properties of powders are critical for an efficient tableting operation. A good flow of the powder or granulation to be compressed is necessary to assure efficient mixing and acceptable weight uniformity for the compressed tablets. The flow property measurements include bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio. The flow property measurements of drugs and blends are determined to select the type of granulation to be carried out in the formulation.

PRECOMPRESSION STUDIES OF DRUG AND POWDER BLENDS

1. Bulk density (ρb)[59,]

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and it was slightly shaken to break any agglomerates formed. The volume occupied by the powder was measured which gave bulk volume.

Bulk density of the powder was calculated using the formula mentioned below. It is expressed in g/ml.

$$Pb = M/Vb$$

Where, M and Vb are mass of powder and bulk volume of the powder respectively.

2. Tapped density (ρt)[59]

It is the ratio of weight of the powder to the tapped volume of powder. An accurately weighed powder was introduced into a measuring cylinder with the aid of a funnel. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume.

Tapped density of the powder was calculated using the formula mentioned below. It is expressed in g/ml.

$$\rho t = M/Vt$$

Where, M and Vt are mass of powder and tapped volume of the powder respectively.

3. Angle of repose (θ) [20,59]

It is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane. It was determined by the funnel method. The powder mixture was allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the formula,

$$\text{Angle of Repose } (\theta) = \tan^{-1}(h/r)$$

Where, h = Height of the pile of powder (in cm). r = Radius of pile of powder (in cm)

4. Compressibility Index (Carr's Index)[20,59]

Compressibility index is the measure of flow property of a powder. It is measured for determining the relative importance of interparticulate interactions. It is expressed in percentage and calculated by the formula,

$$\text{Compressibility Index} = \frac{TD - BD}{TD} \times 100$$

Where, TD is the tapped density and BD is the bulk density

5. Hausner's Ratio[20,59]

Hausner's ratio is an indirect index of ease of powder flow. Hausner's ratio is the measure of propensity to be compressed and also Interparticulate interactions /Interparticulate friction. It was calculated by the following formula,

$$HR = \rho t / \rho b$$

Where, ρt and ρb are tapped density and bulk density respectively

Table : Precompression Parameters [20]

Flow Property	Angle of Repose (in degrees)	Compressibility Index (%)	Hausner's Ratio
Excellent	25 – 30	< 10	1.00 - 1.11
Good	31 – 35	11 – 15	1.12 - 1.18
Fair	36 – 40	16 – 20	1.19 - 1.25
Passable	41 – 45	21 – 25	1.26 - 1.34
Poor	46 – 55	26 – 31	1.35 - 1.45
Very Poor	56 – 65	32 – 37	1.46 - 1.59
Very very Poor	> 65	> 38	> 1.60

FORMULATION DEVELOPMENT

Formulation of Rapid Release core tablets (RRCT) of Lisinopril [22,23,24]

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, super disintegrant, microcrystalline cellulose, lactose were dry blended for 20 minutes, followed by addition of magnesium stearate. The mixtures were further blended for 10 minutes. 100 mg of the resultant powder blend was compressed using 10 station tablet compression machine.

Table : 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

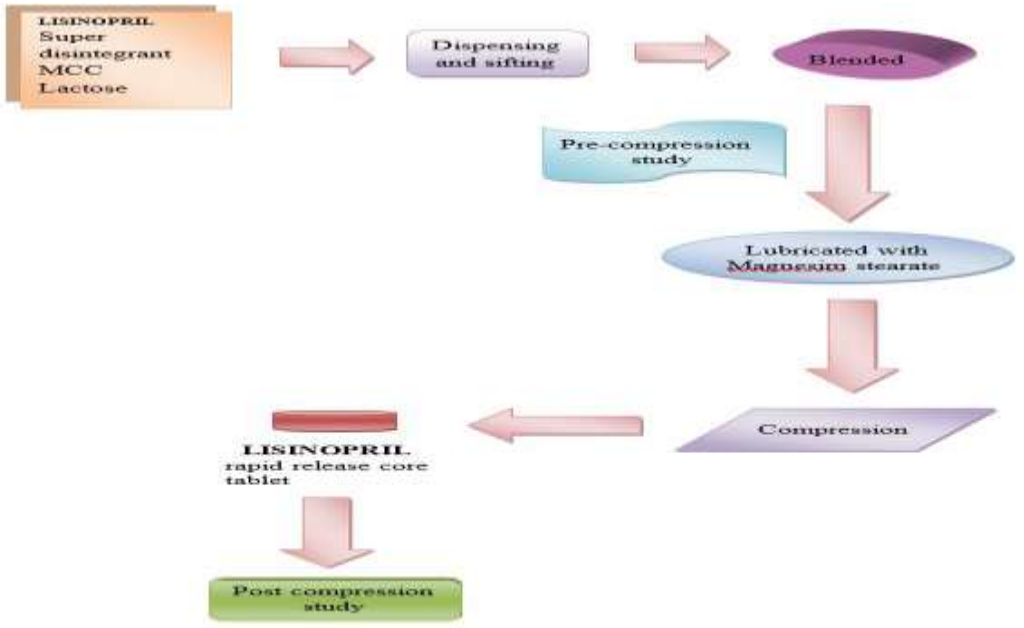


Fig. : Flowchart for formulation of rapid release Lisinopril tablet

Formulation of Lisinopril floating pulsatile release tablet (FPRT)[22,24,27,28]

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 first filling 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.

Table : Formulation of Floating pulsatile release tablets

S. No	Ingredients	FP1	FP2	FP3	FP4	FP5	FP6	FP7	FP8
1.	Optimized core 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

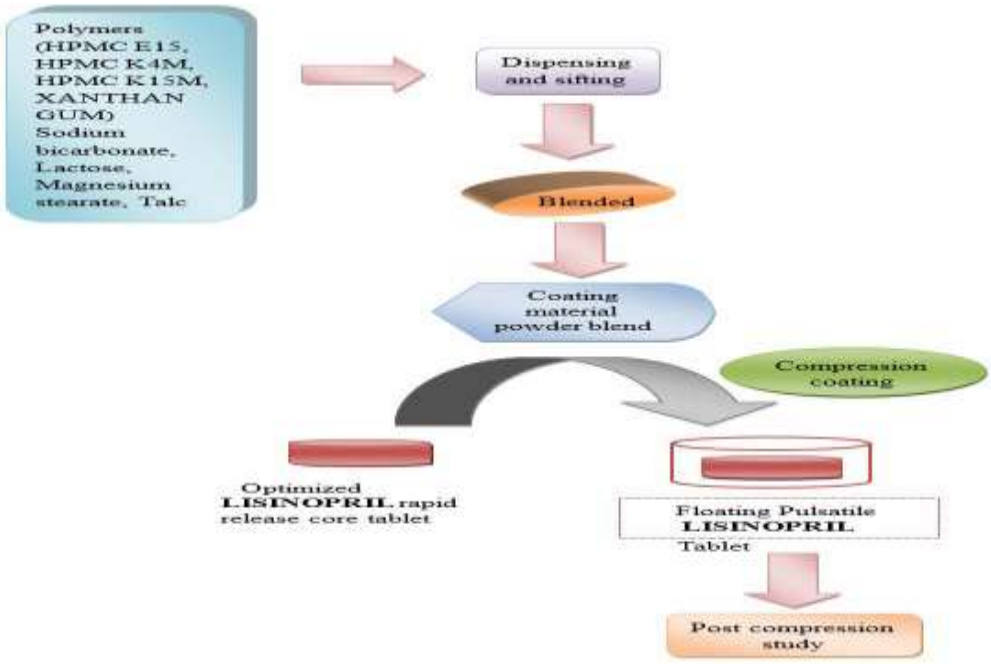


Fig. : Flowchart for formulation of Lisinopril floating pulsatile tablet

POST COMPRESSION STUDIES85

PHYSICAL PARAMETERS [22,26,59]

General appearance

The general appearance of the tablets from each formulation batch was observed. The general appearance parameters, shape and colour were evaluated visually.

Uniformity of Weight

Twenty tablets were randomly selected and weighed individually on an electronic weighing balance. The average weight was calculated. The percentage deviation of tablets was calculated and compared with standard specifications.

Table : 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

Thickness and diameter

The thickness and diameter was measured to determine the uniformity of size and shape. Thickness and diameter of the tablets were measured using Vernier caliper.

Hardness

Hardness is defined as the force required for breaking a tablet at diametric compression test and it is termed as "Tablet Crushing strength". Hardness of the prepared formulations was determined using Monsanto Hardness Tester. It was expressed in kg/cm2.

Friability

Friability of the prepared formulations was determined using Rochelle Friabilator. Pre-weighed sample of Tablets was placed in the Friability tester, which was then operated for 100 revolutions, Tablets were de-dusted and re-weighed. The Friability of the Tablets was calculated using the formula,

Friability is: ((Initial Weight - Final Weight) / Initial Weight) * 100

Disintegration test for Lisinopril Core Tablets[59]

Tablet disintegration was carried out by placing one tablet in each tube of the basket and top portion of the each tube was closed with disc and run the apparatus containing 0.1N Hydrochloric acid (pH 1.2) [SGF (simulated gastric fluid)] maintained at 37 °C as the immersion liquid. The assembly was raised and lowered for 30 cycles per minute. The time taken for the complete disintegration of the tablet with no palpable mass remaining in the apparatus was measured and recorded. The experiment was carried out in triplicate

DRUG CONTENT

I. For Rapid Release Core Tablets (RRCT) [59]

Five tablets were selected randomly, weighed and finely ground. An accurately weighed quantity of powder equivalent to 25mg of Lisinopril was transferred to a 100 ml standard flask and dissolved in few ml of 0.1N HCl and the volume was made up to the mark with 0.1N HCl. The solution was filtered and 10ml portion of the filtrate was further diluted with 0.1N HCl in a 100ml standard flask. The absorbance of the resulting solution was measured at 212nm taking 0.1 N HCl as blank using UV-Visible Spectrophotometer. The concentration was obtained from the calibration graph.

II.For Floating Pulsatile Release Tablets (FPRT) [24 27]

Five tablets were selected randomly, weighed and finely ground. An accurately weighed quantity of powder equivalent to 25mg of Lisinopril was transferred to a 100 ml standard flask and dissolved in few ml of 0.1N HCl and the volume was made up to the mark with 0.1N HCl. The solution was filtered and 10ml portion of the filtrate was further diluted with 0.1N HCl in a 100ml standard flask. The absorbance of the resulting solution was measured at 212nm taking 0.1 N HCl as blank using UV-Visible Spectrophotometer. The concentration was obtained from the calibration graph.

IN-VITRO STUDIES

I. IN-VITRO DISSOLUTION STUDIES

For RRCT [22]

The release of Lisinopril core tablet was determined using USP Type II (paddle type) apparatus. The dissolution test was performed using 900ml of 0.1N HCl (pH 1.2), at 37°C ± 0.5°C. The paddle was rotated at the speed of 50 rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at specific time intervals. Samples were replaced with fresh dissolution medium. The samples were diluted to a suitable concentration with 0.1N HCl. The absorbance of these solutions was measured at 212nm using a UV Spectrophotometer.

For FPRT [24,28]

The release of Lisinopril floating pulsatile tablet was determined using USP Type II (Paddle type) apparatus. The dissolution test was performed using 900ml of 0.1N HCl (pH 1.2), at 37°C ± 0.5°C. The paddle was rotated at the speed of 50 rpm. A sample (10ml) of the solution was withdrawn from the dissolution apparatus at specific time intervals for 24 hrs. Samples were replaced with fresh dissolution medium. The samples were diluted to a suitable concentration with 0.1N HCl. The absorbance of these solutions was measured at 212nm using a UV Spectrophotometer.

II. IN-VITRO BUOYANCY DETERMINATION [22, 24]

Floating behavior of the tablet was determined using USP dissolution apparatus-II (Paddle type) in 900 ml of 0.1 N HCl which is maintained at 37°C ± 0.5°C, rotated at 50 rpm. The floating lag time (the period between placing FPRT in the medium and buoyancy) and floating duration were observed. The matrix integrity of the tablets during the study was also visually monitored.

Lag time

Lag time was considered as the time when the tablet burst and core tablet is out of press coating. This is considered as predetermined off-release period.

Swelling Index Determination [24, 25]

Tablets were weighed individually (W1) and placed separately in glass beaker containing 200 ml of 0.1N HCl and incubated at 37°C ± 0.5°C. At regular 1–hour time intervals until 10hrs, the tablets were removed from the beaker, and the excess surface liquid was removed carefully using the tissue paper. The swollen tablets were then reweighed (W2) and swelling index (SI) was calculated using the following formula

$$SI = W\,2 - W\,1\;W\,1 \times 100$$

Where, W2 is the wet weight and W1 is the dry weight

IN-VITRO RELEASE KINETIC [45]

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).

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.

$$C=K0t$$

Where, K0 = Zero order constant, t = Time in hours

2.First order equation

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

Log C= log C0 – Kt/2.303

Where, C0 = Initial concentration of drug

K = First order

t = Time in hours

3. Higuchi kinetics

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

Q = Kt½

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

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.

Q0 1 /3 – Q t 1/3 = KHC Xt

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

Q0 = Initial Amount of drug

KHC= 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.

$$Mt/M\alpha = Ktn$$

Where, Mt/Mα = Fraction of drug released at time, 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 : 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

STABILITY STUDIES[24, 25]

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, and floating duration

RESULTS AND DISCUSSIONS

The present investigation was to formulate floating pulsatile release tablet for the treatment of morning surge of hypertension

PREFORMULATION STUDIES

DRUG – EXCIPIENT COMPATIBILITY STUDY

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

PHYSICAL COMPATIBILITY

Table: 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

.

The Physical compatibility study 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.

CHEMICAL COMPATIBILITY STUDY [39]

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

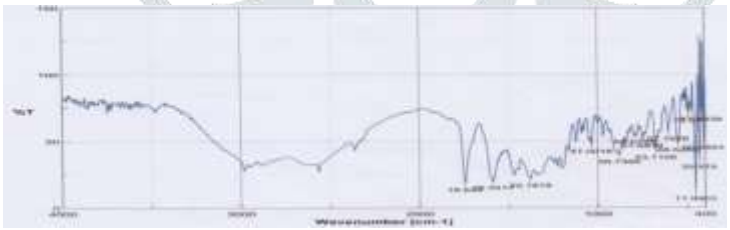


Fig. : FTIR of Lisinopril

Table: IR Spectral interpretation of Lisinopril

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

Table : 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)

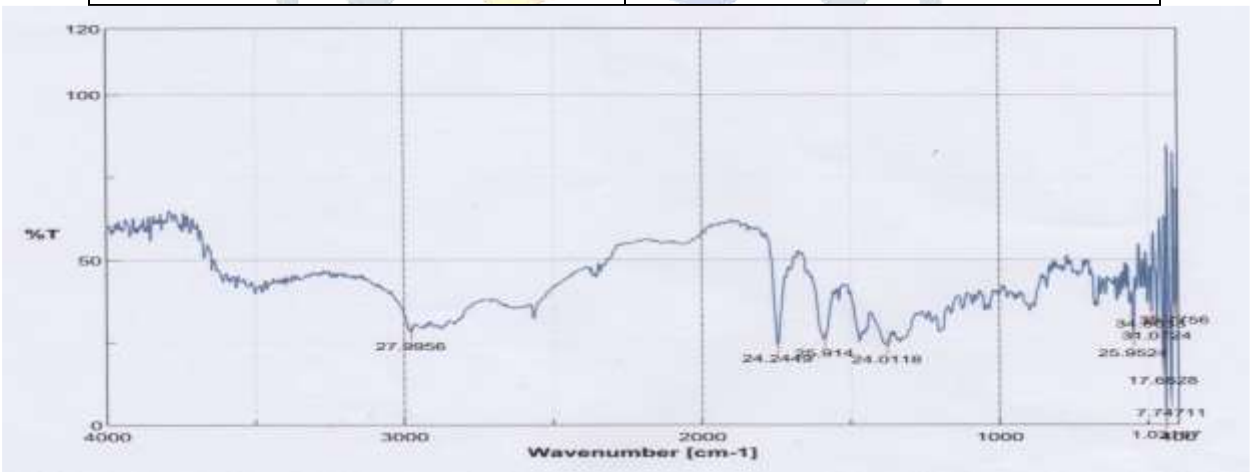


Fig. : FTIR of Lisinopril with HPMC E15

Table : 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.

CALIBRATION CURVE OF LISINOPRIL

Table : 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

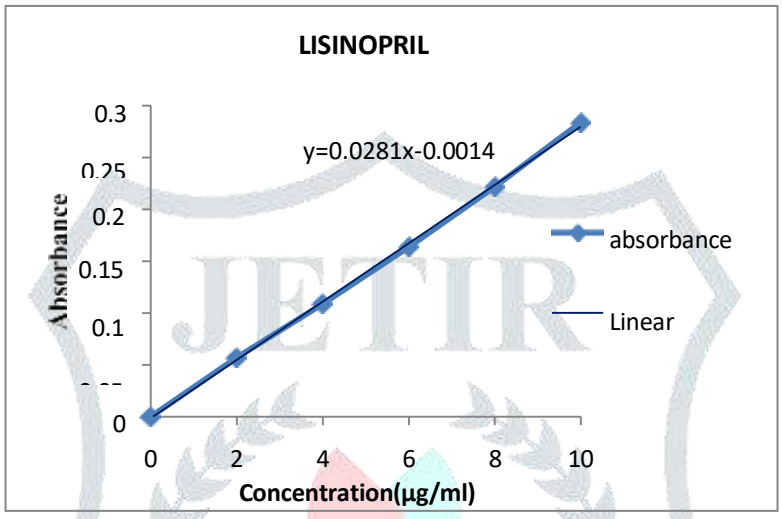


Fig.: Calibration curve of Lisinopril

Fig: Calibration curve of Lisinopril

It was found that the solutions of Lisinopril in 0.1N Hydrochloric acid (pH 1.2) showed linearity (R2 = 0.9996) in absorbance at concentrations of 2 to 10 µg/ml and obey Beer Lambert's Law.

RAPID RELEASE FORMULATION OF LISINOPRIL

PRECOMPRESSION STUDY

The drug and the formulated blends are evaluated for precompression parameters.

The results are given in the table 21

Table: Precompression study of drug and formulated blends

Drug Formulation	Bulk density* (g/cm^3)	Tappe density* (g/cm^3)	Compressibility index* (%)	Hausner's ratio*	Angleof 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/cm3 and tapped density ranged from 0.5322 to 0.6669 g/cm3. The compressibility index of the Lisinopril powder blend ranged from 14.70 to 20.56% and Hausner's ratio ranged from 1.16–1.25whichshowedfair-goodflow.TheangleofreposeofLisinoprilpowder blend ranged from 42°02′ to 45°50′ which showed passable flow property.

Table: Precompression study of formulated blends with lubricant

Drug Formulation	**Bulk density* (g/cm^3)**	**Tapped density* g/cm^3)**	**Compressibility index* (%)**	**Hausner's ratio***	**Angleof 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

The bulk density of Lisinopril blends ranged from 0.4585 to 0.548 g/cm3 and tapped density ranged from 0.5256 to 0.7118 g/cm3. The compressibility index of the Lisinopril powder blend ranged from 11.83 to 18.08% and Hausner's ratio ranged from 1.13–1.23which showed fair-good flow. The angle of repose of Lisinopril powder blend ranged from 33°58′ to 40°43′ which showed fair-good flow property.

POST COMPRESSION STUDY UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in table

Table: Uniformity of weight of the RRCTs

Formulation	Uniformity weight* (mg)
F1	99.54
F2	99.36
F3	99.88
F4	99.50
F5	100.14
F6	100.48
F7	100.30
F8	100.61
F9	100.72

***Mean±S.D(n=20)**

The tablets comply with the test for uniformity of weight

TABLET THICKNESS AND DIAMETER

The thickness and diameter of the formulated tablets is given in table 24

Table:Thickness and diameter of the RRCTs

Formulation	Thickness* (mm)	Diameter* (mm)
F1	2 ±0.0	6 ±0.0
F2	2 ±0.0	6 ±0.0
F3	2 ±0.0	6 ±0.0
F4	2 ±0.0	6 ±0.0
F5	2 ±0.0	6 ±0.0
F6	2 ±0.0	6 ±0.0
F7	2 ±0.0	6 ±0.0
F8	2 ±0.0	6 ±0.0
F9	2 ±0.0	6 ±0.0

*Mean±S.D(n=5)

The tablets have uniform thickness and diameter.

HARDNESS

Table: Hardness of the RRCTs

Formulation	Hardness*(kg/cm^2)

F1	2.7± 0.244
F2	2.3± 0.244
F3	2.5± 0.218
F4	2.8± 0.241
F5	2.5± 0.244
F6	2.3± 0.210
F7	2.8± 0.241
F8	2.7± 0.244
F9	2.6± 0.216

*Mean±S.D(n=5)

The hardness of the tablets was found to be between 2.3 kg/cm2 and 2.8 kg/cm2. All the formulated tablets showed sufficient mechanical strength to resist stress during the transportation

FRIABILITY

Table: Friability of the RRCTs

Formulation	Friability*(%)
F1	0.476±0.284
F2	0.538±0.365
F3	0.348±0.214
F4	0.561±0.341
F5	0.648±0.244
F6	0.636±0.176
F7	0.590±0.198
F8	0.650±0.289
F9	0.562±0.302

***Mean±S.D(n=3)**

The percentage friability of the tablets ranged from 0.348% to 0.648%. The percentage friability of all the formulation was within Pharmacopeial limits[26]

HARDNESS

Table: Hardness of the RRCTs

Formulation	Hardness*(kg/cm^2)
F1	2.7± 0.244
F2	2.3± 0.244
F3	2.5± 0.218
F4	2.8± 0.241
F5	2.5± 0.244
F6	2.3± 0.210
F7	2.8± 0.241
F8	2.7± 0.244
F9	2.6± 0.216

*Mean±S.D(n=5)

The hardness of the tablets was found to be between 2.3 kg/cm2 and 2.8 kg/cm2. All the formulated tablets showed sufficient mechanical strength to resist stress during the transportation26

FRIABILITY

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F9	0.562±0.302

***Mean±S.D(n=3)**

The percentage friability of the tablets ranged from 0.348% to 0.648%. The percentage friability of all the formulation was within Pharmacopeial limits[34]

DRUG CONTENT

The drug content of the Rapid release core tablets is given in the table

Table: Drug content of the RRCTs

Formulation	Drug content* (%)
F1	93.15±0.235
F2	93.68±0.342
F3	96.68±0.215
F4	94.71±0.359
F5	98.61±0.256
F6	100.54±0.328
F7	95.14±0.268
F8	97.60±0.318
F9	95.56±0.275

*Mean±SD (n=3)

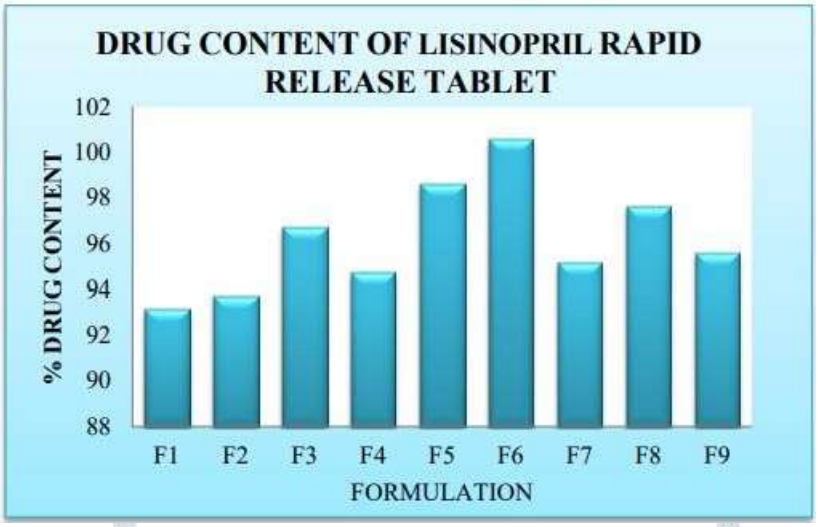

Fig.: Drug content of the formulated rapid release tablets

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

DISINEGRATION TIME

Table: 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)

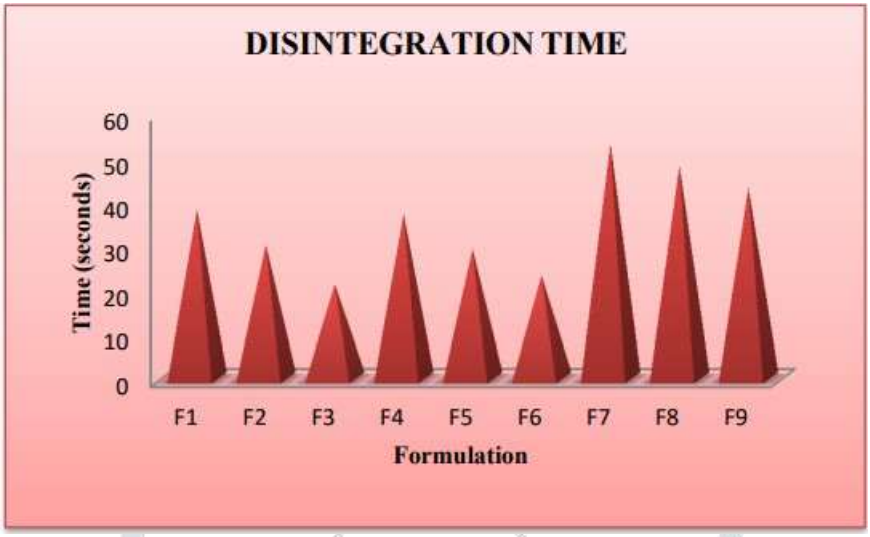

Fig.: Disintegration time of the formulated rapid release tablets

The disintegration time of the Lisinopril tablets ranged from 21 seconds to 53 seconds. The disintegration time of Lisinopril core tablet (F3) containing croscarmellose sodium (2%) as a super disintegrants was found to be the optimum core tablet for final tablet. All the formulations comply with the official standards.[32,,39]

IN-VITRO DISSOLUTION STUDY

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

Table: 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)

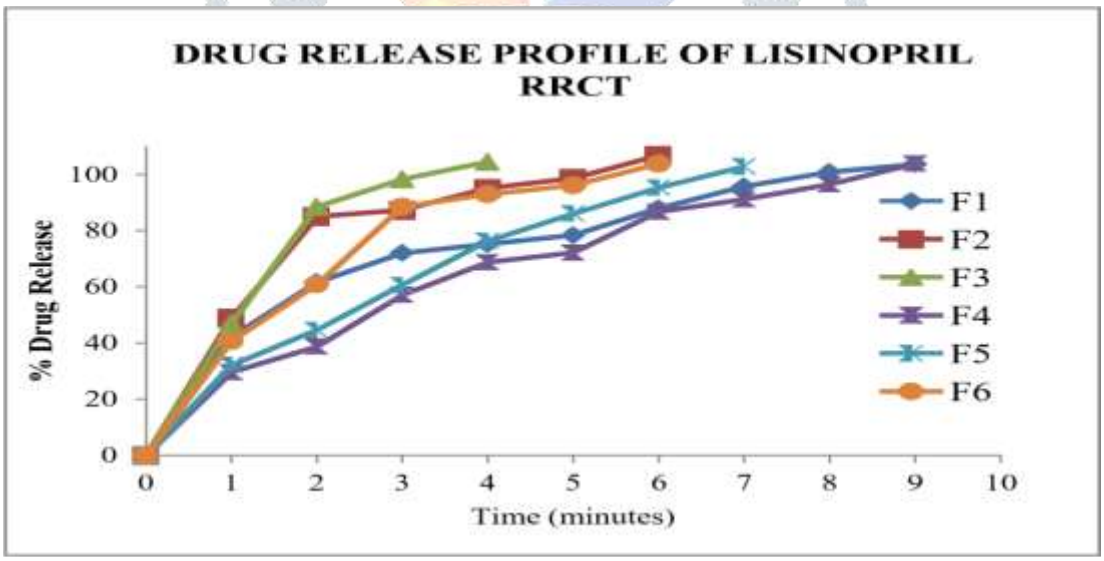

Fig.: in vitro drug release of formulated Lisinopril rapid release tablets

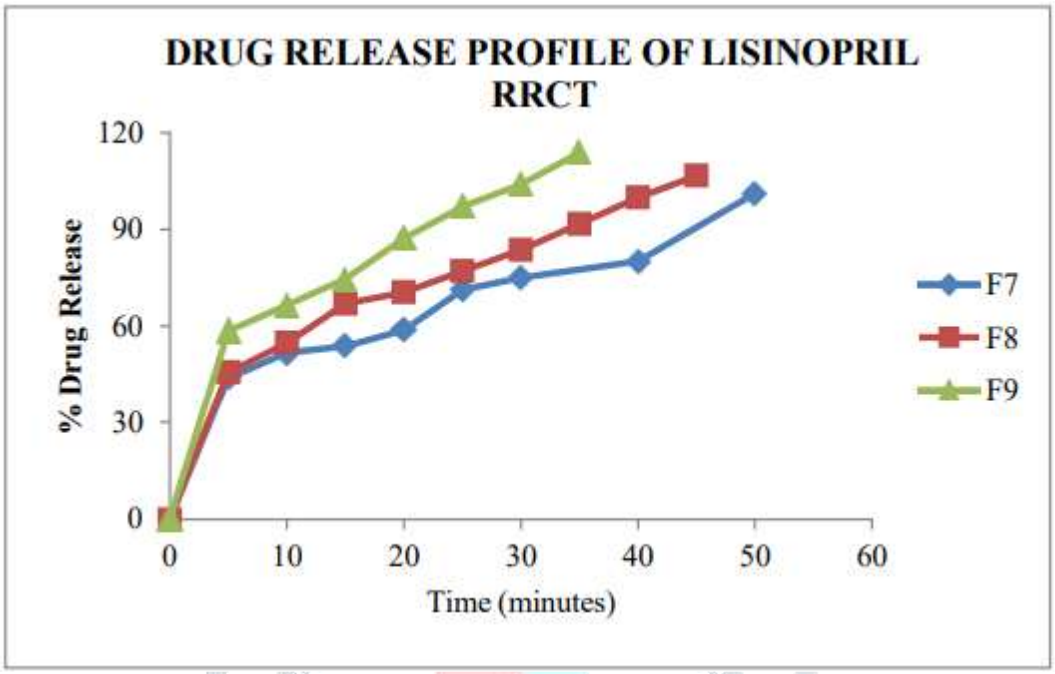

Fig.: in vitro drug release of formulated Lisinopril rapid release tablets

From the in-vitro release study, 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.

FLOATING PULSATILE RELEASE TABLET OF LISINOPRIL

PRECOMPRESSION STUDY

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

Table : Precompression study of formulated blends of coating materials

Drug Formulation	Bulk density* (g/cm^3)	Tappd density*(g/cm)	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/cm3 and tapped density ranged from 0.7147 to 0.820 g/cm3. 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

POST COMPRESSION STUDY

UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in table.

Table: Uniformity of weight of the FPRTs

Formulation	Uniformity weight (mg)
FP1	504.7
FP2	498.11
FP3	498.5
FP4	497.22
FP5	496.34
FP6	499.99
FP7	499.54
FP8	501.22

*Mean ±S.D (n=20)

THICKNESS AND DIAMETER

The thickness and diameter of the formulated tablets is given in table

Table: Thickness and diameter of the FPRTs

Formulation	Thickness* (mm)	Diameter* (mm)
FP1	4 ± 0.0	10 ± 0.0
FP2	4 ± 0.0	10 ± 0.0
FP3	4 ± 0.0	10 ± 0.0
FP4	4 ± 0.0	10 ± 0.0
FP5	4 ± 0.0	10 ± 0.0
FP6	4 ± 0.0	10 ± 0.0
FP7	4 ± 0.0	10 ± 0.0
FP8	4 ± 0.0	10 ± 0.0

*Mean ±S.D (n=5)

The tablets have uniform thickness and diameter.

DRUG CONTENT

The drug content of the Lisinopril FPRT is given in the table

Table: Drug content of the formulated tablets

Formulation	Drug content (%)
FP1	96.56±0.178
FP2	93.71±0.245
FP3	93.00±0.269

FP4	92.01±0.312
FP5	95.99±0.287
FP6	93.71±0.189
FP7	96.13±0.223
FP8	95.29±0.256

***Mean±SD (n=3)**

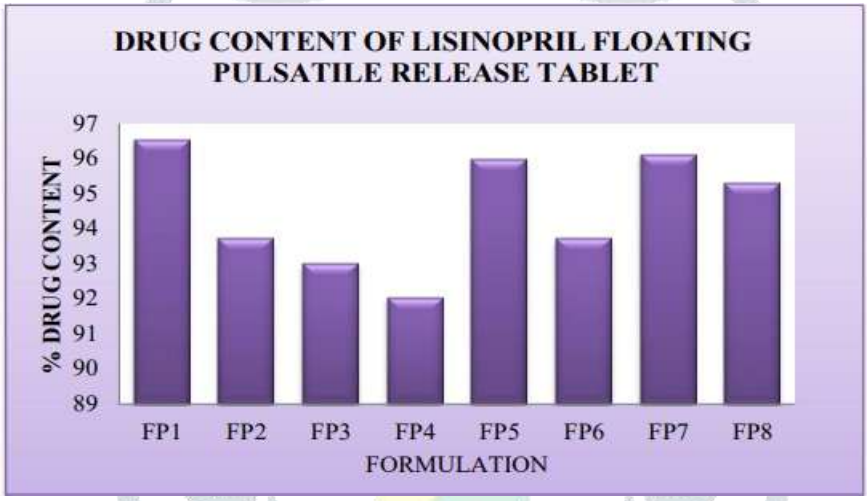

Fig.: Drug content of the formulated floating pulsatile release tablets

The percentage drug content of Lisinopril in all the formulations ranged from 93.00% w/w to 96.56 % w/w. All the formulations comply with the official standards[79]

INVITRO FLOATING STUDIES

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

Table : in-vitro floating characteristics of Lisinopril FPRT

Formulation	Floating lag time* (minutes)	Floating duration* (hours)
FP1	15min30sec	>12hrs
FP2	2min50sec	>24hrs
FP3	2min05sec	>24hrs
FP4	14min08sec	>24hrs
FP5	8min17sec	>12hrs
FP6	9min15sec	>12hrs
FP7	8min32sec	>12hrs
FP8	7min30sec	>12hrs

***MEAN±S.D (n=3)**

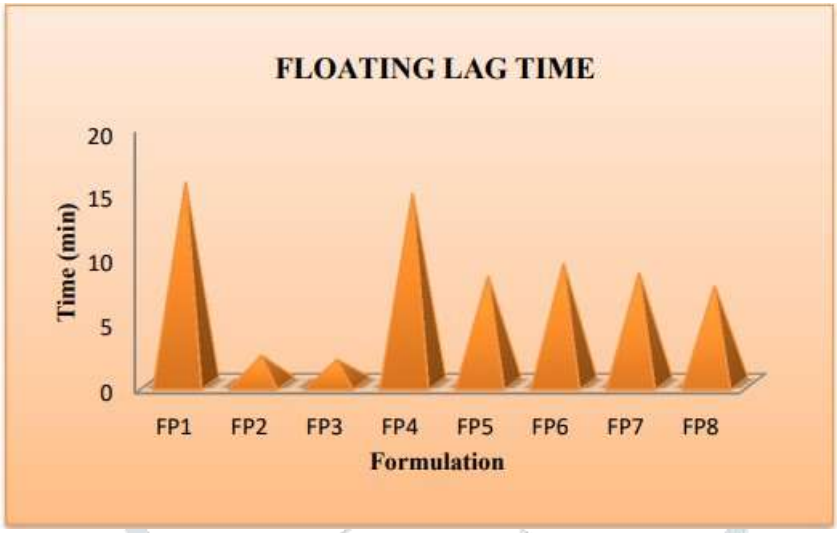

Fig: Floating lag time of the formulated floating pulsatile release tablets

The floating duration was ranged from 12 - >24 hours and the floating lag time ranged from 2 – 15 minutes.25 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.

SWELLING STUDIES [36]

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 and Fig

Table: 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

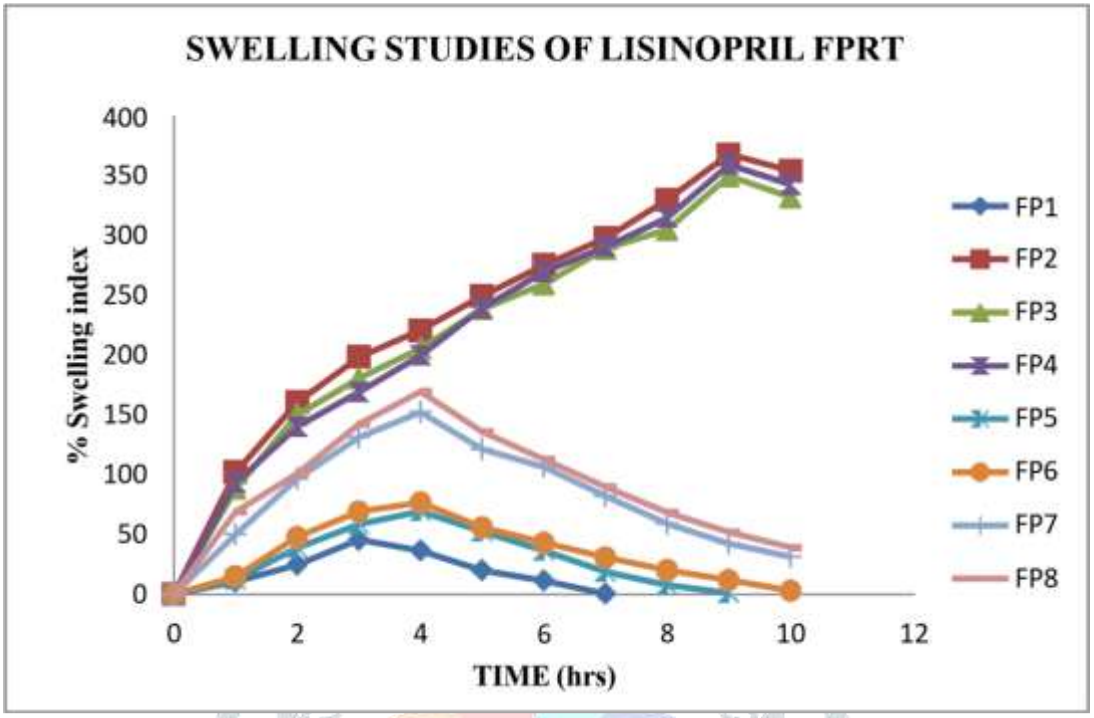

Fig.: Swelling index of Lisinopril FPRTs

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.25

FPRT containing HPMC K15M showed the highest swelling index as compared to 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.

IN-VITRO DISSOLUTION STUDY

The invitro dissolution of floating pulsatile formulations of Lisinopril is given in the Table

Table: 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**	-	-	-	-

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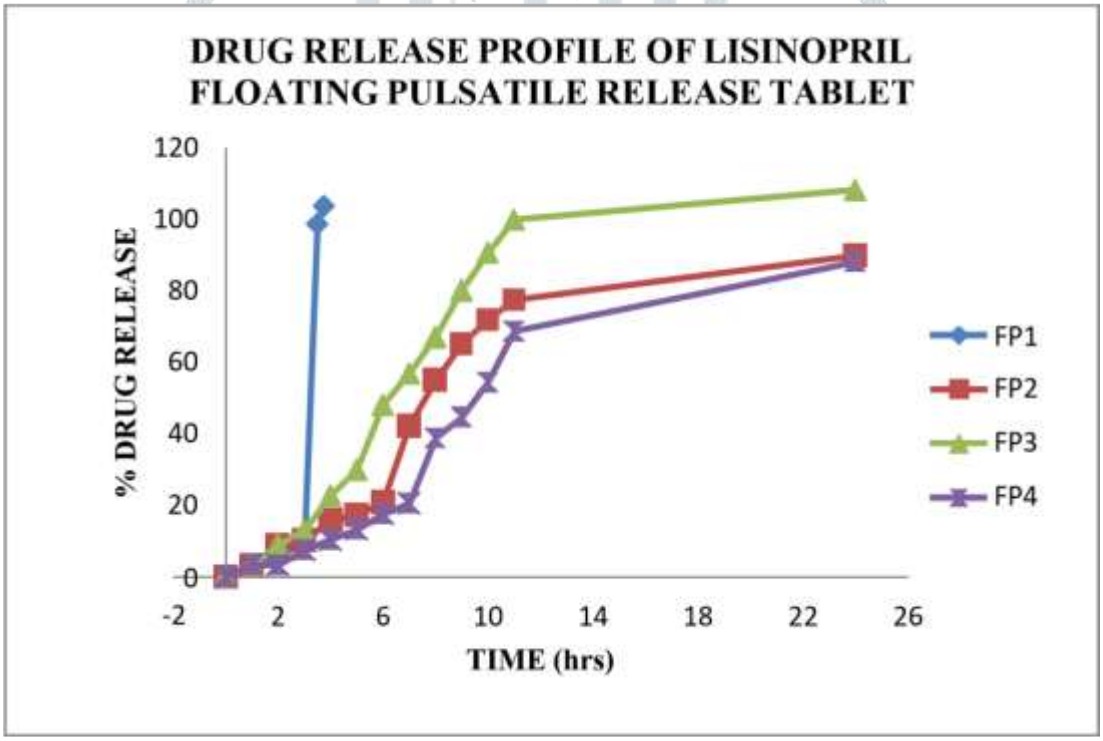

Fig.: in vitro drug release of formulated FPRT

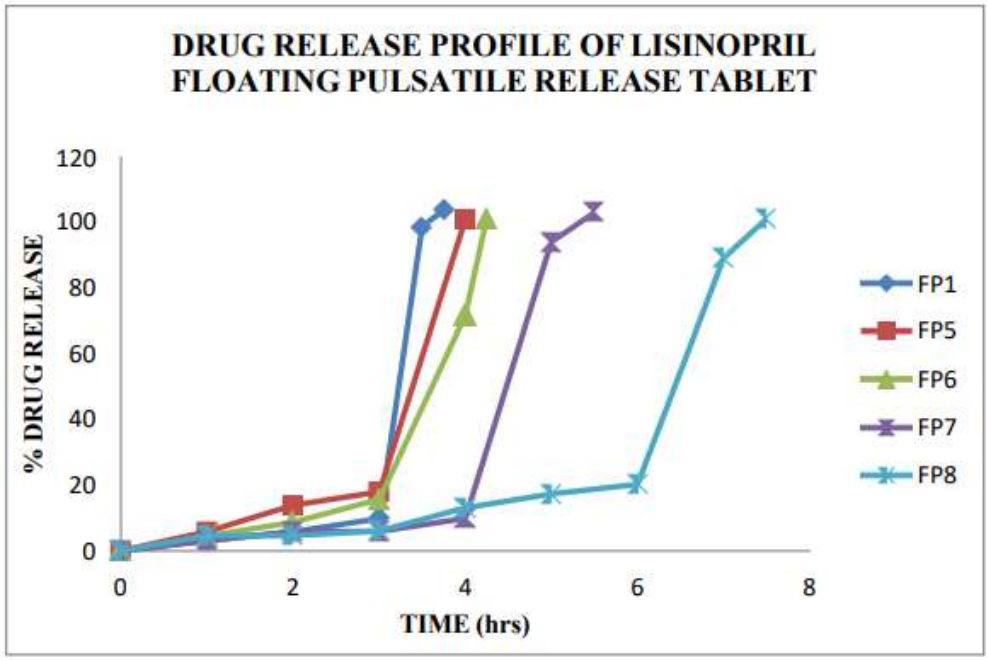

Fig.: in vitro drug release of formulated FPRT

From the invitro 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. So, the formulation was optimized for morning surge of hypertension

STABILITY STUDIES [29]

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: Stability study of Lisinopril FPRT– Optimized formulation

Sample withdrawal period	Drug content (in %w/w)		Percentage drug release (at the end of 7.5 hours)	
	At Ambient temperature	40ºC±2ºC and75%± 5% RH	At Ambient temperature	40ºC±2ºC and75%± 5% RH
0thday	96.54	96.21	101.13	99.65
15thday	96.87	95.80	99.91	101.50
30thday	97.35	96.54	100.67	99.79
45thday	97.15	96.98	98.70	99.32

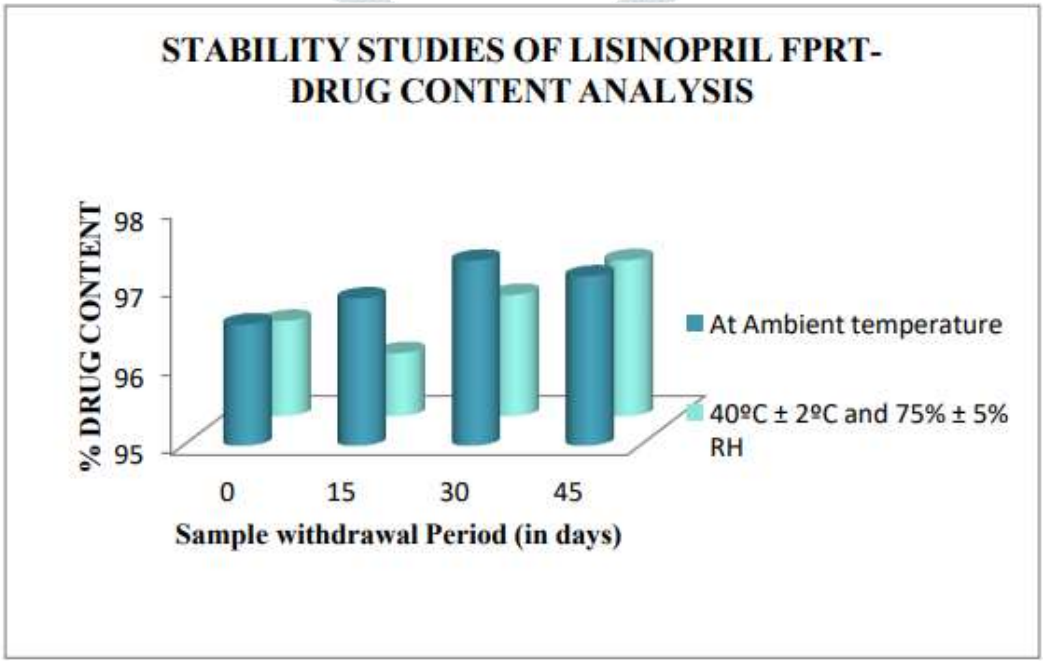

Fig.: Stability study of Lisinopril FPRT – Drug content analysis

There was no significant difference in the physical appearance of the formulation

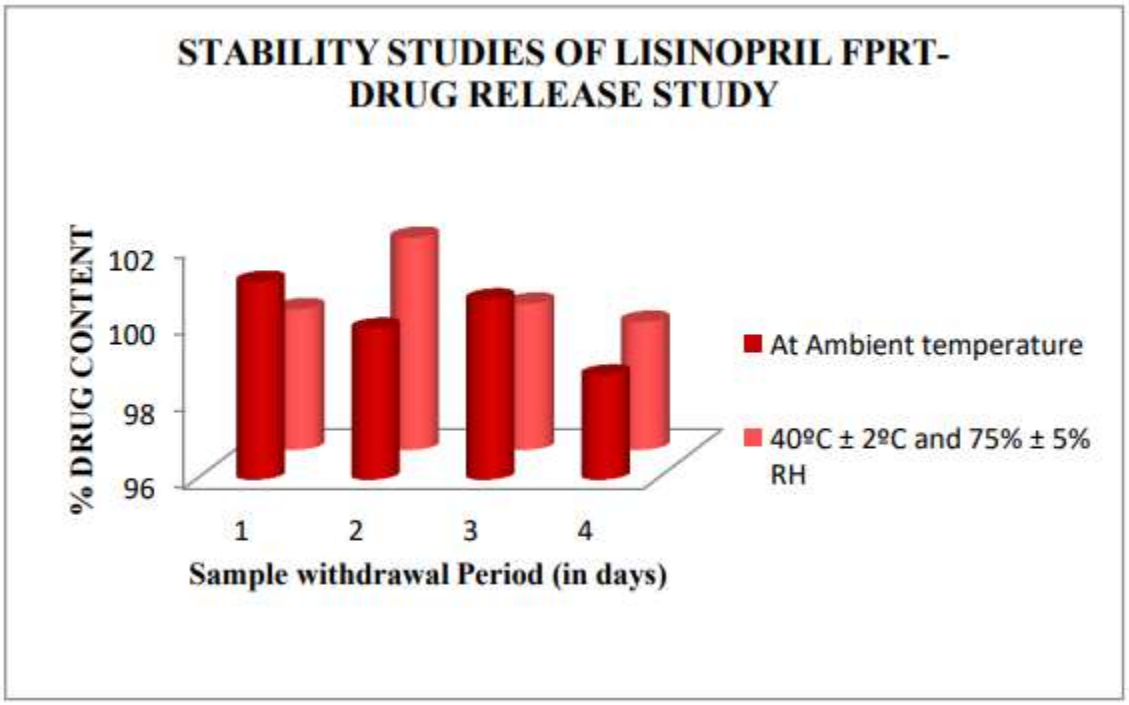

Fig. Stability study of Lisinopril FPRT – Drug release study

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. This shows that the formulations remained stable during the process of storage.

SUMMARY AND CONCLUSION

The present work involves the design, development and in-vitro evaluation of Lisinopril floating pulsatile release tablet, in which the core tablets are rapid release formulation which is coated with hydrophilic polymers such as HPMC E15, HPMC K15M, HPMC K4M, Xanthan gum individually and in combination. FPRT was designed for the treatment of morning surge of Hypertension.

The drug excipient interaction was investigated with FTIR spectroscopy. The study indicated that there was no interaction between the drug and the excipients used in the formulations.

The rapid release core tablets of Lisinopril were formulated with various concentrations of SSG (2%, 3% and 4%), CCS (1%, 1.5% and 2%) and Crospovidone (2 %, 3.5% and 5%) by direct compression.

The formulated RRCT blends were evaluated for pre-compression parameters which showed good flow property.

The formulated tablets were found to be within the limits with respect to Weight uniformity, Hardness, Thickness, Diameter and Friability.

The Drug content of the formulated Tablets was found to be within the Pharmacopoeial limit.

The Disintegration time of Lisinopril rapid release Core Tablet (Formulation F3) containing 2% croscarmellose sodium disintegrated quickly (D.T = 21 seconds).

The in-vitro dissolution studies of the formulated Lisinopril Core tablets were performed using USP type-II dissolution apparatus. From the formulated batches, the formulation F3 released the drug very quickly (within 4 minutes) when compared to other formulations.

Based on the Disintegration and in-vitro release studies of Lisinopril rapid release core tablets, formulation F3 was optimized and selected for Press coating.

The outer coat contains hydrophilic polymers (swellable and erodible) such as HPMC E15, HPMC K15M, HPMC K4M, Xanthan gum. For the formulated coating material blends, micromeritic properties were evaluated which showed good flow. So, the Compression coating of optimized Lisinopril core tablets was done by direct compression technique.

Totally 8 batches of Lisinopril Floating pulsatile release tablets (FPRT) were prepared using HPMC E15, HPMC

K15M, HPMC K4M, Xanthan gum.

The formulated Lisinopril FPRTs were found to be within limits with respect to Weight uniformity, Hardness, Thickness, Diameter and Friability.

The drug content of the Lisinopril FPRTs were estimated and found to be within Pharmacopoeial limits.

A direct correlation between swelling and lag time was observed and found that the formulations having maximum swelling indices showed higher lag time.

The in-vitro dissolution studies of the formulated Lisinopril FPRTs were performed using USP type-II dissolution apparatus. From the formulated batches, the % drug release for the formulation FP8 was 101.23% at the end of 7.5hrs with the lag time of 6hours.

Based on the in-vitro release studies of Lisinopril FPRT, formulation FP8 (formulation contains 200mg of HPMC E15 and 50mg of HPMC K4M) was optimized.

The optimized FPRT (FP8) follows Zero order kinetics up to the lag time, in which 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.

A stability study for the optimized Lisinopril FPRT was performed by storing the tablets at ambient room temperature and at 40ºC ± 2ºC maintained at RH 75% ± 5% for 45 days. There was no significant differences produced in physical appearance, drug content and % drug release, this shows that the formulation remains stable during the storage.

FUTURE PLAN:

Scale up studies of the optimized formulation

in-vivo studies and in vitro-vivo correlation studies

Bioequivalence studies with marketed products

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