DESIGN, DEVELOPMENT AND EVALUATION OF FLOATING PULSATILE TABLETS OF CAPTOPRIL FOR THE MORNING SURGE OF HYPERTENSION

A Dissertation submitted to

THE TAMIL NADU Dr. M.G.R MEDICAL UNIVERSITY

CHENNAI – 600 032

in partial fulfilment of the requirements for the award of degree of

MASTER OF PHARMACY

IN

PHARMACEUTICS

submitted by

Register Number: 261411269

under the guidance of

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COLLEGE OF PHARMACY

MADRAS MEDICAL COLLEGE

CHENNAI – 600 003

APRIL – 2016

DEPARTMENT OF PHARMACEUTICS
COLLEGE OF PHARMACY
MADRAS MEDICAL COLLEGE
CHENNAI-600 003
TAMILNADU

DATE:

CERTIFICATE

This is to certify that the dissertation entitled **"DESIGN, DEVELOPMENT AND EVALUATION OF FLOATING PULSATILE TABLETS OF CAPTOPRIL FOR THE MORNING SURGE OF HYPERTENSION"** submitted by the candidate with **Register No.261411269** to The Tamil Nadu Dr. M.G.R. Medical University is evaluated.

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Place: Chennai – 03

Date:

(Dr. A. JERAD SURESH, M.Pharm., Ph.D., M.B.A)

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Place: Chennai – 03

Date:

[Prof. K.ELANGO, M.Pharm., (Ph.D.),]

ACKNOWLEDGEMENT

This thesis is the last part of my M.Pharmacy course. I have not travelled in a vacuum in this journey. At the end of my thesis I would like to thank all those people who made this thesis possible and an unforgettable experience for me.

I consider this as an opportunity to express my gratitude to all the dignitaries who have been involved directly or indirectly with the successful completion of this dissertation.

First of all I thank the **Almighty** for giving me the strength, endurance and showering his blessing to undertake this project with full dedication and giving me courage always to do hard work.

I consider myself very much lucky with profound privilege and great pleasure in expressing my deep sense of gratitude to **Prof. K. Elango, M.Pharm., (Ph.D.),** Head of Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai, for his supportive suggestions, innovative ideas, help and encouragement which has always propelled me to perform better. It is my privilege and honour to extend my gratitude and express our indebtedness for his enduring support. He has been generous with providing the facilities to carry out this work.

I acknowledge my sincere thanks to **Dr. A. Jerad Suresh, M.Pharm., Ph.D., MBA,** Principal, College of Pharmacy, Madras Medical College, Chennai, for his continuous support in carrying out my project work in this institution.

I am thankful to all of my teaching staff members **Mr. K. Ramesh Kumar, M.Pharm., Dr. N. Deattu, M.Pharm., Ph.D., Dr. S. Daisy Chellakumari, M.Pharm., Ph.D., Dr. R. Devi Damayanthi, M.Pharm., Ph.D.,** of the Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai., for their valuable suggestions, constant support and encouragement.

It’s a great pleasure for me to acknowledge my sincere thanks to **Dr. R. Radha M.Pharm., Ph.D.,** for her timely help and co-operation.

I extend my thanks to all teaching staff members of College of Pharmacy, Madras Medical College, Chennai.

I extend my thanks to all non-teaching staff members **Mr. M. Siva Kumar,** Department of Pharmaceutical Chemistry and **Mr. R. Marthandan, Mrs. R. Shankari, Mrs. Razia Sultana,** Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai.

I am indebted to my many student colleagues for providing a stimulating and fun filled environment. My special thanks go in particular to my beloved seniors **D. Jaison, V.Sundar Raj, B.Prabakaran, K.Gnanasuriyan** with whom I started my journey in M.Pharmacy course and many rounds of discussions on my project with them helped me a lot.

I would like to thank my classmates **M. Nivedita, D. SaiDharshini, Deepa Joseph, D. Immanuel Nesakumar, M. Meenakshi, C. Kanchana, D. Mohanapriya and T. Nandhini** who stood beside me throughout my project.

It's a great pleasure for me to acknowledge my sincere thanks to my friend **V. Sundhar Rajan** for his supportive suggestions, help and encouragement throughout the study to perform better and make my work easy.

It's a great pleasure for me to thank my friends **Ram kumar, Avinash, Vignesh, Krishna, Jagan and Swathi** for their encouragement.

I extend my cordial thanks to all my **seniors, juniors** and **M.pharm. batchmates** for their kind support and co-operation.

Most of I would like to thank my beloved parents and family members for their priceless support, love and encouragement throughout the entire tenure of this course.

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ABBREVIATIONS AND SYMBOLS

FDDS	-	Floating Drug Delivery System
PDDS	-	Pulsatile Drug Delivery System
FPDDS	-	Floating Pulsatile Drug Delivery System
OSDRC	-	One Step Dry Coating
HPMC	-	Hydroxyl Propyl Methyl Cellulose
EC	-	Ethyl cellulose
SA	-	Sodium Alginate
PEO	-	Polyethylene oxide
SSG	-	Sodium Starch Glycolate
CCS	-	Croscarmellose Sodium
CP	-	Crospovidone
MCC	-	Micro Crystalline Cellulose
RRCT	-	Rapid release core tablet
FPRT	-	Floating pulsatile release tablet
BP	-	Blood Pressure
ACE	-	Angiotensin converting enzyme
AT I	-	Angiotensin receptor I
AT II	-	Angiotensin receptor II
HCl	-	Hydrochloric acid
SGF	-	Simulated Gastric Fluid
FTIR	-	Fourier Transform Infra Red
UV	-	Ultra violet Visible Spectroscopy
IP	-	Indian Pharmacopoeia
PhEur	-	European Pharmacopoeia
USP	-	United States Pharmacopoeia
JP	-	Japanese Pharmacopoeia

API	-	Active Pharmaceutical Ingredients
D_T	-	Disintegration time
rpm	-	revolution per minute
g	-	gram
mg	-	Milligram
ml	-	Milliliter
µg	-	Microgram
%	-	Percentage
M.W	-	Molecular Weight
θ	-	Theta
º	-	Degree
nm	-	nanometer
SD	-	Standard Deviation
RH	-	Relative Humidity
NC	-	No Change

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INTRODUCTION

1.1. 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.

1.1.1. 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.

1.1.2. Different types of tablets

A. Tablet ingested orally:

- Compressed tablet
- Multiple compressed tablet
  - Compression coated tablet (Press coated tablet)
  - Layered tablet Inlay tablet
- Repeat action tablet
- Delayed release tablet
- Sugar coated tablet
- Film coated tablet
- Chewable tablet
- Targeted tablet

B. Tablets used in oral cavity:

- Buccal tablet
- Sublingual tablet
- Troches or lozenges
- Dental cone

C. Tablets administered by other route:

- Implantation tablet
- Vaginal tablet

D. Tablets used to prepare solution:

- ❖ Effervescent tablet
- ❖ Hypodermic tablet
- ❖ Tablet triturates

1.2. 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

- ❖ Improved solubility of the pharmaceutical composition;
- ❖ Decreased disintegration and dissolution times for immediate release oral dosage forms;

1.2.2. Super Disintegrants[6]: A disintegrant is an excipient, which is added to a tablet or capsule blend to aid in the breakup of the compacted mass when it is put into a fluid environment.

Advantages:

- Effective in lower concentrations
- Less effect on compressibility and flowability
- More effective intragranularly

Some super disintegrants are:

1. Sodium Starch Glycolate used in concentration of 2-8 % & optimum is 4%. Mechanism of Action: Rapid and extensive swelling with minimal gelling.
2. Microcrystalline cellulose used in concentration of 2- 15% of tablet weight
3. Cross-linked Povidone or crospovidone used in concentration of 2-5% Mechanism of Action: Water wicking, swelling and possibly some deformation recovery. Rapidly disperses and swells in water, but does not gel even after prolonged exposure.
4. Croscarmellose sodium: Effective Concentrations: 1-3% Direct Compression, 2-4% Wet Granulation. Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling.

1.3. Press-coated delivery systems[4, 7, 8]

Press coating technology

Press-coating, also referred to as double compression coating, compression coating, or dry coating, is an old technique first proposed by Noyes in an 1896 patent. An industrial application of this technique was introduced during the period 1950–1960 to allow the formulation of incompatible drugs. Press coating found increasing application during the past two decades; the process does not require solvents, has a relatively short manufacturing process, and achieves a greater increase in mass of the core tablet than solvent-based methods do. Although it is an old concept, press coating is a novel technology for the formulation of new DDS systems.

The technique requires a specific tablet press, with compression coating capability. The press coating technique offers many advantages, such as protection of hygroscopic, light sensitive, oxygen labile, and acid-labile drugs, isolation of incompatible drugs from each other, and provides a method for both sustained drug release and modification of the drug release profile.

In general, a press-coated tablet consists of an inner core tablet and an outer coating shell. The outer layer surrounds the inner core, and so selection of outer layer materials has a significant impact on the performance of the tablet, including the coating's mechanical strength, drug release characteristics, and tablet stability. It is also possible to produce combination dosage forms, in which two active substances target different areas of the gastrointestinal tract.

Press coating allows the physical separation of incompatible drugs in the core and coat within the same dosage form. Direct compression of both the core and the coating shell can remove the necessity for a separate coating process. Any type of material with adequate compaction properties can be used for the coating shell. More recently, DDSs based on press-coated functional layers have been proposed for delayed, pulsatile, and programmable release of different drugs in a single tablet. The press- coating technique has been used to modify the drug release of many drugs, mask a medication's bitter taste, and protect volatile substances. The technique offers several unique features, such as no requirement for special coating solvents or coating equipment and short manufacture times. Recently, the application of this technology was investigated in the development of timed release dosage forms, time clock systems, and delayed-release tablets.

The press-coated tablet may consist of a fast disintegration or modified release core coated by compression with a solid barrier, commonly made of polymeric material, a diluent (as a release modifier) and drug (for either rapid or extended release).

Press-coated tablets may be modified to provide different release patterns, by varying the drug distribution and type of polymers used in the core and outer coating shell. The resulting modified drug release may be dependent on the time, pH, or microbial control to target a specific region in gastrointestinal tract. Thus, press-coating may be classified as a chronopharmaceutical technology, in that it provides a solid dosage form for drug

delivery in a pulsatile fashion rather than continuously, and at predetermined times and sites following oral administration.

1.3.1 Manufacturing process of press coating[8]

The inner core tablet is formulated, and then compressed under appropriate conditions. The tableting machine die is pre-filled with shell-coating materials to form a powder bed, the compressed inner core tablet is placed at the center of the bed, and any remaining outer coating shell materials added. Finally, the outer coating shell is compressed around the inner core tablet.

1.3.2. Factors Affecting Performance and Drug Release of Press-Coated Delivery Systems[7, 8]

Press-coated tablets have two layers, an inner core compressed as a small tablet and an outer shell. The core tablet may additionally be dry-coated with rate controlling materials such as controlled release polymers and fillers

Inner core tablet

The inner core of the press-coated tablet may comprise pure drug crystals, drug-excipient blends, granules, microspheres and beads. It is also possible to incorporate materials into the core tablet to facilitate disintegration, or otherwise modify the drug release.

- ✓ Drug solubility
- ✓ Core composition variables
    - o Osmotic agent incorporated.
    - o Excipients and polymers contained within the core.
- ✓ Amounts of inner core
- ✓ Compression pressure
- ✓ Location of inner core

Outer coating shell

To design a press-coated tablet, the outer shell is a key in ensuring that medication will reliably reach the predetermined site following oral administration. Press coating involves direct compression of both the inner core and the outer coating shell, without separate coating processes or the use of coating solutions. The drug form is manufactured

by compressing a tablet within a tablet, so that the outer shell becomes a coating layer. Various drug release mechanisms become available by incorporating different polymers or other materials into the outer shell formulation, or by increasing the layer's thickness. An outer shell made of a rupturable, swellable, or erodible coating, or a permeation coating using combinations of hydrophilic and hydrophobic polymers, can modulate the speed of water penetration into the outer layer to control drug release. The outer coating shell of the press-coated tablet may also provide the initial dose of drug.

- ✓ Polymer particle size
- ✓ Formulation variables
- ✓ Compression pressure
- ✓ Amounts of outer shell
- ✓ Double layered outer shell
- ✓ Compressibility and layer-binding

1.3.3. Recent techniques for press coating technology[7]

- The novel ENCORE™
- One-step dry-coated tablet (OSDRC) method
- Pulse-echo ultrasonic approach and
- X-ray computed tomography (CT) technique

The technique has been applied to solve manufacturing problems with central position deviation and absence of a core in the press-coated tablet.

1.4. 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.

1.4.1. Suitable Drug Candidates for FDDS[12]

- ➢ Drugs with narrow absorption window in GIT, e.g., Riboflavin and Levodopa
- ➢ Drugs that primarily absorbed from stomach and upper part of GIT, e.g., Calcium supplements, chlordiazepoxide and cinnarazine.
- ➢ Drugs that act locally in the stomach, e.g., Antacids and Misoprostol.
- ➢ Drugs that degrade in the colon, e.g., Ranitidine HCl and Metronidazole.
- ➢ Drugs that disturb normal colonic bacteria, e.g., Amoxicillin Trihydrate.

1.5. 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.

1.5.1. 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.1

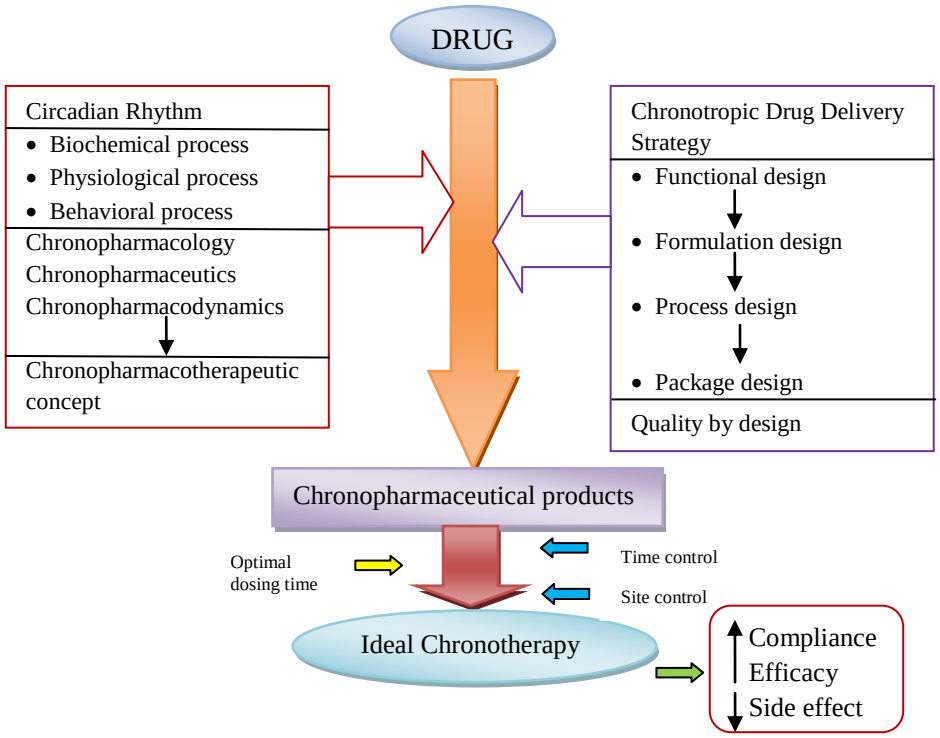


Fig.1: Design and development of new chronotropic DDSs in accordance with circadian rhythm of human body.

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.

1.5.2. 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 rhythms[11]: Oscillations of shorter duration are termed Ultradian rhythms (more than one cycle per 24 hours) E.g. 90 minutes sleep cycle.

Infradian rhythms[11]: 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. 2)

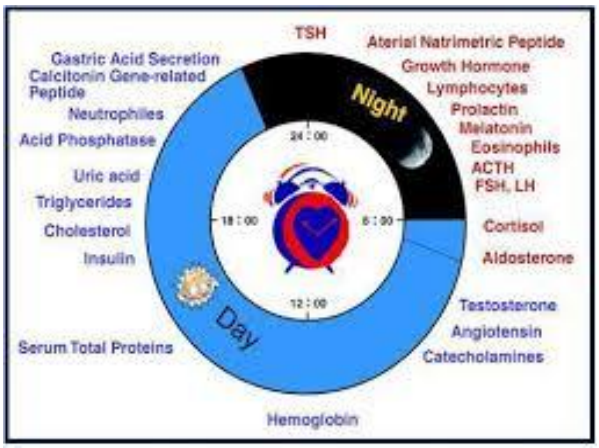


Fig. 2: Human circadian time structure-dependent pulsatile hormones secretion

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.

1.5.3. 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 (Fig. 3).

Many common diseases also display a marked circadian variation during onset or exacerbation of symptoms, as shown in Fig.4.

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.

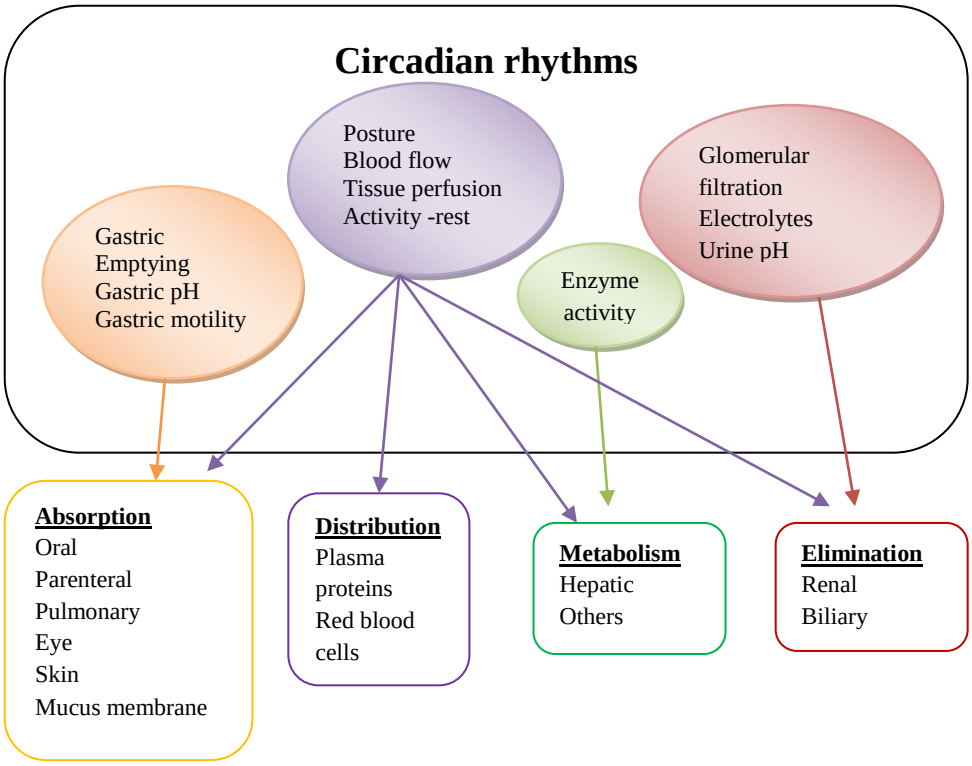


Fig. 3: Effect of circadian rhythms on the ADME of drugs.

Fig. 4: The circadian pattern of disease

1.6. 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. 5.

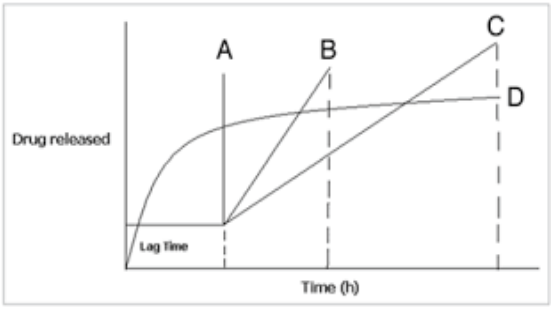


Fig. 5: Different release patterns for various pharmaceutical dosage forms

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.

1.6.1. 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.

1.6.2. 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.

1.6.3. 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.

1.6.4. 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

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

1.6.5.1. 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 (Fig. 2).

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.

1.6.5.2. Disease status[8]

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.

Table 1: Diseases that require pulsatile drug delivery[18]

Disease	Chronological behavior	Drugs used
Peptic ulcer	Acid secretion is high in the afternoon and at night.	H_2 blockers
Cancer	The blood flow to tumors is threefold greater during each daily activity phase of the circadian cycle than during the daily rest phase	Vinca alkaloids, Taxanes
Duodenal ulcer	Gastric acid secretion is highest at night, while gastric and small bowel motility and	Proton pump inhibitors

	gastric emptying are all slower at night.	
Neurological disorders	The central pathophysiology of epilepsy and the behavioral classification of convulsive events.	MAO-B inhibitors
Hypercholesterolemia	Cholesterol synthesis is generally higher during night than day time.	HMG CoA reductase, Inhibitors
Diabetes mellitus	Increase in the blood sugar level after meal.	Sulfonylurea, Insulin
Arthritis	Level of pain increases at night.	NSAIDs, Glucocorticoids
Cardiovascular diseases	BP is at its lowest during the sleep cycle and rises steeply during the early morning.	Nitroglycerin, calcium channel, blocker, ACE inhibitors
Asthma	Precipitation of attacks during night or at early morning	B_2 agonist, Antihistamines
Attention deficit syndrome	Increase in DOPA level in afternoon.	Methylphenidate

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.

1.6.6. Polymers used in PDDS[15]

- Hydroxypropyl methyl cellulose (HPMC)
- Ethyl cellulose
- Cellulose Acetate Phthalate
- Eudragit
- Hydroxypropyl cellulose (HPC)
- Xanthan gum

1.7. 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.

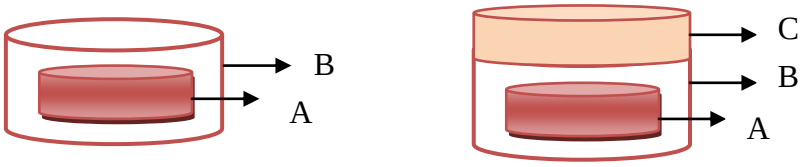
1.7.1. Advantages[14]

- ✓ 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.

1.7.2. 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.

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



A- Rapid release core tablet B- Hydrophilic polymer C- Buoyant layer

Fig. 6: Schematic diagram of floating pulsatile drug delivery

FLOATING PULSATILE DRUG DELIVREY

S. C. Jagdale et al.[22] developed the press coated floating pulsatile drug delivery of Lisinopril for the treatment of hypertension. In this formulation, the core tablet was formulated using the Superdisintegrants crospovidone and croscarmellose sodium. A press coated tablet contained the polymer carrageenan, xanthan gum, HPMC K4M, and HPMC K15M. The buoyant layer was optimized with HPMC K100M, sodium bicarbonate and citric acid. 5% superdisintegrant showed good results. The formulation containing xantham gum showed drug retaining properties and failed to float. The tablet containing HPMC K15M showed a high swelling index. The lag time for the tablet coated with 200 mg carrageenan was 3±0.1 hrs with 99.99±1.5 % drug release; with 140 mg HPMC K4M, the lag time was 3±0.1 hrs with 99.71±1.2 % drug release; and with 120 mg of HPMC K15M, the lag time was 3±0.2 hrs with 99.98±1.7 % drug release. The release mechanism of the tablet followed the Korsmeyer-Peppas equation and first order release pattern.

Mishra et al.[23] formulated a dry coated floating pulsatile drug delivery system of Enalapril maleate in the treatment of hypertension. The dry coated tablet consists in a drug containing core, coated by a hydrophilic erodible polymer (HPMC E50 and lactose) which is responsible for a lag phase in the onset of pulsatile release. The Buoyant layer consists of Methocel E50, Carbopol 934P and sodium bicarbonate. Results reveal that coating composition affects the lag time. Formulation containing lactose as filler with 6.67% crospovidone and coating composition using 30% lactose provide lag time of 4 hr with 93.03% drug release in 6 hr that shown a sigmoidal release pattern.

S.C Jagdale et al.[24] developed the compression coated floating pulsatile drug delivery of Bisoprolol. The system consisted of two parts core tablet containing active ingredient and erodible outer shell with gas generating agent. Rapid release core tablet was prepared using superdisintegrant with active ingredient which is then press coated with the polymer. A 3^2 full factorial design was used for optimization. The amount of polyox WSR205 and polyox WSR N12K was selected as independent variables. Lag period, drug release and swelling index was selected as dependant variables. Floating

pulsatile release formulation F13 at level 0 (55mg) for polyox WSR205 and level +1 (65mg) for polyox WSR N12K showed a lag time of 4 hr with more than 90% drug release. Release kinetics of the optimized formulation best fitted the zero order model.

Anuradha K.Salunkhe et al.[25] formulated the floating pulsatile drug delivery system of Metoprolol tartrate for the treatment of morning surge of hypertension. The rapid release core tablet (RRCT) was prepared by using Superdisintegrants along with active ingredient. The dry coating of optimized RRCT was done by using different grades of HPMC E15, E5, E50 and uppermost buoyant layer was prepared with HPMC K15M and sodium bicarbonate. The results reveal that FPRT F9 showed a floating lag time of 4 minutes and floating time of 112 hrs and release lag time of 6 hrs.

Raja et al.[26] developed the floating pulsatile drug delivery system of Metoprolol succinate intended for chronopharmacotherapy of hypertension. The dry coated system consisting of drug containing core, coated with hydrophilic erodible polymer (HPMC E5, E15, E50), which is responsible for lag phase of pulsatile release, top cover buoyant layer prepared with HPMC K4M and sodium bicarbonate. FPRT containing the floating material HPMC K4M and $NaHCO_3$ (80:20) showed a lag time less than 1 min and floating time more than 12 hrs. FPRT prepared using HPMC E50 (200 mg) showed a satisfactory lag time and drug release.

Gagganapalli Santhoshi Reddy et al.[27] prepared the Gastroretentive pulsatile release tablets of Lercanidipine HCl to enhance bioavailability and treat early morning surge in blood pressure. Immediate release core tablets containing lercanidipine HCl were prepared and optimized core tablets were compression-coated using buoyant layer containing polyethylene oxide (PEO) WSR coagulant, sodium bicarbonate and directly compressible lactose. DoE optimization of data revealed FPRTs containing PEO (20% w/w) with coat weight 480 mg were promising systems exhibiting good floating behavior and lag time in drug release. Abdominal X-ray imaging of rabbits after oral administration of the tablets, confirmed the floating behavior and lag time. A quadratic

model was suggested for release at 7^{th} and 12^{th} hr and a linear model was suggested for release lag time.

Swati C. Jagdale et al.[28] worked on Application of Design of Experiment for Polyox and Xanthan gum coated floating pulsatile delivery of Sumatriptan succinate in migraine treatment. Burst release was achieved through immediate release tablet using crospovidone as superdisintegrant (10%). Pulse lag time was achieved using swellable polymer polyox WSR205 and xanthan gum. 3^2 experimental design was applied. The results revealed that optimized formulation F8 containing polyox WSR205 (72.72%) and xanthan gum(27.27%) of total weight of polymer has shown floating lag time of 55±2 sec, drug content of 100.35±0.4%, hardness of 6±0.1Kg/cm^2, and 98.69±2% drug release in pulse manner with lag time of 7±0.1 hr. Optimized formulation showed prolong gastric residence which was confirmed by *invivo* X-ray study.

Sunil Patel et al.[29] designed and developed the floating pulsatile drug delivery system of meloxicam for the treatment of rheumatoid arthritis and osteoarthritis. The rapid release core tablet (RRCT) was prepared by using Superdisintegrants along with active ingredient. Dry coating of optimized RRCT was done by using different grades of HPMC (E5, E15, E50) and upper most buoyant layer was prepared with HPMC K15M and sodium bicarbonate. The developed formulations were evaluated. The results revealed that floating pulsatile release tablet F8 showed floating lag time of 4 min, floating time of 12 hrs and release lag time of 6 hrs. The optimized formulation showed compliance with chronotherapeutic objective of rheumatoid arthritis.

Zou et al.[30] worked on design and evaluation of a dry coated drug delivery system with floating pulsatile release of verapamil. The dry coated tablet consists in a drug containing core, coated by a hydrophilic polymer (HPMC E15) which is responsible for a lag phase in the onset of pulsatile release. The buoyant layer, prepared with Methocel K4M, carbopol 934P and sodium bicarbonate provides buoyancy to increase the retention of the oral dosage form in the stomach. Developed formulations were evaluated for their buoyancy, dissolution and pharmacokinetic, as well gamma-scintigraphically. The results

showed that a certain lag time before the drug released generally due to the erosion of the dry coated layer. Floating time was controlled by the quantity and composition of the buoyant layer. Both pharmacokinetic and gamma-scintigraphic data point out the capability of the system of prolonged residence of the tablets in the stomach and releasing drugs after a programmed lag time.

Swati C. Jagdale et al.[31] formulated and evaluated the floating pulsatile drug delivery system of Atenolol. The rapid release core tablet (RRCT) of drug was prepared with croscarmelllose sodium and KYRON T314. RRCT then compression coated with erodible outer shell- HPMC K4M, HPMC E15 LV, carboxymethyl cellulose sodium. The buoyant layer was prepared with HPMC K100M, sodium bicarbonate and citric acid. Developed formulations were evaluated. The results showed that K3 (180mg HPMC K4M) and K6 (290mg of HPMC E15LV) with a buoyant layer were the best formulations with the lag times of 5.2±0.1 hr and 4.1±0.2 hr.

Galgatte et al.[32] studied the floating pulsatile drug delivery of ranitidine hydrochloride for nocturnal acid breakthrough: design, optimization, *in-vitro* and *in-vivo* evaluation. The core tablet was prepared with the drug by direct compression, which was coated with ethyl cellulose (EC N10) and hydroxypropyl methyl cellulose (HPMC E15) followed by coating of HPMC E15and sodium bicarbonate for generation of effervescence which was further coated by eudragit RL 100 for effervescence entrapment to produce density <1. Optimization was done by central composite design (CCD). The results showed that ratio of EC N10 and HPMC E15 (80:20%w/w) was optimized which provide drug release 97.56% in pulsatile manner with a lag time of 3 to 3.5 hr. HPMC E15 and sodium bicarbonate (1:4%w/w) provide floating lag time of 5 min. Eudragit RL100 (5% w/w) provide good floating property.

A. Shahiwala et al.[33] worked on statistical optimization of ranitidine HCl floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. In this study, investigation of the functionality of the outer polymer coating to predict lag time and drug release was statistically analyzed using the response surface methodology (RSM).

Percentage weight ratios of ethyl cellulose to hydroxypropyl methyl cellulose in the coating formulation and coating level (% weight gain) were optimized with a 3^2 full factorial design. The coating formulation containing EC ad HPMC in percentage weight ratio of 78.75:21.25 at 7% coating level was in the optimum zone and has the potential for time-controlled pulsatile delivery of ranitidine.

Piyush Patel et al.[34] formulated and evaluated the floating drug delivery system of famotidine. Floating core tablet was prepared, which is pan coated with EC and HPMC. Optimization done by using response surface methodology and 3^2 factorial design. The optimized coating level %weight gain was 7.50% and percentage weight ratio of ethyl cellulose to hydroxypropyl methyl cellulose was 78.50% that provide lag time of 218 minute and drug release of 88.21% with minimum percentage error with predicted values from the software.

Shinde PV et al.[35] formulated and evaluated the floating press-coated pulsatile release of aceclofenac tablets for the treatment of rheumatoid arthritis. The core tablets were prepared by direct compression with drug and different concentration of sodium starch glycolate, which is then compression coated with hydroxypropyl methyl cellulose and sodium bicarbonate. The results showed that dry coated formulations F15 (27.5% of HPMC K4M), F18 (25% of HPMC K15M) and F22 (25% of HPMC K100M) shows 8 hr floating with pulsatile release pattern.

Zine et al.[36] developed single unit floating pulsatile site specific drug delivery system for chronotherapeutic release of aceclofenac. In this method, triple layer tablet and dry coated tablet of aceclofenac were prepared and compared for pulsatile release. The trilayer consisted of floating layer, drug containing layer and polymer layer. The core tablet containing was prepared and dry coated with different percentage of polymers. The results revealed that dry coating of drug provides pulsatile release pattern. The polymer coating level and amount of polymer plays a major role in buoyancy and pulsatile release pattern.

N. Tejaswini et al.[37] formulated and Evaluated the Floating Pulsatile Tablet of Eprosartan. Floating pulsatile tablets were formulated by compression coating technique containing active ingredient, croscarmellose sodium, microcrystalline cellulose, magnesium stearate in the core, ethyl cellulose and different grades of hydroxypropyl methyl cellulose in an erodible outer shell, sodium bicarbonate and HPMC K15 in the top buoyant layer. The results showed that the thickness of the outer coat and core: polymer ratios significantly affect the lag time and drug release. Change in viscosity grade of polymer altered the lag time along with its swelling index in an order: HPMC E50 > HPMC E15 >HPMC E5. Floating time was controlled by the quantity and composition of buoyant layer.

Rajesh Asija et al.[38] formulated and evaluated the floating pulsatile drug delivery for chronotherapy of hypertension. Nifedipine floating beads were prepared by ionotropic cross linking method using acidified calcium chloride as cross linking agent. Various process parameters like drug: polymer ratio, amount of sodium bicarbonate, concentration of calcium chloride, concentration of acetic acid were optimized to get the required lag time and release. The optimized formulation A11 showed 83.79% drug entrapment, 79% buoyancy, 6 hrs lag time with 7.31% drug release.

M. S. Sokar et al.[39] formulated and evaluated the pulsatile core-in-cup valsartan tablet. Core tablets were prepared by direct compression of homogenous mixture of valsartan and croscarmellose sodium. Core in cup tablets were formulated using different polymers as a plug layer, including sodium alginate (SA), Sodium carboxymethyl cellulose (NaCMC) and hydroxypropyl methyl cellulose (HPMC). The results showed that the release lag time of the tablets increased when the quantity of the plug layer increased thus decreasing the drug release. Plug layer polymers showed a lag time with rank order: SA < NaCMC < HPMC. The optimized formulations F5 (having SA as plug polymer) released drug after a lag time of 2 hr while F6 released the drug in two successive pulses with a reasonable lag time in between due to its floating behavior.

Shaji Jessy et al.[40] formulated and optimized the floating pulsatile aceclofenac microspheres using response surface methodology. The floating pulsatile microspheres were prepared by emulsion solvent diffusion technique. A 3^2 factorial design was employed to study the effect of independent variables, drug to polymer ratio and stirring speed, on dependent variables, particle size and drug entrapment efficiency. The optimized batch (Drug to polymer ratio of 1:3 and stirring speed of 500 rpm) showed high entrapment efficiency of 90.1% and mean particle size 118.66µm. The floating microsphere provides two phase release pattern with initial lag time during floating in acidic medium followed by rapid release in phosphate buffer.

Shinde et al.[41] developed and evaluated the floating pulsatile release tablet of aceclofenac. Triple layer tablet was prepared using hydrophilic polymer (HPMC K4M) as bottom layer and hydrophobic polymer (EC) as top layer. The formulation F8 possessed good floating property with floating time 470minutes and showed pulsatile drug delivery pattern.

Kshirsagar et al.[42] optimized the floating pulsatile drug delivery system for chronotherapy of hypertension. The floating beads were prepared by simple process of acid-base reaction during ionotropic cross linking by low viscosity sodium alginate and calcium chloride as a cross linking agent. The functionality of the sodium alginate to predict lag time and drug release was statistically analyzed using the response surface methodology (RSM). The chosen independent variables, i.e. sodium alginate and potassium bicarbonate were optimized with a 3^2 full factorial design. The results revealed that the optimized formulation prepared according to computer-determined levels provided a release profile, which was close to the predicted values. The floating beads obtained were porous (21-28% porosity), hollow with bulk density <1 and had Ft70 of 2–11 h. The floating beads provided expected two-phase release pattern with initial lag time during floating in acidic medium followed by rapid pulse release in phosphate buffer.

Shivhare et al.[43] developed and evaluated the floating pulsatile microspheres of metoprolol tartrate using emulsification-solvent evaporation technique. Polymers used for the preparation were Eudragit L 100 and Eudragit S 100. The floating microspheres provided two phase release pattern with initial lag time during floating in acidic medium followed by rapid release in phosphate buffer. The optimized formulation G3 containing drug: polymer ratio (1:2), span 80 (2% w/v) and Sodium bicarbonate (1.5%w/v) showed 95% of drug release for 9 hrs and particle size of 803.3µm and follow Korsmeyer-Peppas model in dissolution studies.

Jain et al.[44] formulated and evaluated the floating pulsatile drug delivery system for chronotherapy of rheumatoid arthritis. The system developed consists of drug containing core tablets, which were coated with pH-dependent polymer Eudragit S100 and outer effervescent layer of polymers and sodium bicarbonate showed floating in acidic medium with no drug release followed by rapid release of drug in basic medium. The results showed that formulation FPRT II (40% HPMC K 100M) with no drug release for 6-7 hrs followed by rapid and burst release of drug.

PULSATILE DRUG DELIVERY

Kamat Akshay Ramesh et al.[45] formulated and evaluated the pulsatile drug delivery system containing indomethacin using natural polymers. The press-coated pulsatile release tablet contains drug in the inner rapid core tablet formulated by direct compression method using plantago ovata mucilage and modified agar as Superdisintegrants and the external coat formulated using natural polymers such as dammar gum, chitosan, xanthan gum and guar gum by both direct and wet granulation method. The prepared tablets were evaluated. Formulation A1, A8, B2 and B7 were selected as best formulations. The formulation B2 prepared by wet granulation method containing xanthan gum and dammar gum in the ratio of 2:1 showed maximum lag time of 7hr and 15 min, highest swelling index of 89.44% and cumulative percentage drug release of 99.29% at the end of 10hr.

Kumar et al.[46] formulated and Evaluated the Two-Pulse Drug Delivery System of Amoxicillin Trihydrate. The core tablets were compressed and coated with hydroxypropyl methylcellulose (HPMC) of different viscosities with spray-dried lactose (SDL) as a pore former. The final two-pulse release tablet was prepared with the remaining drug fraction (to be released as the first immediate release pulse) with a disintegrant, giving the final tablet. The tablets were evaluated. The results showed that the core tablet disintegrated within 30 to 40sec and drug content ranged from 97.85 to 98.23%. In vitro drug release showed prolongation of lag time as polymer viscosity increased. With 25 % HPMC and 75 % SDL, drug release was 97.5 % by the end of 8th, 9th &10th hr and viscosity was 100, 400 and 4000 cps respectively.

Aggarwal et al.[47] formulated and optimized the chronotherapeutic drug delivery of Carvedilol sulphate compression coated tablets by using design of experiment approach. Optimization done by response surface methodology based on 3^2 factorial designs. Compression coated tablet containing carvedilol phosphate in the core was formulated with an outer coat by eudragit L 100 and ethyl cellulose. The percentage weight ratio of ethyl cellulose to eudragit L 100 and coating level were selected as critical process parameters (CPPs), whereas critical quality attributes (CQAs) were lag time and cumulative percentage drug release at 8 hr in current study. The optimized formulation with 19.34 % ratio of ethyl cellulose with eudragit L 100 at 31.03 % coating level showed 267 minute lag time and 76.2 % cumulative drug release after 8 hr.

Sayantan Mukhopadhyay et al.[48] formulated and evaluated the Pulsatile drug delivery system for sequential release of Atorvastatin. The core tablets of Atorvastatin were prepared by direct compression technique using SSG as super disintegrants. Then the core tablets are coated with the different concentrations of polymers such as Eudragit RS 100, Eudragit S 100, Ethyl cellulose, CAP, HPC. All prepared multilayered tablets were subjected for evaluation parameters. *In-vitro* drug release profiles of the prepared tablets were suggested that, the release of drug from compression coated tablets match with chronobiological requirement of disease.

P. Shafi et al.[49] formulated and evaluated the pulsatile drug delivery system of lansoprazole by using press coated method. The core tablet of lansoprazole was prepared with different concentrations of sodium starch glycolate. The optimized core tablet was then compression coated different ratios of Klucel EXF and EC N20. The prepared tablets were evaluated. The results revealed that F2 formulation with ratio Klucel EXF: EC N20 (87.5:12.5) showed 6 hr release. From the work, it was concluded that, press coating is necessary to provide pulsatile release. The polymer coating level and quantity of polymer played a main role for providing pulsatile release pattern.

Patil B S et al.[50] developed and evaluated the time controlled pulsatile release Lisinopril tablets. The core containing Lisinopril was prepared by direct compression method and evaluated. The coating materials consisted of hydrophobic polymer of ethyl cellulose and hydrophilic materials (HPMC 15 CPS) were used in different concentration. The optimized formulation (HPMC 15 CPS-150mg and EC-100mg) showed good lag time with drug release of 99.10%. From the results, it was concluded that the prepared pulsatile drug delivery system is suitable for chronotherapeutic management of hypertension.

Singh et al.[51] designed and evaluated the compression coated pulsatile release tablets of Losartan potassium. Two types of core tablets were prepared by direct compression, one containing superdisintegrant crospovidone(C) and other containing effervescent agent (E) for producing burst release. The core tablets were compression coated with three different polymers i.e. sodium carboxymethyl cellulose R(NaCMC), HPMC K4M and HPMC E50. It was found that core tablets containing superdisintegrant failed to produce burst drug release pattern while effervescent agent was able to do so. Results also reveal that coating composition and coating level affects lag time. Formulation containing effervescent agent in core and coated with 200mg hydroxypropyl cellulose provide lag time of 4.5 hr with 73% drug release in 6 hr that followed a sigmoidal release pattern. These values were close to the desired objective of producing lag time of 5-6 hr followed by fast drug release.

Krishnaveni.G et al.[52] developed and evaluated the pulsatile drug delivery system of Montelukast sodium by press coated tablet using natural polysaccharides. The core tablet was prepared by direct compression with different concentrations of Superdisintegrants. The core tablet was then coated with a natural polymers such xanthan gum, guar gum and mixture of it. The prepared tablets were evaluated. The formulation P5F3 was optimized with the drug release of 92.8% at the end of 10^{th} hr and follows peppas model with R^2 of 0.983.

Kumud Upadhyaya et al.[53] Developed and evaluated the nifedipine pulsatile tablet for colon drug delivery. The core tablet of nifedipine was prepared by wet granulation. The core tablet was compression coated with polymer blend of ethyl cellulose (water insoluble polymer) and Eudragit L 100 (Enteric polymer). The results revealed that the formulation having a coating level of 50% w/w of core and weight ratio of ethyl cellulose to Eudragit L 100 (20%) showed lesser release profile as compared to other formulation i.e. 52.83% in 12hrs. As we increase the weight ratio of ethyl cellulose to Eudragit L 100 better entrapment of drug leading to controlled release of drug.

Patel Tejaskumar et al.[54] formulated and evaluated the erodible pulsatile drug delivery system of Salbutamol sulphate for Nocturnal asthma. The core tablet was prepared by direct compression. The core tablet is coated with the different concentrations of inner swellable polymer HPMC E5. The prepared tablet again enteric coated with 5% cellulose acetate phthalate. Salbutamol sulphate coated with 30% HPMC E5 layer then by 5% CAP coating solution was optimized.

Singh et al.[55] developed and evaluated the pulsatile drug delivery system of Aceclofenac sodium. The core tablet was prepared with the drug and varying concentrations of Superdisintegrants. The core tablet was compression coated with different ratio of ethyl cellulose (EC) and HPMC K4M. The optimized tablet was then enteric coated with cellulose acetate phthalate solution. Formulation C5 containing HPMC K4M & EC (20:80) was found to provide maximum lag time of 5hrs and thus, enteric coated with 3% CAP (cellulose acetate phthalate) solution, so as to increase the

lag time and minimize the variability in gastric region. The CAP coated formulation showed lag time of 7 hrs and 98% drug release.

D. Pavani et al.[56] developed and evaluated the Metoprolol tartrate chronotherapeutic drug delivery system. The core tablets were prepared by using various concentrations of Superdisintegrants, the formulated core tablets were compression coated with the polymers (EC N50 and HPMC K100M). The core and press coated tablets were evaluated. The results revealed that C5 and C9 showed maximum drug release after 8th hr. Time dependent pulsatile drug delivery system has been achieved from tablet of formulation C5 and C9 with 98.37% and 99.9%.

Janugade B. U. et al.[57] formulated and evaluated the press coated Montelukast sodium tablets for pulsatile drug delivery system. The core tablet of Montelukast was prepared by direct compression. The core tablet is press coated with different compositions of hydrophobic polymer ethyl cellulose and hydrophilic polymer low-substituted hydroxypropyl cellulose by both wet granulation and direct compression. The results revealed that lag time decreases with increasing concentration of low-substituted hydroxypropyl cellulose. Press coated tablets coated by dry mixing and by wet granulation showed variations in lag time. As compared to dry mixed blend method wet granulation method gives less lag time.

Rajesh Asija et al.[58] formulated and evaluated the pulsatile tablet of Ramipril. The core tablet of ramipril was prepared with croscarmellose sodium by direct compression. The optimized core is then press coated with the hydrophilic polymer HPMC K100M and hydrophobic polymer ethyl cellulose. The results obtained indicated that optimum amounts of HPMC K100M and ethyl cellulose more essential to produce pulsatile release tablets with desirable lag time and release characteristics. The combination of HPMC K100M and ethyl cellulose showed the synergistic effect on lag time. The finding indicates that the lag time of a press coated tablet can be modulated from 4 to 6 hrs by combining ethyl cellulose with HPMC K100M in different weight ratio. The release profile of optimized formulation of ramipril was close to korsmeyer peppas model.

CAPTOPRIL

Gangane et al.[59] formulated and evaluated the chronomodulated pulsatile therapeutic system for early morning surge in blood pressure. The core tablet was prepared using drug and different concentrations of croscarmellose sodium by direct compression method. Core tablet was then press coated with different ratio of polymers (HPMC K4M and Ethyl cellulose). From the results, it was concluded that the lag time decreases with increase in concentration of HPMC K4M. When the concentration of the hydrophilic polymer was increased, hydration property of the system increases, causing more rapid dissolution or rupturing of the external shell resulting in the reduction of lag time.

Sameer Singh et al.[60] formulated and evaluated the floating tablet of Captopril. The floating tablets were prepared using different grades of hydroxypropyl methyl cellulose (HPMC K4M, K15M and K100M). Lactose and citric acid were used in different concentration as a channeling and chelating agent. Results revealed that the effect of channeling and chelating agent at different concentration had significant effect on the release of the drug from hydrophilic matrix tablet. Different viscosity grades of HPMC influence the drug release from the hydrophilic matrix and also affect the floating property.

Patil B. S. et al.[61] formulated and evaluated the floating matrix tablets using HPMC 50cps. The floating matrix tablets contained drug, a gas generating agent (6%-18% of $NaHCO_3$) and water soluble polymer (40%-60% of HPMC 50cps) was prepared by direct compression. The prepared tablets were subjected to hardness, friability, weight variation, thickness, drug content, lag time subsequently buoyancy time, and in-vitro dissolution studies. The optimized formulation C3 showed a drug release of 91.32% in 10 hrs with floating lag time of 2min 27sec.

Shahtalebi et al.[62] formulated and evaluated the orally disintegrating tablets of Captopril using natural Superdisintegrants. The disintegrating Captopril tablets were prepared using croscarmellose sodium, crospovidone and two natural Superdisintegrants:

karaya gum and natural agar. A 3^2 full factorial design was applied to optimize the formulation and 9 batches were prepared and evaluated. The results revealed that Karaya gum in the concentration of 9% w/w with Avicel PH 102 in 25% w/w gave rapid disintegration in 25sec and showed 100% drug release within 5 minutes, it was concluded that orally disintegrating tablets of captopril can be successfully formulated using karaya gum.

Patil et al.[63] developed and characterized the chronomodulated drug delivery system of captopril. The core tablet containing drug was prepared by direct compression method and then coated sequentially with an inner swelling layer containing hydrocolloid HPMC E5 and an outer rupturable layer consisted of Eudragit RL/RS (1: 1). The results showed that as the amount of inner swelling layer increases, the lag time decreases and as the Eudragit coating level increases, the lag time increases and percent water uptake of time-dependent pulsatile release system decreases. The presence of an osmotic agent and effervescent agent helped in shortening of lag time.

Singla et al.[64] formulated and evaluated the floating matrix tablets of captopril. The floating matrix tablets of varying concentrations of HPMC K15M, HPMC K4, chitosan and sodium bicarbonate (gas former) were prepared by direct compression. Floating capacity and drug release studies were conducted in 0.1 N HCl at 37 ± 0.5 0C. The matrix tablets revealed a gradual drug release during an 8 h period following a non-Fickian diffusion process. The optimized batch with 30% wt. of HPMC K4M and HPMC K15M, showed floating lag time of 5-10 min whereas batch with 30% chitosan and other entire batches showed immediate floatation. From the results, it was concluded that floating matrix tablets holds a lots of potential for drug which are unstable in alkaline pH or are which mainly absorbed in acidic pH.

Bolourtchian N et al.[65] formulated and optimized the captopril sublingual tablet using D-optimal design. Captopril containing tablets were prepared by direct compression method using different ingredients such as polyvinyl pyrrolidone, starch 1500, sodium starch glycolate and lactose (independent variables) and magnesium

stearate, talc and aspartame (fixed components). Tablets were evaluated for the physical properties including hardness, disintegration time and friability which were considered as responses in a D-optimal experimental plan. Results were statistically examined using special cubic model and polynomial mathematical equations and found to be statistically significant ($p<0.05$) for disintegration time and friability data. Meanwhile linear model was best fitted with hardness data. The obtained results were used to generate optimized overlay plot. The physical data from the numerical optimization were verified and found to be very close to those predicted from the regression analysis. Additional experiments including drug content, in vitro drug dissolution rate and accelerated stability studies were also performed on the optimum formulation. All results were in accordance with the requirements of a sublingual tablet.

Z. Rahman et al.[66] designed and evaluated the bilayer floating tablets of captopril. The bilayer tablets were prepared by direct compression. HPMC K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p. The floating behavior and *in vitro* dissolution studies were carried out in a USP 23 apparatus 2 in simulated gastric fluid (without enzyme, pH 1.2). *In vitro* dissolution studies showed controlled release of 95% for 24 h with floating lag time of 10 min followed the Higuchi diffusion mechanism and in vivo studies indicated increased GRT. From the results, it was concluded that the captopril floating system was an alternative approach to the conventional dosage form.

Vijayasankar G R et al.[67] formulated and evaluated the captopril gastro-retentive floating drug delivery system. The tablets were prepared using drug with different grades of hydroxypropyl methyl cellulose and sodium bicarbonate by direct compression method. The prepared tablets were evaluated for floating lag time, floating time, swelling studies and *invitro* drug release. The results revealed that formulation F5 showed high swelling index with floating time more than 8hr with immediate floating lag time. Formulation F5 was optimized with the drug release of 96.22% at the desired time of 8hr.

Lingam Meka et al.[68] prepared the matrix type multiple unit gastro retentive floating drug delivery systems for captopril based on gas formation technique: *invitro* evaluation. The system consisted of the drug-containing core units prepared by direct compression process, which were coated with three successive layers of an inner seal coat, effervescent layer (sodium bicarbonate) and an outer gas-entrapped polymeric membrane of an polymethacrylates (Eudragit RL30D, RS30D, and combinations of them). The results revealed that the time to float was decreased as amount of the effervescent agent increased and coating level of gas-entrapped polymeric membrane decreased. The optimum system floated completely within 3 min and maintained the buoyancy over a period of 12 h. The drug release was controlled and linear with the square root of time.

Suman Rawat et al.[69] formulated and evaluated the floating microspheres of Captopril. Floating microspheres were prepared by Non-aqueous solvent evaporation technique using Ethyl cellulose, Eudragit RS-100, Eudragit RL-100 polymers in varying concentration. Formulations were evaluated for percent yield, particle size, entrapment efficiency, in vitro buoyancy and in vitro drug release studies. Results revealed that F3 and F9 showed no significant changes in percentage drug entrapment efficiency, particle size, percentage buoyancy and in vitro controlled release of Captopril. The optimized formulation F3 and F9 follows zero order, non fickian diffusion mechanism.

Hisakazu Sunada et al.[70] prepared and evaluated the captopril elementary osmotic pump tablets. The core tablet was prepared using drug, microcrystalline cellulose, sodium chloride and HPMC K15by wet granulation. The core tablet was coated with cellulose acetate solution by pan coating. An orifice was drilled in the centre of each coating tablet by micro drill. In the drug release study *in vitro*, the influence of the tablet formulation variables, the amount of NaCl, hydroxypropyl methylcellulose K15 (HPMCK15), microcrystalline cellulose (MCC) in the core, the concentration of cellulose acetate (CA), dibutylphthalate (DBP), and polyethylene glycol 400 (PEG-400) in the coating solution have been investigated. From the results, it was found that the drug release was mostly affected by the amount of NaCl, HPMCK15, and MCC in the core, and the amount of

PEG-400 in the coating solution. To a certain extent, drug release was less affected by the orifice size, concentration of coating solution, and the coating weight. It was also independent of the pH of the dissolution medium and orifice quantum. The drug release mechanism has been shown to involve release kinetic derived from differences in the osmotic pressure across the membrane. The relative bioavailability of EOPT was 119.9%. EOPT showed a good correlation between absorption *in vivo* and drug release *in vitro*.

Mohammed G Ahmed et al.[71] formulated and evaluated the gastric mucoadhesive drug delivery systems of captopril. Gastro-retentive beads of captopril were prepared by orifice ionic gelation method in 1:1 and 9:1 ratio of alginate along with mucoadhesive polymers: hydroxypropyl methyl cellulose, carbopol 934P, chitosan and cellulose acetate phthalate. The prepared beads were subjected for various evaluation parameters. The results showed that Alginate-chitosan (9:1) beads showed excellent microencapsulation efficiency (89.7 percent). Alginate-Carbopol 934P exhibited maximum efficiency of mucoadhesion in 0.1N Hydrochloric acid (44% for 1:1 and 22% for 9:1) at the end of 8 hours, whereas least mucoadhesion was observed with alginate-Cellulose acetate phthalate beads. The in vitro release studies were carried out in 0.1 N Hydrochloric acid and the release were found to be more sustained with Alginate-chitosan beads (9:1) than Alginate-Carbopol 934P (1:1) beads. The alginate-cellulose acetate phthalate beads showed the better sustained release as compared to all other alginate- polymer combinations. Regression analysis showed that the release followed zero order kinetics.

Harish Gopinath et al.[72] formulated and evaluated the captopril microencapsules – A sustained release approach. Microspheres and micropellets of captopril were prepared with different polymers (chitosan, ethyl cellulose, hydroxypropyl methyl cellulose and sodium alginate) by different techniques of microencapsulation (emulsion-phase separation, solvent-evaporation and ionotropic-gelation). The results revealed that all the formulations prepared, showed good drug incorporation efficiency and an extended release of the drug, thereby enhancing the duration of action.

Sahu et al.[73] formulated and evaluated the captopril microspheres by ionic gelation technique. Captopril microspheres were prepared with a coat consisting of alginate and polymer such as HPMC, Sodium alginate, Sodium Carboxymethyl cellulose, by Ionic cross linking technique using $CaCl_2$. From this study it is concluded that the drug polymer ratio and stirring speed were important for obtained desired spherical particles. The yield was found to be high in the formulations. The release rate of captopril from the microspheres was slow depending upon the amount and type of polymers used.

AIM AND PLAN OF WORK

AIM OF THE WORK

- To formulate and evaluate Floating Pulsatile tablet of Captopril providing chronomodulated therapy for better treatment of Hypertension
- To prepare the rapid release core tablets of Captopril 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 (40^{o} 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 CAPTOPRIL

III. Pre-formulation studies of drug and formulations

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

V. Evaluation of Rapid release core tablet of Captopril

- 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 Captopril

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
- Release kinetics of optimized formulation
- Stability study of optimized formulation as per ICH guidelines

RATIONALE OF STUDY

4. 1. RATIONALE FOR SELECTION OF DRUG[60, 76]

- ✓ CAPTOPRIL belongs to the class of ACE inhibitors, mainly used in the treatment of hypertension, congestive heart failure, nephropathy and myocardial infarction.
- ✓ It has a shorter half life (<2hours)
- ✓ It is unstable in lower part of GIT, well absorbed in stomach.
- ✓ Bioavailability of 60-70%. Presence of food affects the absorption.

4. 2. RATIONALE FOR SELECTION OF DOSAGE FORM[10, 13, 14]

- ✓ Chronopharmacotherapy of diseases which show circadian rhythms in their pathophysiology.
- ✓ Avoiding first pass metabolism.
- ✓ For targeting the specific site e.g. Stomach.
- ✓ For time programmed administration of drugs.
- ✓ For drugs having short half life.
- ✓ Improved bioavailability
- ✓ Reduced side effects and dosage frequency, improved patient compliance

4.3. RATIONALE FOR SELECTION OF HYPERTENSION[16]

Heart rate and blood pressure will be high at the time we wake up in the morning i.e. A.M and it will begin to decrease in the afternoon and it reaches to the minimum at midnight. But the blood pressure is comparatively high in case of hypertension patients upon awakening. This physiological condition is described as morning surge or A.M. surge. The systolic blood pressure rises up to 3mmHg/hour for 4-6 hours after getting up called post-awakening and the diastolic myocardial ischemia takes the lead as well in the morning

DISEASE PROFILE

5.1. HYPERTENSION[75, 76, 77, 78]

Hypertension is defined as the condition in which the arteries have persistently elevated blood pressure. Arteries are the blood vessels that carry oxygenated blood from the heart to the body tissues.

5.2. EPIDEMIOLOGY[77]

Hypertension is one of the leading causes of the global burden of disease. Approximately 7.6 million deaths (13–15% of the total) and 92 million disability-adjusted life years worldwide were attributable to high blood pressure in 2001. Hypertension doubles the risk of cardiovascular diseases, including coronary heart disease (CHD), congestive heart failure (CHF), ischemic and hemorrhagic stroke, renal failure, and peripheral arterial disease. It often associated with additional cardiovascular disease risk factors, and the risk of cardiovascular disease increases with the total burden of risk factors. Although antihypertensive therapy clearly reduces the risks of cardiovascular and renal disease, large segments of the hypertensive population are either untreated or inadequately treated.

Both environmental and genetic factors may contribute to regional and racial variations in blood pressure and hypertension prevalence. Studies of societies undergoing "acculturation" and studies of migrants from a less to a more urbanized setting indicate a profound environmental contribution to blood pressure. Obesity and weight gain are strong, independent risk factors for hypertension. It has been estimated that 60% of hypertensive's are >20% overweight. Among populations, hypertension prevalence is related to dietary NaCl intake, and the age-related increase in blood pressure may be augmented by a high NaCl intake. Low dietary intakes of calcium and potassium also may contribute to the risk of hypertension. Alcohol consumption, psychosocial stress, and low levels of physical activity also may contribute to hypertension.

5.3. CLASSIFICATION[78]

- Primary hypertension: It is also called essential or idiopathic hypertension, affects 90-95% of hypertensive individuals. The causes include genetic and environmental factors.

- Secondary hypertension: It is caused by another medical condition or treatment. Their cause includes kidney problems, adrenal gland tumors, thyroid disease and narrowing of aorta.
- Isolated systolic hypertension: In this, systolic pressure is above 140mm of Hg but diastolic pressure remains normal.
- Malignant hypertension: It is a severe form of hypertension and death may occur within few months, if left untreated.

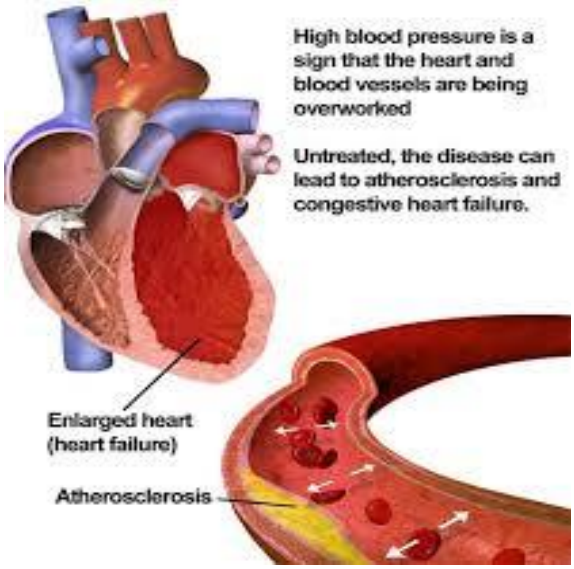


Fig. 7: Etiology of hypertension

Table 2: Criteria for diagnosis

CATEGORY	SYSTOLIC (mm/Hg)	DIASTOLIC (mm/Hg)
Normal	90-119	60-79
High normal (Pre hypertension)	120-139	80-89
Stage I hypertension	140-159	90-99
Stage II hypertension	160-179	100-109
Stage III hypertension (emergency)	≥ 180	≥110
Isolated systolic hypertension	≥140	<90

5.4. RISK FACTORS

FOR PRIMARY HYPERTENSION:

- Family history
- High intake of sodium and fat
- Sedentary life style
- Obesity, stress
- Excessive alcohol consumption

FOR SECONDARY HYPERTENSION:

- Renal Artery disease
- Mineral deficiencies(calcium, potassium, magnesium)
- Brain tumor, quadriplegia, head injury
- Thyroid, pituitary or parathyroid dysfunction.

5.5. PATHOPHYSIOLOGY OF BP REGULATION[75, 76]

The exact cause of hypertension is unknown. Arterial Blood Pressure is a product of cardiac output and peripheral resistance. Peripheral resistance is increased by factors that increase blood viscosity or reduce the lumen size of vessels

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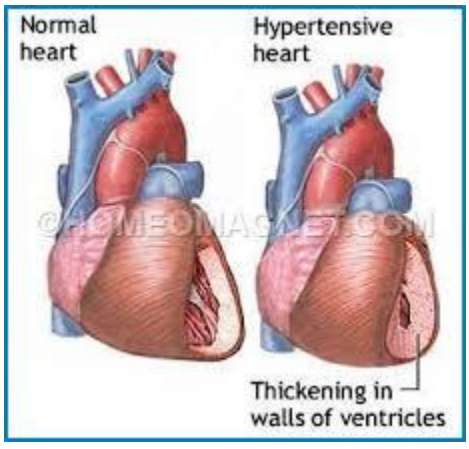


Fig. 8: Pathology of hypertensive heart

Mechanisms leading to hypertension are

- Changes in the arteriolar blood causing increased peripheral vascular resistance.
- Increased blood volume resulting from renal or hormonal dysfunction.

- Thickening of arteriolar caused by genetic factors leading to increased peripheral resistance.
- Renin Angiotensin aldosterone system along with abnormalities in renal tubules also plays a part.
- Increased circulatory blood volume and increased peripheral resistances are main pathophysiological mechanisms.

1. Abnormal Na transport

In many cases of hypertension, Na transport across the cell wall is abnormal, because the Na-K pump (Na^+, K^+-ATPase) is defective or inhibited or because permeability to Na^+ is increased. The result is increased intracellular Na, which makes the cell more sensitive to sympathetic stimulation. Ca follows Na, so accumulation of intracellular Ca may be responsible for the increased sensitivity. Because Na^+, K^+-ATPase may pump norepinephrine back into sympathetic neurons (thus inactivating this neurotransmitter), inhibition of this mechanism could also enhance the effect of norepinephrine , increasing BP. Defects in Na transport may occur in normotensive children of hypertensive parents.

2. Sympathetic nervous system

Sympathetic stimulation increases BP, usually more in patients with prehypertension (systolic BP 120 to 139 mm Hg, diastolic BP 80 to 89 mm Hg) or hypertension (systolic BP $\geq$ 140 mm Hg, diastolic BP $\geq$ 90 mm Hg, or both) than in normotensive patients. Whether this hyperresponsiveness resides in the sympathetic nervous system or in the myocardium and vascular smooth muscle is unknown. A high resting pulse rate, which may result from increased sympathetic nervous activity, is a well-known predictor of hypertension. In some hypertensive patients, circulating plasma catecholamine levels during rest are higher than normal.

3. Renin-angiotensin-aldosterone system

This system helps regulate blood volume and therefore BP. Renin, an enzyme formed in the juxtaglomerular apparatus, catalyzes conversion of angiotensinogen to angiotensin I. This inactive product is cleaved by ACE, mainly in the lungs but also in the kidneys and

brain, to angiotensin II, a potent vasoconstrictor that also stimulates autonomic centers in the brain to increase sympathetic discharge and stimulates release of aldosterone and ADH. Aldosterone and ADH cause Na and water retention, elevating BP. Aldosterone also enhances K excretion; low plasma K (< 3.5 mEq/L) increases vasoconstriction through closure of K channels. Angiotensin III, present in the circulation, stimulates aldosterone release as actively as angiotensin II but has much less pressor activity. Because chymase enzymes also convert angiotensin I to angiotensin II, drugs that inhibit ACE do not fully suppress angiotensin II production.

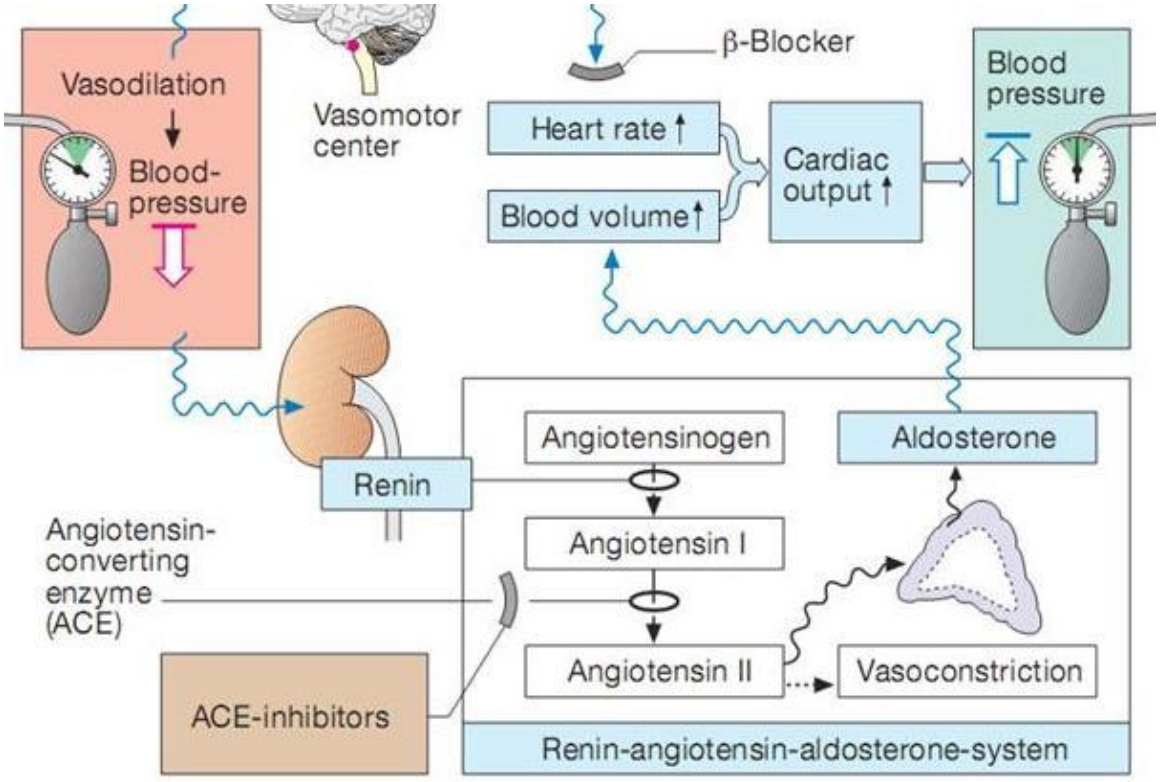


Fig. 9: Renin-Angiotensin-Aldosterone mechanism

Renin secretion is controlled by at least 4 mechanisms:

(1) A renal vascular receptor responds to changes in tension in the afferent arteriolar wall;

(2) a macula densa receptor detects changes in the delivery rate or concentration of NaCl in the distal tubule;

(3) circulating angiotensin has a negative feedback effect on renin secretion; and

(4) via the renal nerve, the sympathetic nervous system stimulates renin secretion mediated by β-receptors.

4. Vasodilator deficiency

Deficiency of a vasodilator (eg, bradykinin, nitric oxide) rather than excess of a vasoconstrictor (eg, angiotensin, norepinephrine) may cause hypertension. If the kidneys do not produce adequate amounts of vasodilators (because of renal parenchymal disease or bilateral nephrectomy), BP can increase. Vasodilators and vasoconstrictors (mainly endothelin) are also produced in endothelial cells. Therefore, endothelial dysfunction greatly affects BP.

5.6. SIGNS AND SYMPTOMS[78]

- ✓ Headache, some quite severe
- ✓ Dizziness
- ✓ Fatigue
- ✓ Irregular heart beat
- ✓ Confusion
- ✓ Vision problems
- ✓ Chest pain
- ✓ Nocturia

5.7. DIAGNOSIS[77]

- Multiple measurements of BP to confirm
- Urinalysis and urinary albumin:creatinine ratio; if abnormal, consider renal ultrasonography
- Blood tests: Fasting lipids, creatinine, K
- Renal ultrasonography if creatinine increased
- Evaluate for aldosteronism if K decreased
- ECG: If left ventricular hypertrophy, consider echocardiography
- Sometimes thyroid-stimulating hormone measurement
- Evaluate for pheochromocytoma or a sleep disorder if BP elevation sudden and labile or severe

Hypertension is diagnosed and classified by sphygmomanometer. History, physical examination, and other tests help identify etiology and determine whether target organs are damaged.

5.8. MANAGEMENT OF HYPERTENSION [76, 78]

LIFESTYLE MODIFICATIONS

The first line of treatment for hypertension is lifestyle changes, including dietary changes, physical exercise, and weight loss. These have all been shown to significantly reduce blood pressure in people with hypertension. Their potential effectiveness is similar to and at times exceeds a single medication.

Dietary changes shown to reduce blood pressure include diets with low sodium, the DASH diet, vegetarian diets and high potassium diets.

Physical exercise regimens which are shown to reduce blood pressure include isometric resistance exercise, aerobic exercise, resistance exercise, and device-guided breathing.

Stress reduction techniques such as biofeedback or transcendental meditation may be considered as an add-on to other treatments to reduce hypertension, but do not have evidence for preventing cardiovascular disease on their own.

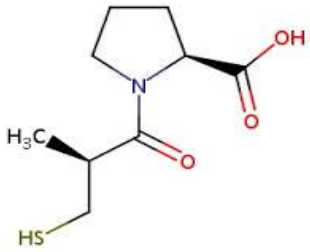
MEDICATIONS

- Diuretics
- Angiotensin converting enzymes (ACE) inhibitors
- Angiotension receptor blockers
- Alpha adrenergic receptor blockers
- Beta adrenergic receptor blockers
- Calcium channel blockers
- Central adrenergic inhibitors
- Vasodilators

CAPTOPRIL[76, 79, 80]

PHYSIOCHEMICAL PROPERTIES

Structure:



Molecular formula	**:** $C_9H_{15}NO_3S$
Molecular weight	**:** 217.285
Chemical Name	**:** (2S)-1-[(2S)-2-methyl-3-sulfanylpropanoyl] pyrrolidie-2-carboxylic acid
CAS Number	**:** 62571-86-2
Category	**:** Angiotensin – Converting Enzyme Inhibitors Antihypertensive agents
Description	**:** A white to off-white, crystalline powder; odour, characteristic, sulphide-like.
Solubility	**:** freely soluble
Storage	**:** Store protected from moisture
Melting Point	**:** 104°C to 110°C

INDICATION[76]

- For the treatment of essential or renovascular hypertension (usually administered with other drugs, particularly thiazide diuretics).
- It is used to treat congestive heart failure in combination with other drugs (e.g. cardiac glycosides, diuretics, β-adrenergic blockers).
- It improves survival in patients with left ventricular dysfunction following myocardial infarction.
- It can be used to treat nephropathy, including diabetic nephropathy.

DOSE: Initially, 12.5 to 50mg twice daily; usual maintenance dose, 25mg twice daily; maximum, 50mg twice daily

PHARMACOKINETICS[76]

- **Absorption:** 60-75% in fasting individuals; food decreases absorption by 25-40%
- **Protein Binding:** 25-30% bound to plasma proteins, primarily albumin
- **Metabolism:** Hepatic. Major metabolites are captopril-cysteine disulfide and the disulfide dimer of captopril. Metabolites may undergo reversible interconversion.
- **Elimination $T_{1/2}$:** 2 Hours
- **Excretion**: Renal

PHARMACODYNAMICS[80]

Captopril, an ACE inhibitor, antagonizes the effect of the RAAS. The RAAS is a homeostatic mechanism for regulating hemodynamics, water and electrolyte balance. During sympathetic stimulation or when renal blood pressure or blood flow is reduced, renin is released from the granular cells of the juxtaglomerular apparatus in the kidneys. In the blood stream, renin cleaves circulating angiotensinogen to ATI, which is subsequently cleaved to ATII by ACE. ATII increases blood pressure using a number of mechanisms. First, it stimulates the secretion of aldosterone from the adrenal cortex. Aldosterone travels to the distal convoluted tubule (DCT) and collecting tubule of nephrons where it increases sodium and water reabsorption by increasing the number of sodium channels and sodium-potassium ATPases on cell membranes. Second, ATII stimulates the secretion of vasopressin (also known as antidiuretic hormone or ADH) from the posterior pituitary gland. ADH stimulates further water reabsorption from the kidneys via insertion of aquaporin-2 channels on the apical surface of cells of the DCT and collecting tubules. Third, ATII increases blood pressure through direct arterial vasoconstriction. Stimulation of the Type 1 ATII receptor on vascular smooth muscle cells leads to a cascade of events resulting in myocyte contraction and vasoconstriction. In addition to these major effects, ATII induces the thirst response via stimulation of hypothalamic neurons. ACE inhibitors inhibit the rapid conversion of ATI to ATII and antagonize RAAS-induced increases in blood pressure. ACE (also known as kininase II)

is also involved in the enzymatic deactivation of bradykinin, a vasodilator. Inhibiting the deactivation of bradykinin increases bradykinin levels and may sustain its effects by causing increased vasodilation and decreased blood pressure.

MECHANISM OF ACTION[80]

There are two isoforms of ACE: the somatic isoform, which exists as a glycoprotein comprised of a single polypeptide chain of 1277; and the testicular isoform, which has a lower molecular mass and is thought to play a role in sperm maturation and binding of sperm to the oviduct epithelium. Somatic ACE has two functionally active domains, N and C, which arise from tandem gene duplication. Although the two domains have high sequence similarity, they play distinct physiological roles. The C-domain is predominantly involved in blood pressure regulation while the N-domain plays a role in hematopoietic stem cell differentiation and proliferation. ACE inhibitors bind to and inhibit the activity of both domains, but have much greater affinity for and inhibitory activity against the C-domain. Captopril, one of the few ACE inhibitors that are not a prodrug, competes with ATI for binding to ACE and inhibits and enzymatic proteolysis of ATI to ATII. Decreasing ATII levels in the body decreases blood pressure by inhibiting the pressor effects of ATII as described in the Pharmacology section above. Captopril also causes an increase in plasma renin activity likely due to a loss of feedback inhibition mediated by ATII on the release of renin and/or stimulation of reflex mechanisms via baroreceptors. Captopril's affinity for ACE is approximately 30,000 times greater than that of ATI.

TOXICITY[76, 80]

- Symptoms of overdose include emesis and decreased blood pressure.
- **Side effects** include dose-dependent rash (usually maculopapular), taste alterations, hypotension, gastric irritation, cough, and angioedema.

7. PHARMACEUTICAL EXCIPIENTS[1, 2]

Excipients are substances other than the pharmacologically active drug or prodrugs, which are included in the manufacturing process or contained in the pharmaceutical finished product or dosage form.

Excipients play a wide variety of functional role in pharmaceuticals dosage forms including;

- Modifies the solubility and bioavailability of active pharmaceutical ingredients (APIs).
- Increasing the stability of active ingredients the dosage forms.
- Maintaining the pH and/or osmolarity of liquid formulations.
- Helping active ingredients maintained preferred polymorphic Forms or conformation
- Modulating immunogenic responses of active ingredients (e.g.adjuvants).

7.1. HYDROXY PROPYL METHYL CELLULOSE[82]

1. **Non-proprietary Name:**

   BP: Hypromellose, JP: Hypromellose PhEur: Hypromellose USP: Hypromellose

2. **Synonyms:**

   Benecel MHPC; E464; hydroxyl propyl methyl cellulose; HPMC hypromellosum; methocel; methyl cellulose propylene glycol ether; methyl hydroxyl propyl cellulose; metolose; MHPC; Pharmacoat; Tylophor; Tylose

3. **Chemical Name:**

   Cellulose hydroxyl propyl methyl ether

4. **Molecular weight:**

   Molecular weight approximately 10000-1500000

5. **Functional category:**

   Bio adhesive material, coating agent, controlled release agent, emulsifying agent, film forming agent, extended-release agent, suspending agent, sustained release agent, tablet binder.

6. **Description:**

   Hypromellose is an odourless and tasteless, white or creamy – white fibrous or granular powder.

7. **Solubility :**

   Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%) and ether

8. **Applications:**

   HPMC is widely used in oral, ophthalmic, nasal and topical pharmaceutical formulations. It is used as tablet binder in film-coating and as a matrix for extended release tablet formulations, concentrations between 2-5% used as binder in either wet or dry granulation processes. High viscosity grades may be used to retard the release of drugs from a matrix at levels of 10-80%w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25-5.0%

7.2. XANTHAN GUM[82]

1. Non-proprietary names:

BP: Xanthan gum, PhEur: Xanthani gummi, USP-NF: Xanthan gum

2. Synonyms:

Corn sugar gum; E415; Keltrol; polysaccharide B-1459, Rhodigel, Vansan NF, Xantural.

3. Chemical name:

Xanthan gum

4. Empirical formula and Molecular weight:

$(C_{35}H_{49}O_{29})_n$. Xanthan gum as a high molecular weight polysaccharide gum. It contains D-glucose and D-mannose as a dominant hexose units, along with D-glucuronic acid and is prepared as the sodium, potassium or calcium salt.

5. Structural formula:

Each xanthan gum repeat units contains five sugar residues: two glucose, two mannose and one glucuronic acid. The polymer backbone consist of four b-D-glucose units linked the 1 and 4 positions and is therefore identical in structure to cellulose

6. Functional category:

Stabilizing agent; viscosity increasing agent; suspending agent.

7. Description:

Xanthan gum occurs as a cream or white colored odourless, free flowing, fine powder

8. Applications:

Xanthan gum is widely used in oral and topical formulation cosmetics and food as a stabilizing agent. It is also used as emulsifying agent and thickening agent, it is non-toxic, compatible with most other pharmaceutical ingredients and has good stability and viscosity properties over wide pH and temperature range, it is also used as a matrix former in sustained release tablets, and it increases the retention time of the ophthalmic solutions in eye and as Bioadhesive polymer.

9. Stability:

Xanthan gum is a stable material. Aqueous solutions are stable over a wide pH range (pH 3-12), the stability at pH 4- 10 and temperature at 10-60 is maximum.

7.3. CROS CARMELLOSE SODIUM[82]

1. Non-proprietary Name:

BP: Croscarmellose sodium, PhEur: Carmellosum natricum conexum, USPNF: Croscarmellose sodium

2. Synonyms:

Ac-Di-Sol; croslinked carboxy methyl cellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol

3. Chemical Name:

Cellulose, carboxymethyl ether, sodium salt,cross-linked

4. Empirical formula and Molecular Weight:

$C_{12}H_{10}Ca_3O_{14}$. $4H_2O$; 570.49

5. Functional Category:

Tablet and capsule disintegrant

6. Description:

Croscarmellose sodium occurs as an odourless, white or grayish white powder.

7. Incompatibilities:

The efficacy of disintegrants, such as croscarmellose sodium, may be slightly reduced in tablet formulations prepared by either the wet-granulation or direct-compression process that contain hygroscopic excipients such as sorbitol.

8. Applications:

Croscarmellose sodium may be used in both direct compression and wet granulation processes. When used in wet granulation's, the croscarmellose sodium should be added in both wet and dry stages of the process (intra and extra granularly) so that the wicking and swelling ability of the disintegrant is best utilized. Croscarmellose sodium at concentrations up to 5% w/w may be used as tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by wet granulation process.

7.4. SODIUM STARCH GLYCOLATE[82]

1. Non-proprietary Name:

BP: Sodium Starch Glycolate, PhEur: Sodium Starch Glycolate

2. Synonyms:

Carboxymethyl starch, Sodium salt, Carboxymethyl amylum natricum; Explosol,glycols, primojel, tablo; vivastar p.

3. Chemical Name:

Sodium Carboxymethyl Starch

4. Functional Category:

Tablet and Capsule disintegrant

5. Description:

Sodium starch glycolate is a white or almost white free-flowing hygroscopic powder

6. Solubility:

Practically insoluble in methylene chloride. It gives a translucent suspension in water

7. Applications:

It is widely used in oral pharmaceuticals as a disintegrant in capsule and tablet formulations. It is commonly used in tablet prepared by direct compression or wet granulation process. The usual concentration employed in formulation is between 2% and 8%, with the optimum concentration of about 4%. Disintegration occurs by rapid uptake of water and enormous swelling. Increasing the tablet compression pressure also appears to have no effect on disintegration time.

7.5. CROS POVIDONE[82]

1. Non-proprietary Name:

BP: Crospovidone, PhEur: Crospovidonum, USPNF: Crospovidone

2. Synonyms:

Cross-linked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10; Polyvinylpolypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer

3. Chemical Name:

1-Ethenyl-2-pyrrolidinone homopolymer

4. Empirical formula and Molecular Weight:

$(C_6H_9NO)n > 1000000$

5. Functional Category:

Tablet disintegrant

6. Description:

Crospovidone is a creamy white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.

7. Solubility:

Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol (95%) and ether.

8. Incompatibilities:

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts with some materials

9. Applications:

Crospovidone is a water insoluble tablet disintegrant and dissolution agent used at 2-5% concentration I tablets prepared by direct compression or wet and dry granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.

7.6. SODIUM BICARBONATE[82]

1. Non-proprietary name:

BP: Sodium bicarbonate, JP: Sodium bicarbonate, PhEur: Natrii hydrogeno carbonas, USP: Sodium bicarbonate

2. Synonyms:

Baking soda; E500; Effer –soda; monosodium carbonate; Sal de vichy; Sodium acid carbonate; sodium hydrogen carbonate.

3. Chemical Name:

Carbonic acid monosodium salt

4. Empirical Formula:

$NaHCO_3$ 84.01

5. Functional Category:

Alkalizing and therapeutic agents

6. Description:

Sodium bicarbonate occurs as an odourless, white, crystalline powder with saline, slightly alkaline taste. The crystal structure is monoclinic prisms.

7. Incompatibilities:

Reacts with acids, acidic salts and alkaloidal salts

8. Applications:

Sodium bicarbonate is used as a source of CO2 in the formulation or technology effervescent tablets and granules. In effervescent tablet and granules, sodium bicarbonate is usually formulated with citric acid or tartaric acid; tablets prepared with sodium bicarbonate alone since the gastric fluid is sufficient to produce the effervescences; it is also used in tablet formulations to buffer the drug molecules that are weak acids, thereby increasing the rate of dissolution and reducing gastric irritation. Recently it is used as a gas generating agent in floating systems and alginate raft systems.

7.7. MICROCRYSTALLINE CELLULOSE[82]

1. Non-proprietary Name:

BP: Microcrystalline Cellulose, USP-NF: Microcrystalline Cellulose

2. Synonyms:

Avicel PH; Cellulose gel, Crystalline cellulose

3. Chemical Name:

Cellulose

4. Empirical Formula:

$(C_6H_{10}O_5)_n$; where n = 220

5. Functional Category:

Tablet and capsule diluents, Adsorbent, tablet disintegrant, suspending agent

6. Description:

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white odourless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particles sizes and moisture grades that have different properties and applications

7. Solubility:

Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids and most organic solvents

8. Incompatibilities:

Microcrystalline cellulose is incompatible with strong oxidizing agents

9. Applications:

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct-compression processes. In addition to its use as binder/diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting

7.8. LACTOSE[82]

1. Non-proprietary Names:

BP: Lactose, PhEur: Lactose Monohydrate, USP-NF: Lactose monohydrate

2. Synonyms:

CapsuLac, GranuLac, Lactochem; lactosum monohydricum Monohydrate; Pharmatose, PrismaLac; SacheLac; SorboLac; SpheroLac; SuperTab 30GR; Tablettose.

3. Chemical Name:

O-b-D-Galactopyranosyl - (1-4)-a-D-glucopyranose monohydrate

4. Empirical Formula:

$C_{12}H_{22}O_{11}$. H_2O

5. Molecular Weight:

360.31

6. Functional Category:

Dry powder inhaler carrier; lyophilisation aid; tablet binder; tablet and capsule diluent; tablet and capsule filler.

7. Description:

The stable crystalline forms of lactose are a-lactose monohydrate, b-lactose anhydrous and stable α-lactose anhydrous. Lactose occurs as white to off-white crystalline particles or powder. Lactose is odourless and slightly sweet-tasting; α-lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet.

8. Solubility:

Practically insoluble in chloroform, ethanol, ether; soluble in water.

9. Applications:

Lactose is widely used as a filler and diluent in tablets and capsules. Lactose is also used as a diluent in dry-powder inhalation. Lactose is also used in the manufacture of dry powder formulations for use as aqueous film-coating solutions or suspensions. Lactose is also used in combination with sucrose (approximately 1: 3) to prepare sugar-coating solutions.

7.9. MAGNESIUM STEARATE[82]

1. Non-proprietary Name:

BP: Magnesium Stearate, JP: Magnesium Stearate, PhEur: Magnesium Stearate,USP-NF: Magnesium Stearate

2. Synonyms:

Dibasic Magnesium stearate, Magnesium distearate; Magnesia stearas, Magnesium octadeconoate; Octadecanoic acid, Magnesium salt; Synpro 90

3. Chemical Name:

Octadecanoic acid, Magnesium salt

4. Empirical Formula:

$C_{36}H_{70}MgO_4$

5. Molecular weight:

591.24

6. Functional Category:

Tablet and Capsule lubricant

7. Description:

Magnesium stearate is a very fine, light white, impalpable powder of low bulk density, having a faint odour of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

8. Incompatibility:

Incompatible with strong acids, alkalis and iron salts

9. Applications:

It is primarily used as lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5% w/w. It is hydrophobic and may retard the dissolution of a drug from solid dosage form. The lowest possible concentration is therefore used in such formulations

7.10. TALC[82]

1. Non-proprietary Name:

BP: Purified Talc, JP: Talc, PhEur: Talc, USP-NF: Talc

2. Synonyms:

Magnesium hydrogen metasillicate, Magsil Osmanthus, Magsil Star

3. Chemical Name:

Talc

4. Empirical Formula:

$Mg_6 (Si_2O_5)_4(OH)_4$

5. Functional Category:

Anticaking agent, glidant, tablet and capsule diluents, tablet and capsule lubricant

6. Description:

Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder

7. Solubility:

Practically insoluble in dilute acids and alkalis, organic solvents and water

8. Incompatibility:

Incompatible with quaternary ammonium compounds

9. Applications:

Talc was once widely used in oral solid dosage formulations as a lubricant and diluents. It is widely used as a dissolution retardant in the development of controlled release products. Talc is additionally used to clarify liquids and is also used in cosmetics and food products, mainly for its lubricant properties.

7.11. ERYTHROSIN[82]

1. Non-proprietary Name:

Erythrosine natrium

2. Synonyms:

Erythrosine B; Erythrosine B; Acid Red 51; C.I. 45430; FD & C Red No.3; E127; 2',4',5',7'–Tetraiodo-3',6'-dihydroxy-spiro[3H-isobenzofuran-1,9'-xanthen]-3-one disodium salt; Tetraiodofluorescien sodium salt; Calcoid Erthrosine N; 2',4',5',7' –Tetraiodo-3',6'-dihydroxyxanthen-9-spiro-1'-3H-isobenzofuran-3'-one disodium salt; 2',4',5',7' –Tetraiodofluorescein disodium salt; C.I.Food Red 14; Aizen Erythrosine; Tetraiodifluorescein disodium salt; Spiro[isobenzofuran-1(3H),9'-[9H]xanthen]-3-one, 3',6'-dihydroxy-2',4',5',7'-tetraiodo disodium salt

3. Chemical Name:

2-(6-Hydroxy-2,4,5,7-tetraiodo-3-oxo-xanthen-9-yl) benzoic acid

4. Empirical Formula:

$C_{20}H_6I_4Na_2O_5$

5. Molecular Weight:

879.86 g/mol

6. Melting Point:

303º C

7. Functional Category:

It is a cherry pink synthetic colourant

8. Description:

Maroon colour powder and hygroscopic

9. Application:

Erythrosine B is an iodo derivative of fluoresin with distinctly bluish shade whereas eosin is a bromine derivatives of fluoresin. It is used in colouring cosmetics and food. It is used in colouring cosmetics and food. It is used as a plasma stain for nerve cells and staining bacteria in soil. It is used as a phosphorescent triplet probe to detect rotational diffusion of membrane proteins

Table 3: List of materials and their application in formulation

S.No.	Name of the material	Manufacturer / Supplier	Use in formulation
1	Captopril	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

Table 4: List of Equipments used

S.No.	Equipments / Instruments	Manufacturer / Supplier
1	Electronic weighing balance	Asha scientific company, Mumbai
2	Hot air oven	MC Dalal, Chennai
3	10 station compression machine	Rimek India
4	Vernier caliper	Mitutoya, Japan
5	Monsanto Hardness tester	Standard steel, India
6	Friabilator	Electrolab, India
7	pH Meter	MC Dalal, Chennai
8	Dissolution test apparatus	Campbell, India
9	UV-Visible Spectrophotometer	Schimadzu, India
10	Fourier Transform Infrared Spectrophotometer	Schimadzu, India
11	Disintegration Apparatus	Electrolab, India

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 STUDY[83]

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)[84]

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, 73]

100 mg of Captopril 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[85]

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[84, 85]

1. Bulk density (ρ_b) [59, 86]

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.

$$\rho_b = M/V_b$$

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

2. Tapped density (ρ_t) [59, 86]

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.

$$\rho_t = M/V_t$$

Where, M and V_t 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,

$$\mathbf{HR = \rho_t / \rho_b}$$

Where, ρ_t and ρ_b are tapped density and bulk density respectively

Table 5: Precompression Parameters[85]

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 Captopril [22, 23, 24]

The inner core tablets of captopril 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 captopril, superdisintegrant, 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 6: Formulation of rapid release core tablets

S.No.	Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	CAPTOPRIL	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

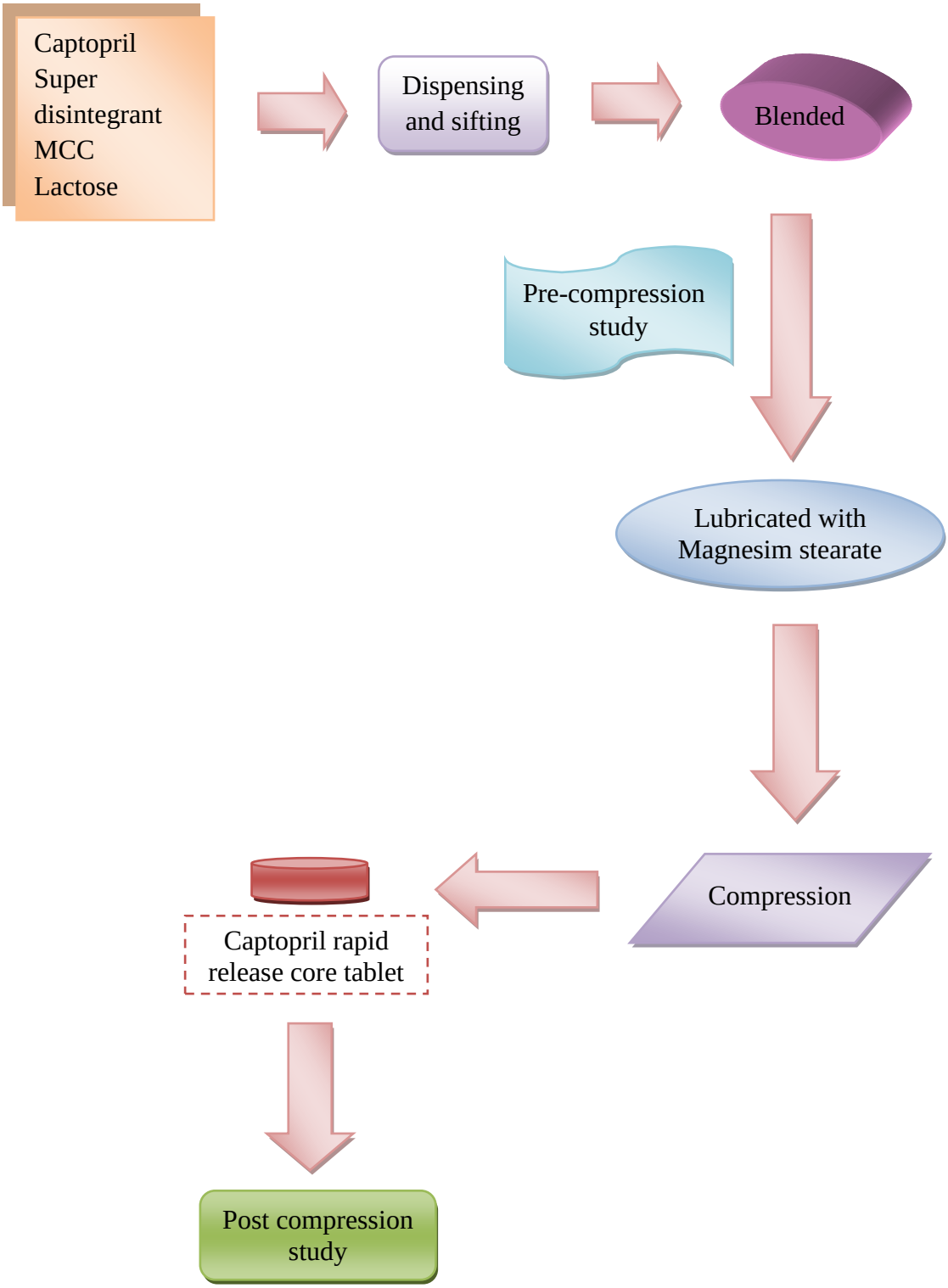


Fig. 10: Flowchart for formulation of rapid release captopril tablet

Formulation of Captopril 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 7: 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

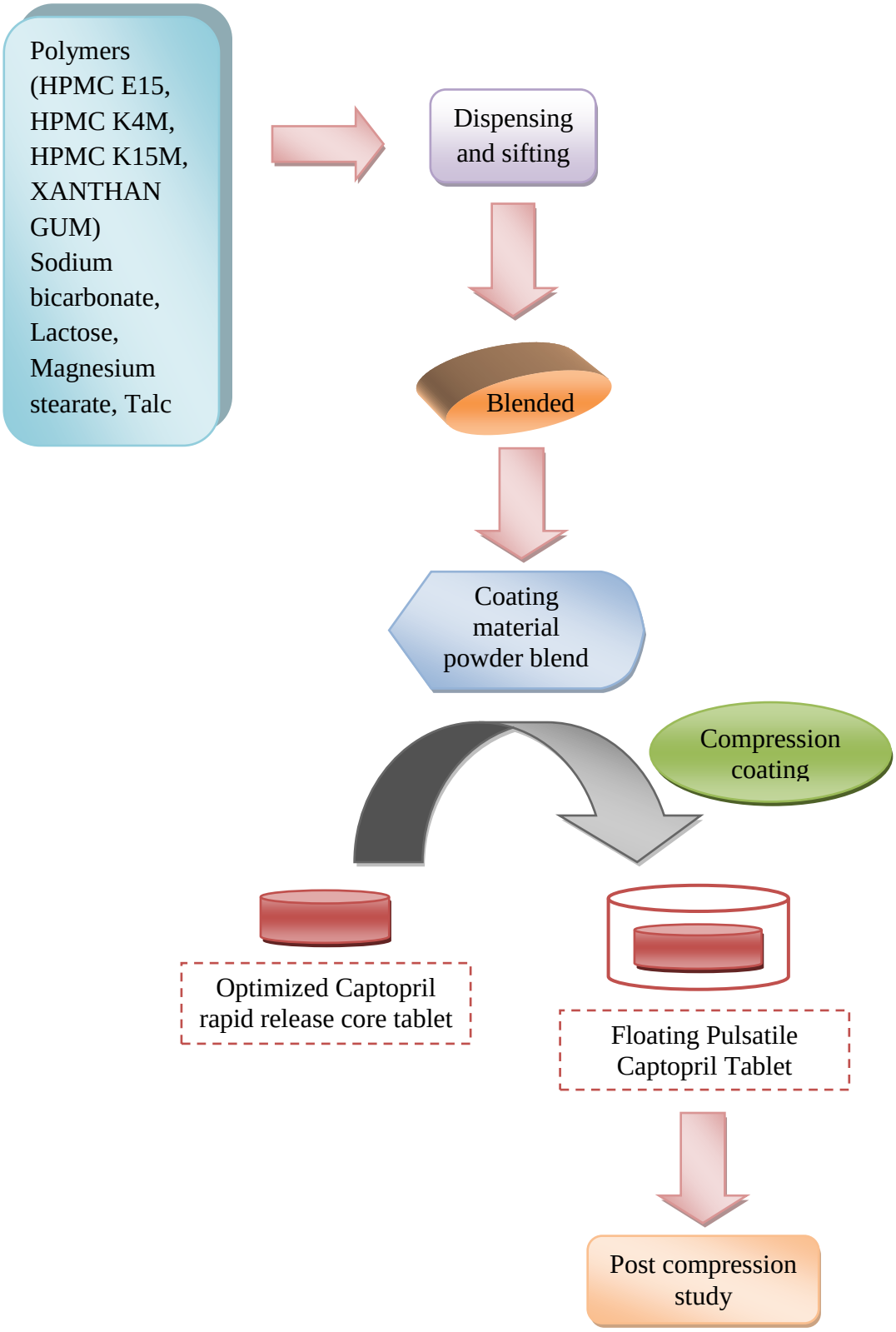


Fig. 11: Flowchart for formulation of captopril floating pulsatile tablet

POST COMPRESSION STUDIES[85]

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 8: 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/cm^2.

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,

$$\% \text{ Friability} = \frac{(\text{Initial weight of the tablets} - \text{Final weight of the tablet}) \times 100}{\text{Initial weight of the tablets}}$$

Disintegration test for Captopril 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 Captopril 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 Captopril 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, 59]

The release of Captopril 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 Captopril 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[24]

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 (W_1) 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 (W_2) and swelling index (SI) was calculated using the following formula

$$SI = \frac{W_2 - W_1}{W_1} \times 100$$

Where, W_2 is the wet weight and W_1 is the dry weight

***IN-VITRO* RELEASE KINETICS[87]**

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.

$$\mathbf{C = K_0 t}$$

Where, K_0 = Zero order constant

t = Time in hours

2. First order equation

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

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

Where, C_0 = 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

$$\mathbf{Q = Kt^{½}}$$

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.

$$\mathbf{Q_0^{1/3} - Q_t^{1/3} = K_{HC}Xt}$$

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.

$$\mathbf{M_t/M_\alpha = Kt^n}$$

Where, $\mathbf{M_t/M_\alpha}$ = 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 9: 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.

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

9.1. PREFORMULATION STUDIES

9.1.1. DRUG – EXCIPIENT COMPATIBILITY STUDY

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

9.1.1.1. PHYSICAL COMPATIBILITY

Table 10: Physical compatibility study of Drug and Excipients

S. No.	Drug + Excipient	Description and Condition			
		Initial	Room temperature and 40°C / 75% RH in days		
			10^{th}	20^{th}	30^{th}
1	Captopril	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	Captopril + SSG	White / off white powder	NC	NC	NC
16	Captopril + CCS	Grayish-white powder	NC	NC	NC
17	Captopril + CP	Creamy white powder	NC	NC	NC
18	Captopril + Xanthan gum	Creamy white free flowing fine powder	NC	NC	NC
19	Captopril + HPMC E15	White or Creamy white Powder	NC	NC	NC
20	Captopril + HPMC K4M	White or Creamy white Crystalline Powder	NC	NC	NC
21	Captopril + HPMC K15M	White or Creamy white Crystalline Powder	NC	NC	NC
22	Captopril + Sodium bicarbonate	White, Crystalline Powder	NC	NC	NC
23	Captopril + Lactose	Off white crystalline powder	NC	NC	NC
24	Captopril + MCC	White, Crystalline Powder	NC	NC	NC
25	Captopril + Magnesium stearate	White or Off white crystalline Powder	NC	NC	NC
26	Captopril + Talc	White or Off white crystalline Powder	NC	NC	NC
27	Captopril + 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.

9.1.1.2. CHEMICAL COMPATIBILITY STUDY [81]

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

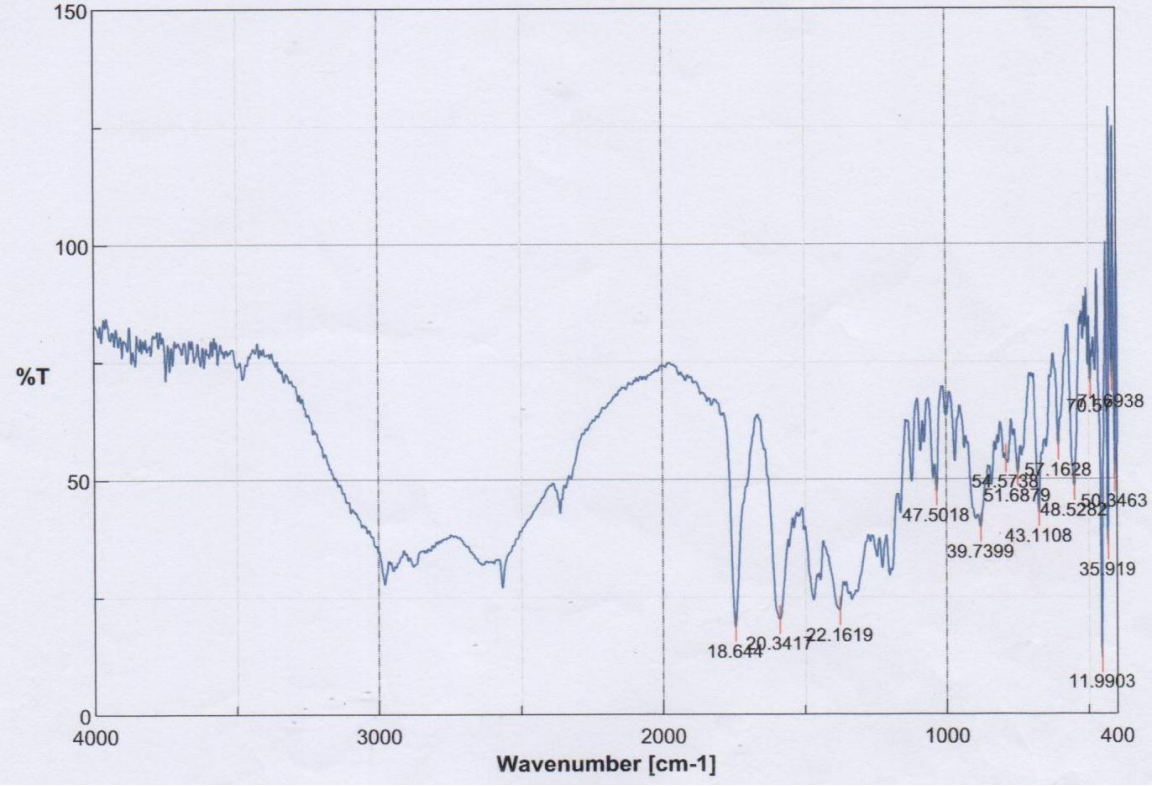


Fig. 12: FTIR of Captopril

Table 11: IR Spectral interpretation of Captopril

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

FTIR SPECTROSCOPY OF CAPTOPRIL AND EXCIPIENTS

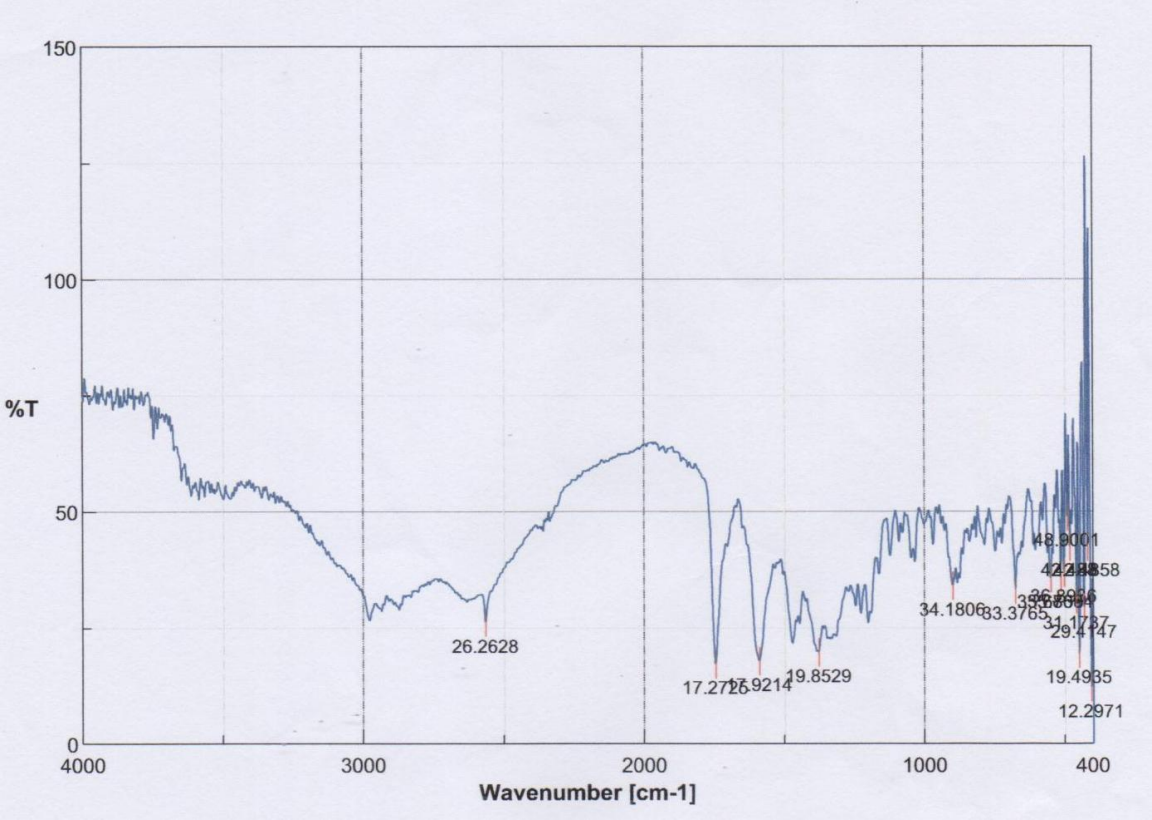


Fig. 13: FTIR of Captopril with croscarmellose sodium (CCS)

Table 12: IR Spectral interpretation of Captopril 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.

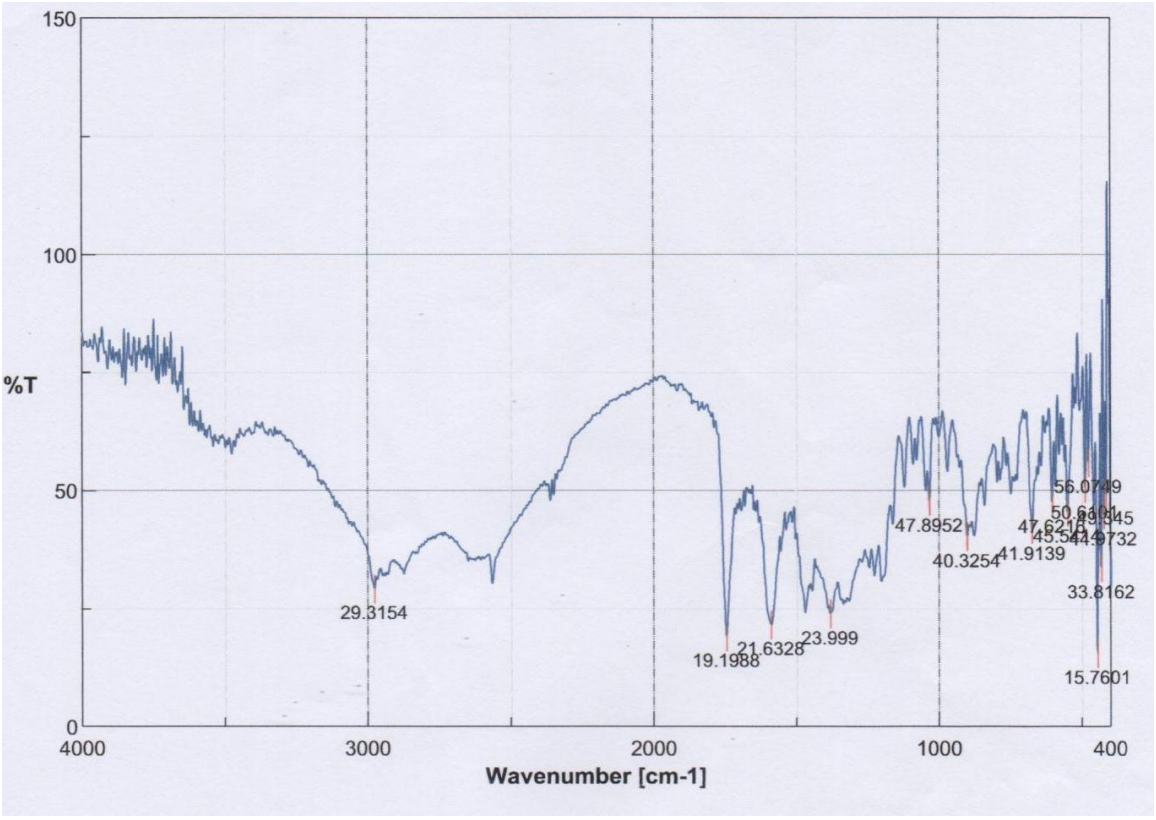


Fig. 14: FTIR of Captopril with crospovidone (CP)

Table 13: IR Spectral interpretation of Captopril 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.

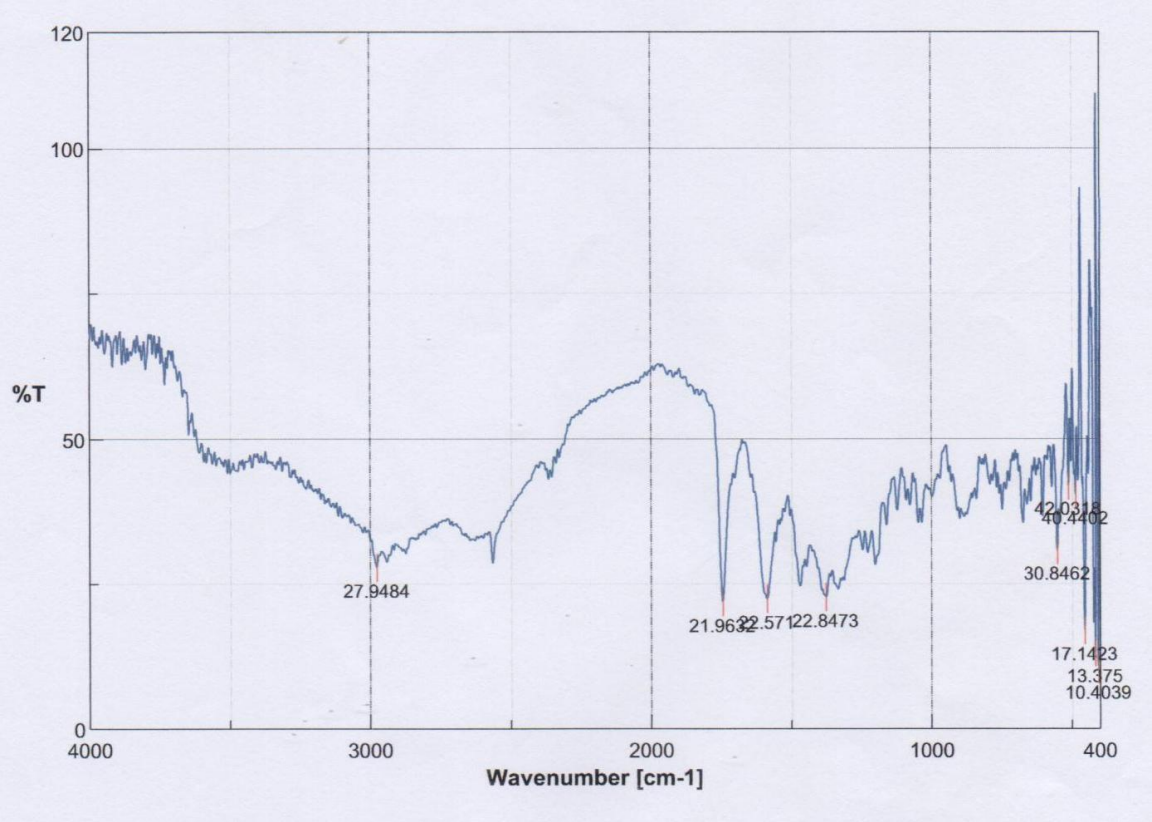


Fig. 15: FTIR of Captopril with sodium starch glycolate (SSG)

Table 14: IR Spectral interpretation of Captopril 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.

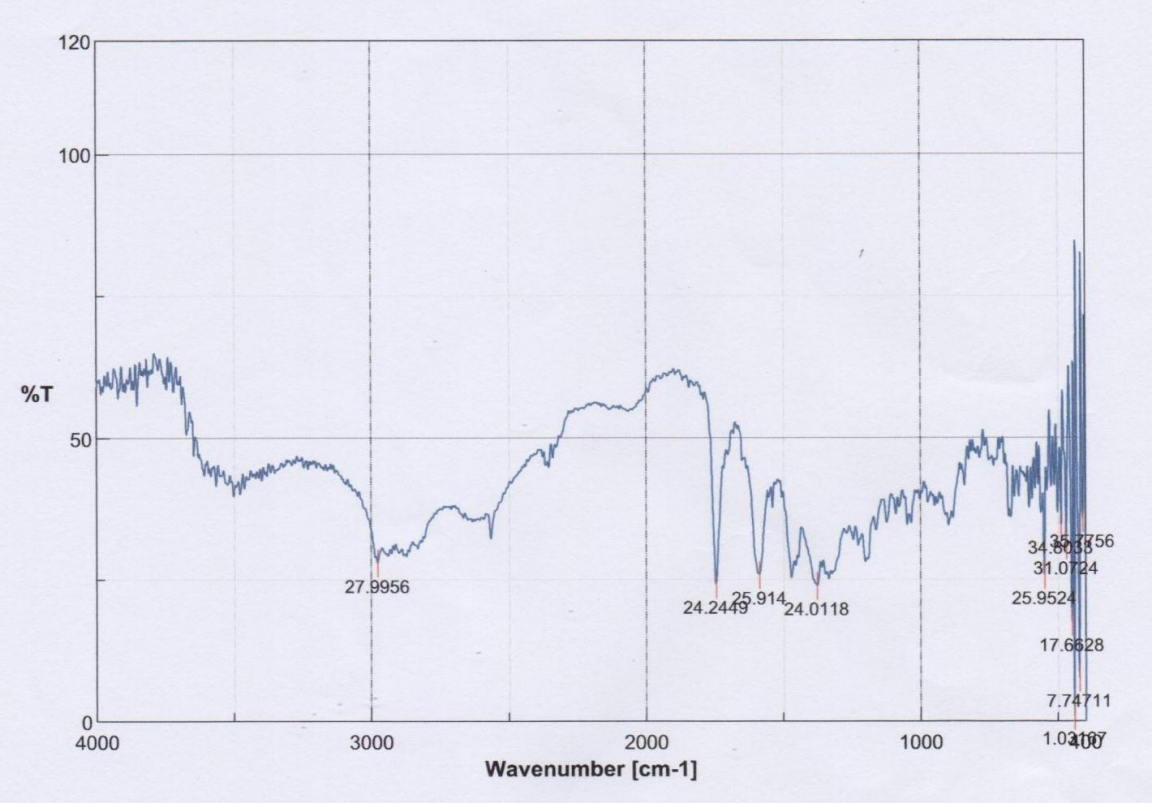


Fig. 16: FTIR of Captopril with HPMC E15

Table 15: IR Spectral interpretation of Captopril 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.

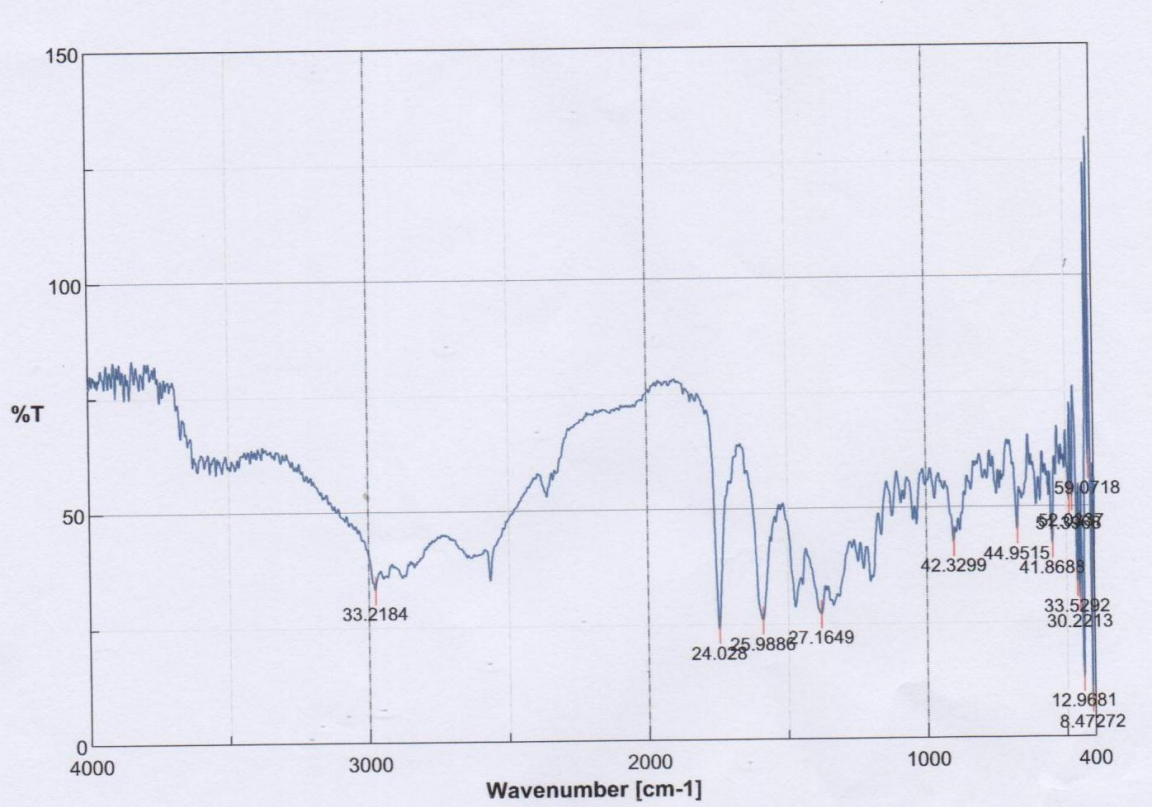


Fig. 17: FTIR of Captopril with HPMC K15M

Table 16: IR Spectral interpretation of Captopril 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 interaction between the drug and HPMC K15M.

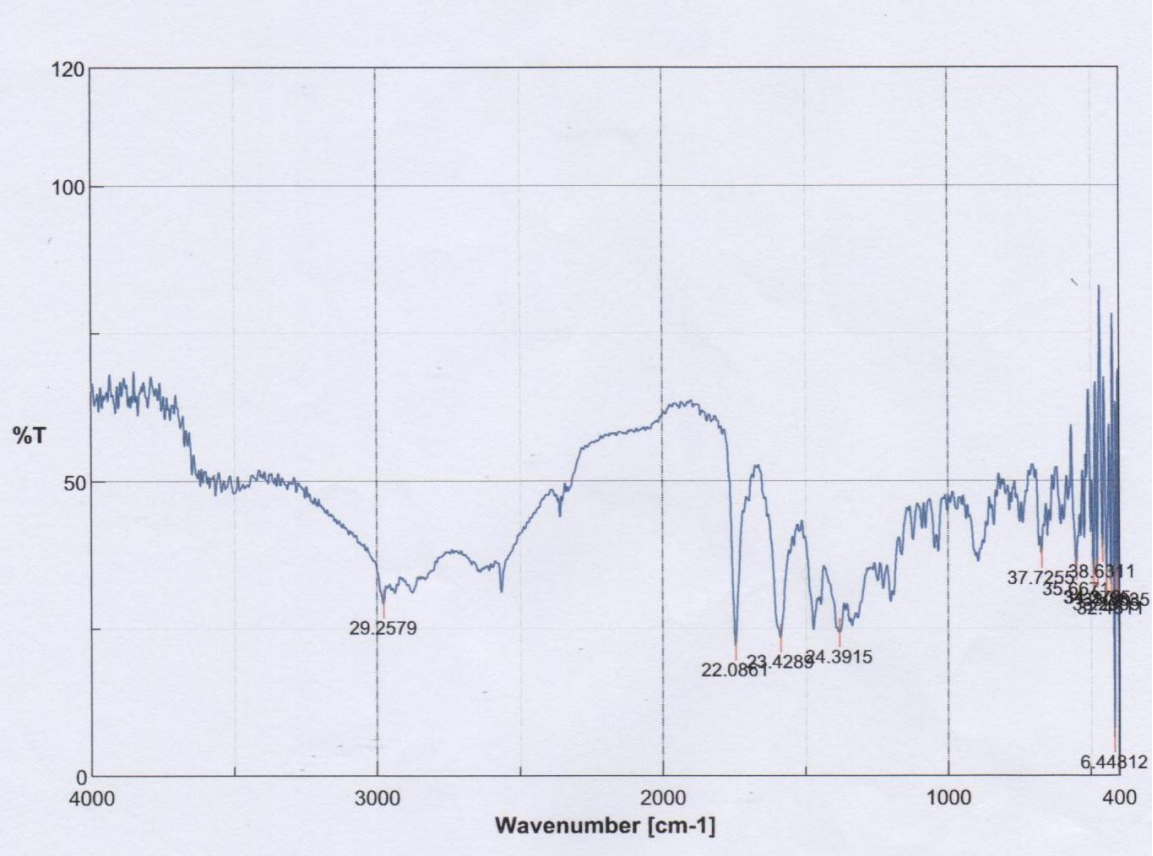


Fig. 18: FTIR of Captopril with HPMC K4M

Table 17: IR Spectral interpretation of Captopril 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 interaction between the drug and HPMC K4M.

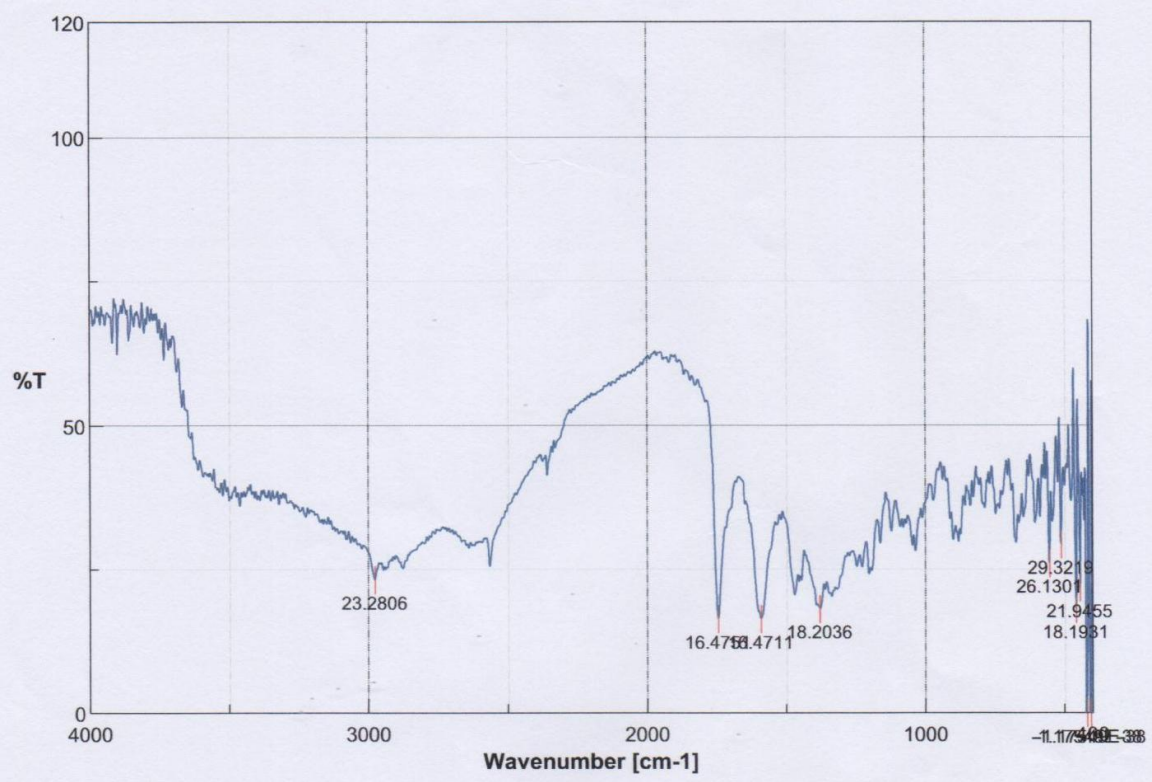


Fig. 19: FTIR of Captopril with Xanthan gum

Table 18: IR Spectral interpretation of Captopril 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 interaction between the drug and Xanthan gum.

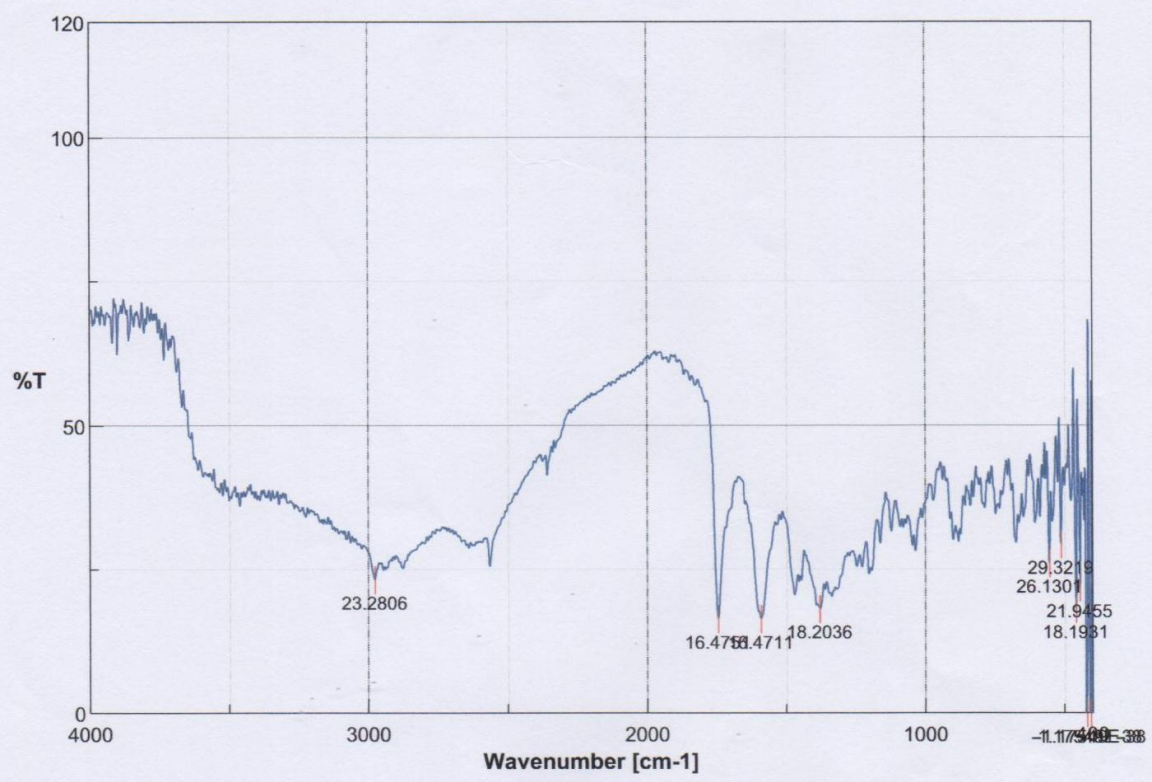


Fig. 20: FTIR of Captopril powder blend

Table 19: IR Spectral interpretation of Captopril 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).

9.2. CALIBRATION CURVE OF CAPTOPRIL

Table 20: Data for calibration curve of Captopril 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)

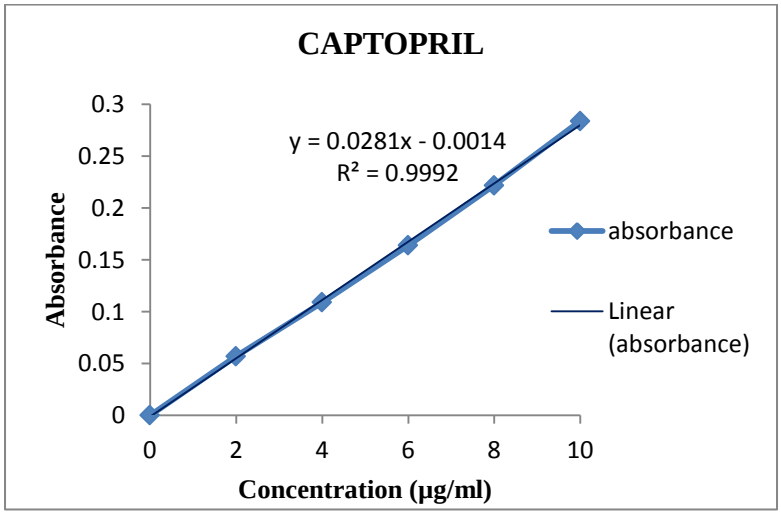


Fig. 21: Calibration curve of Captopril

It was found that the solutions of Captopril 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.

9.3. RAPID RELEASE FORMULATION OF CAPTOPRIL

9.3.1. PRECOMPRESSION STUDY

The drug and the formulated blends are evaluated for precompression parameters. The results are given in the table 21.

Table 21: Precompression study of drug and formulated blends

Drug Formulation	Bulk density* (g/cm^3)	Tapped density* (g/cm^3)	Compressibility index* (%)	Hausner's ratio*	Angle of repose*
Captopril	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 Captopril 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 Captopril 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 Captopril powder blend ranged from 42°02' to 45°50' which showed passable flow property.

Table 22: 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 Captopril 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 Captopril 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 Captopril powder blend ranged from 33°58' to 40°43' which showed fair-good flow property.

9.3.2. POST COMPRESSION STUDY

UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in table 23

Table 23: 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 24: 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 25: 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/cm^2 and 2.8 kg/cm^2. All the formulated tablets showed sufficient mechanical strength to resist stress during the transportation[26]

FRIABILITY

Table 26: 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[84]

DRUG CONTENT

The drug content of the Rapid release core tablets is given in the table 27

Table 27: 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)

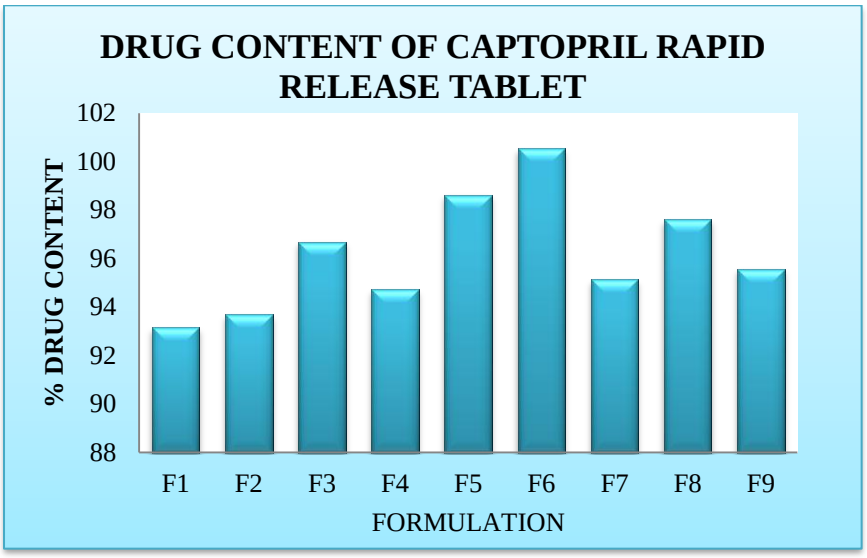


Fig. 22: Drug content of the formulated rapid release tablets

The percentage drug content of Captopril in all the formulations ranged from 93.15 %w/w to 100.54 %w/w. All the formulations comply with the official standards[79]

DISINEGRATION TIME

Table 28: 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)

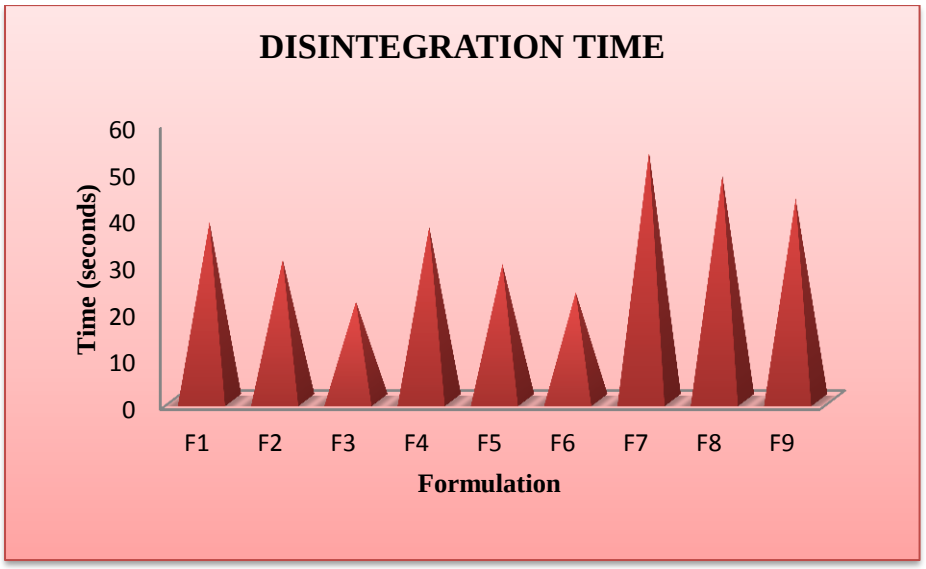


Fig. 23: Disintegration time of the formulated rapid release tablets

The disintegration time of the Captopril tablets ranged from 21 seconds to 53 seconds. The disintegration time of captopril 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.[84, 85]

IN-VITRO DISSOLUTION STUDY

The *invitro* dissolution of RRCTs of Captopril is given in the Table 29

Table 29: *in-vitro* dissolution of rapid release formulation of Captopril

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)

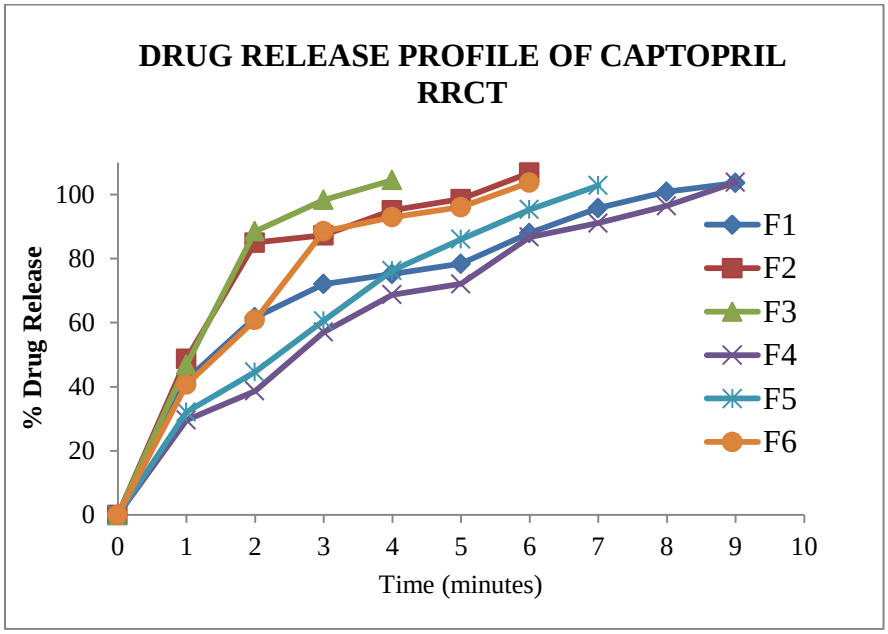


Fig. 24: *in vitro* drug release of formulated captopril rapid release tablets

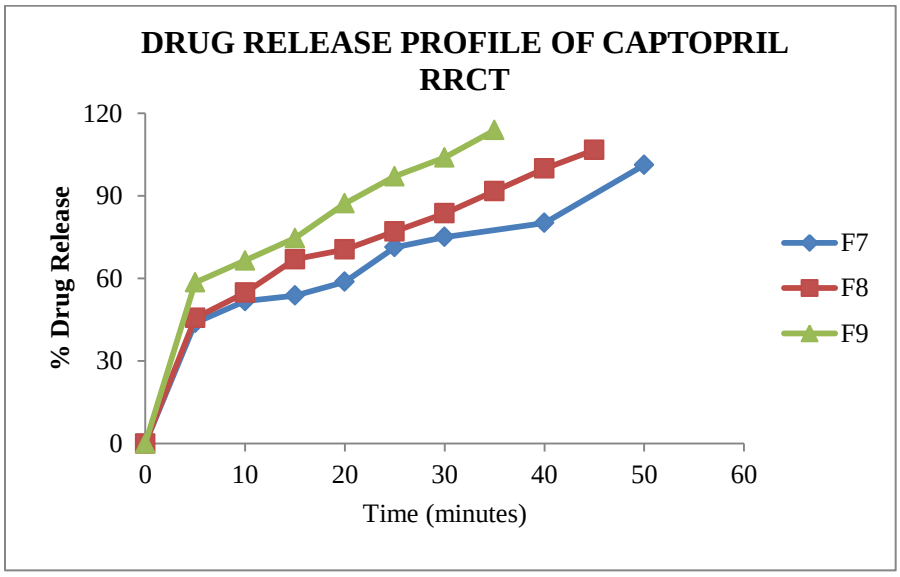


Fig. 25: *in vitro* drug release of formulated captopril rapid release tablets

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.

9.4. FLOATING PULSATILE RELEASE TABLET OF CAPTOPRIL

9.4.1. PRECOMPRESSION STUDY

The formulated coating material blends are evaluated for Pre-compression parameters. The results are given in the table 30.

Table 30: Precompression study of formulated blends of coating materials

Drug Formulation	Bulk density* (g/cm^3)	Tapped density* (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.

9.4.2. POST COMPRESSION STUDY

UNIFORMITY OF WEIGHT

The uniformity of weight of the formulated tablets is given in table 31.

Table 31: 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)

The tablets comply with the test for uniformity of weight

THICKNESS AND DIAMETER

The thickness and diameter of the formulated tablets is given in table 32.

Table 32: 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.

HARDNESS

Table 33: Hardness of the FPRTs

Formulation	Hardness* (kg/cm^2)
FP1	4.9 ± 0.374
FP2	5.1 ± 0.374
FP3	4.8 ± 0.244
FP4	4.8 ± 0.244
FP5	4.7 ± 0.244
FP6	4.9 ± 0.210
FP7	4.6 ± 0.244
FP8	4.8 ± 0.210

***Mean ±S.D (n=5)**

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[84]

FRIABILITY

Table 34: Friability of the FPRTs

Formulation	Friability* (%)
FP1	0.741 ± 0.0351
FP2	0.649 ± 0.0265
FP3	0.572 ± 0.0376
FP4	0.560 ± 0.0278
FP5	0.736 ± 0.0198
FP6	0.589 ± 0.0267
FP7	0.638 ± 0.0356
FP8	0.654 ± 0.0263

***Mean ±S.D (n=3)**

The percentage friability of the tablets ranged from 0.560 % to 0.741 %. The percentage friability of all the formulation was within Pharmacopeial limits[84]

DRUG CONTENT

The drug content of the Captopril FPRT is given in the table 35

Table 35: 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)**

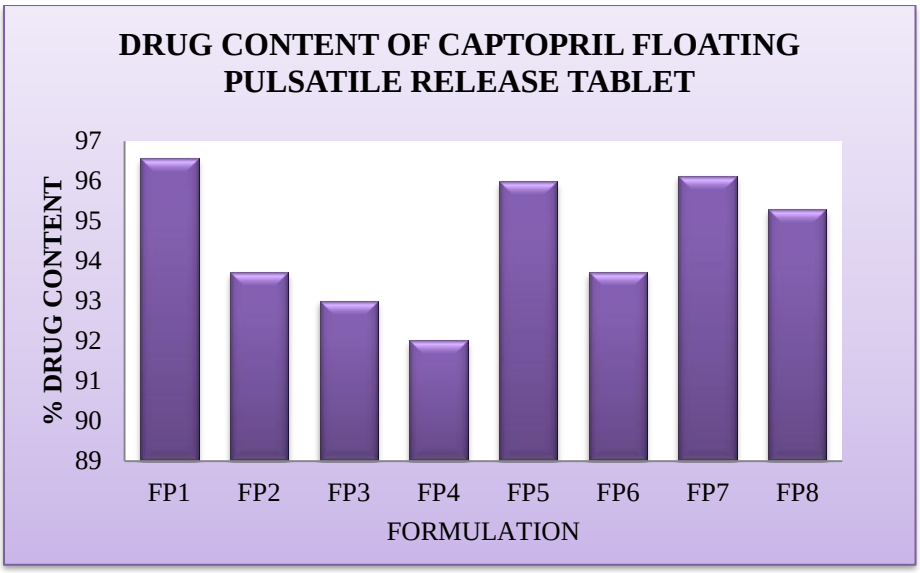


Fig. 26: Drug content of the formulated floating pulsatile release tablets

The percentage drug content of Captopril 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 Captopril floating FPRT is given in the table 36.

Table 36: *in-vitro* floating characteristics of Captopril 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)

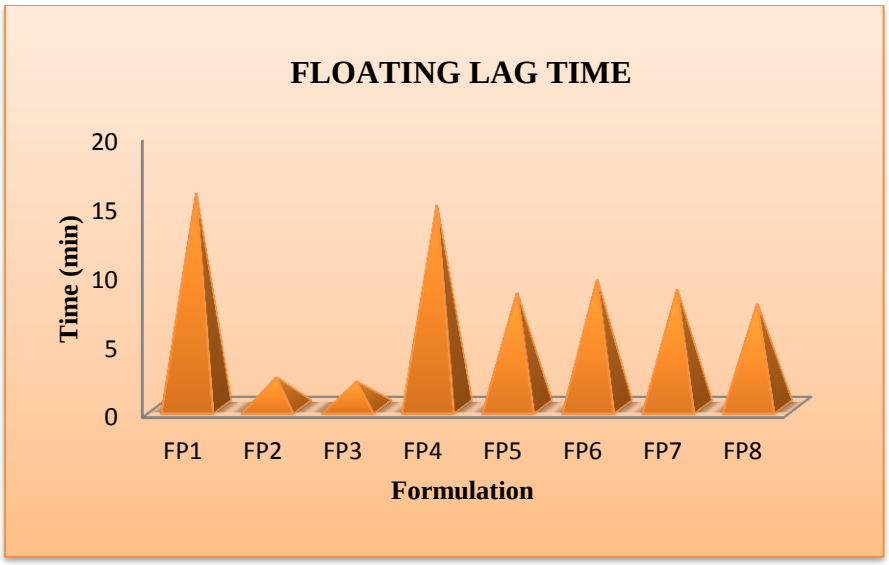


Fig. 27: Floating lag time of the formulated floating pulsatile release tablets

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.[22]

SWELLING STUDIES

Swelling study was carried out for floating pulsatile release tablets of captopril. The % swelling index of the captopril floating pulsatile tablets were given in the Table 37 and Fig. 26

Table 37: Swelling index (%) of Captopril 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

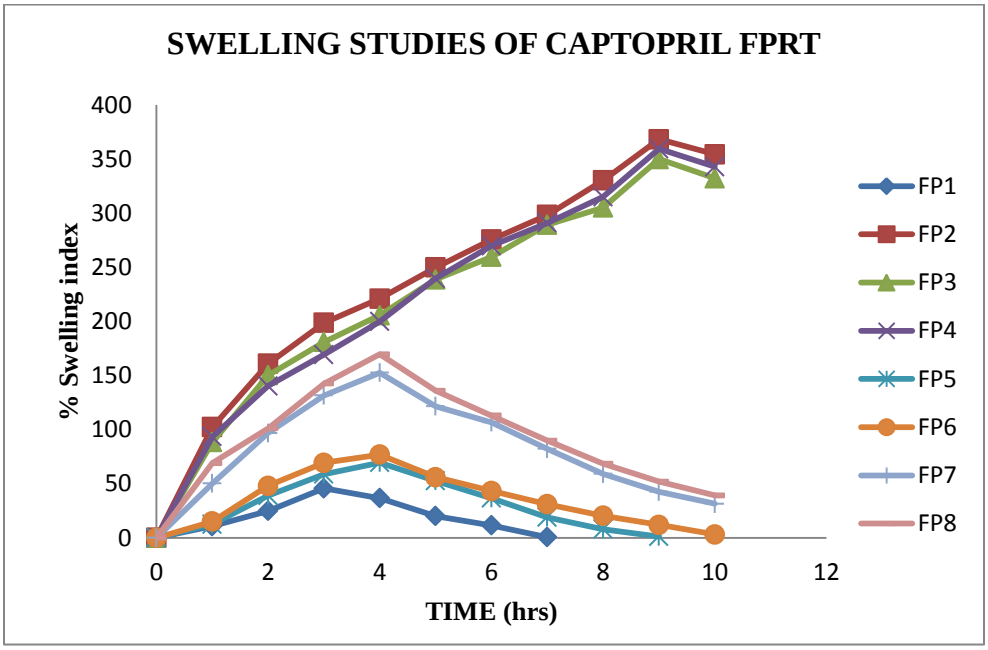


Fig. 28: Swelling index of Captopril FPRTs

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.[22]

IN-VITRO DISSOLUTION STUDY

The *invitro* dissolution of floating pulsatile formulations of Captopril is given in the Table 38

Table 38: *in-vitro* dissolution of floating pulsatile formulations of Captopril

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**	-	-	-	-

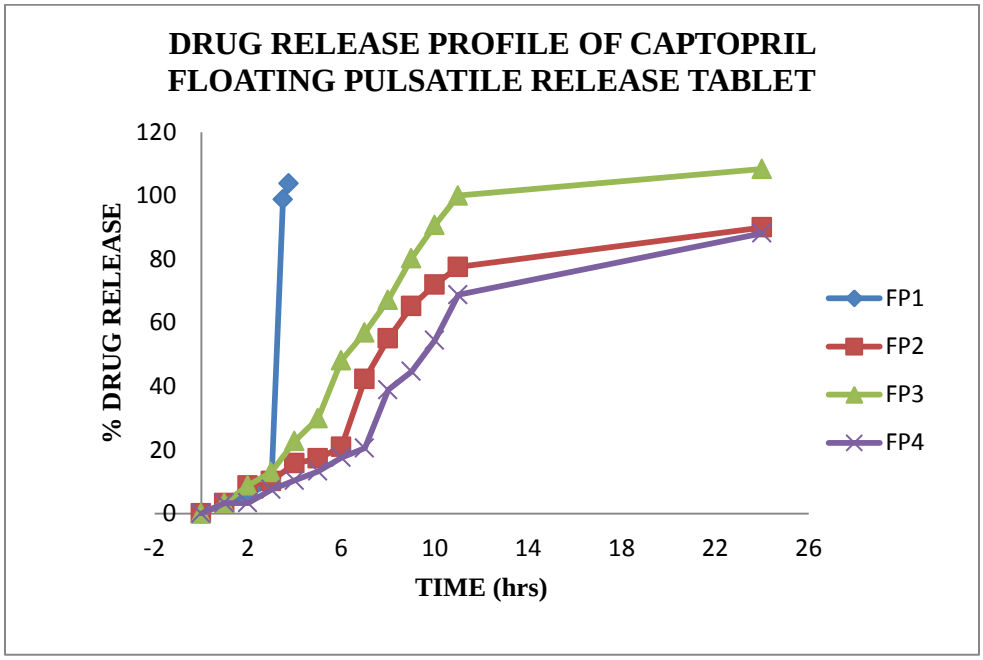


Fig. 29: *in vitro* drug release of formulated FPRT

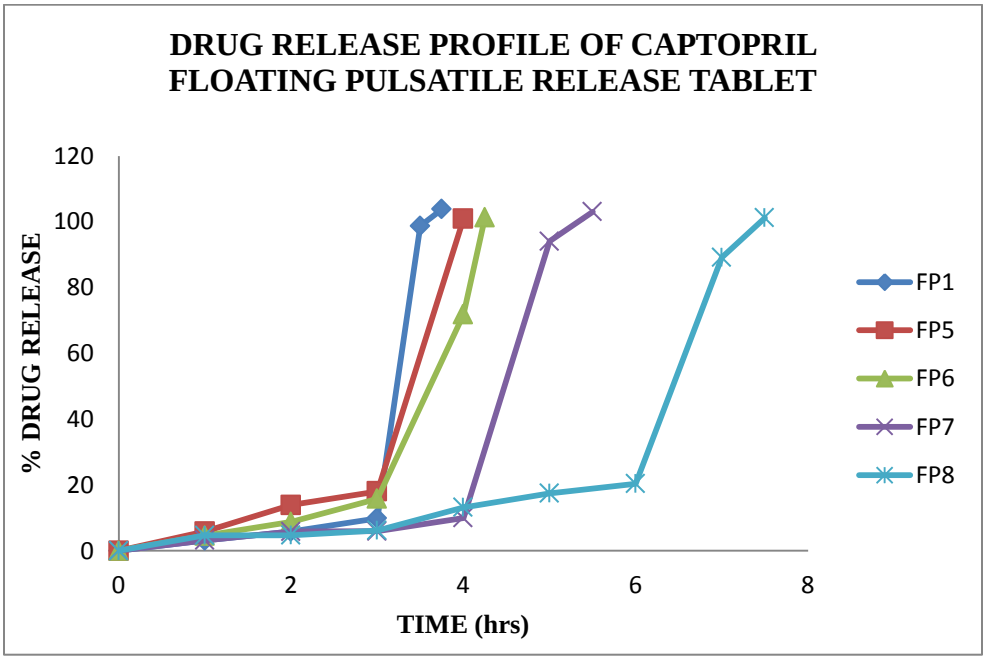


Fig. 30: *in vitro* drug release of formulated FPRT

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

9.5. *INVITRO* RELEASE KINETICS

The values obtained from invitro dissolution of Captopril floating pulsatile release tablet were fitted in various kinetic models. The results are given in table 39 and Figure 30, 31, 32, 33 and 34.

Table 39: *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 root of 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

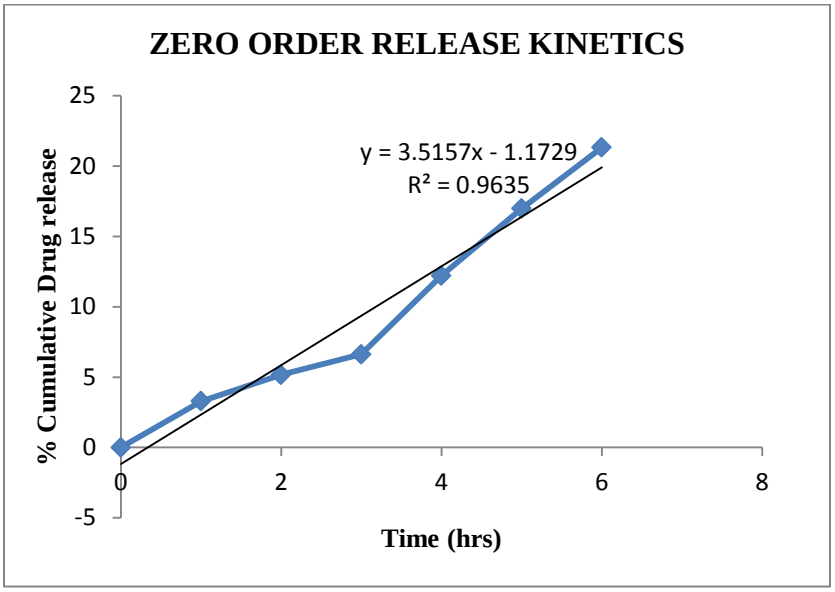


Fig. 31: Zero order kinetics

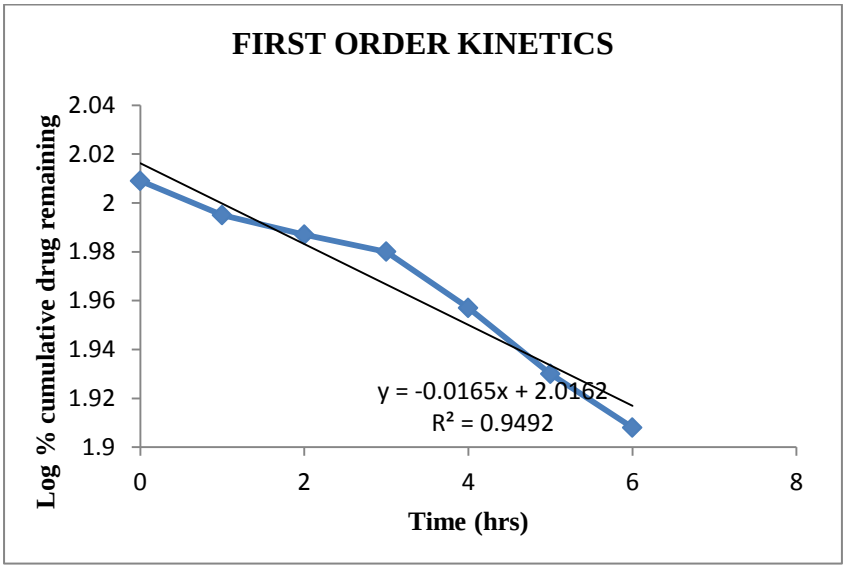


Fig. 32: First order kinetics

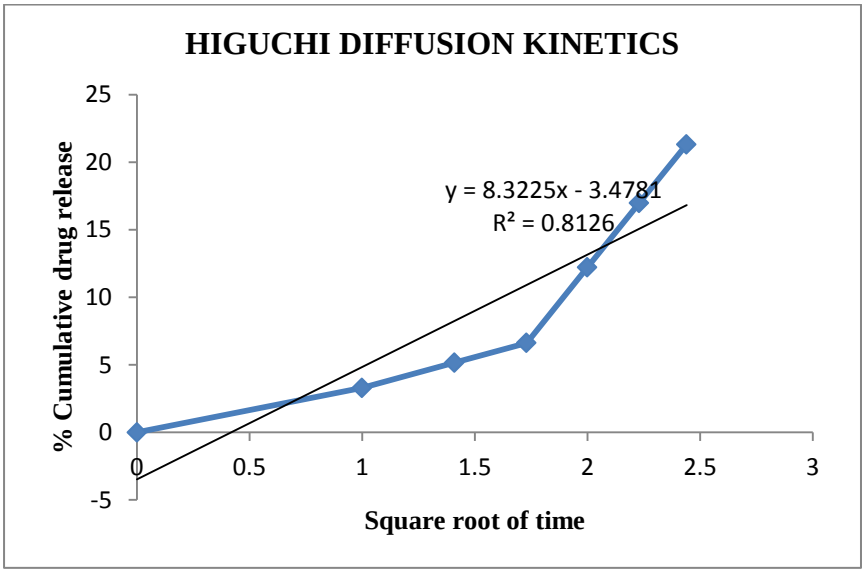


Fig. 33: Higuchi diffusion kinetics

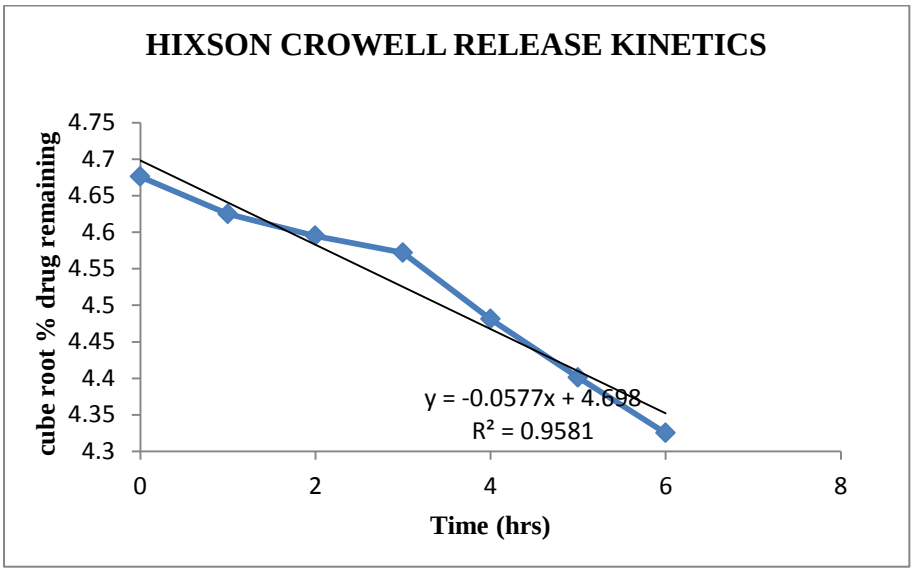


Fig. 34: Hixson crowell release kinetics

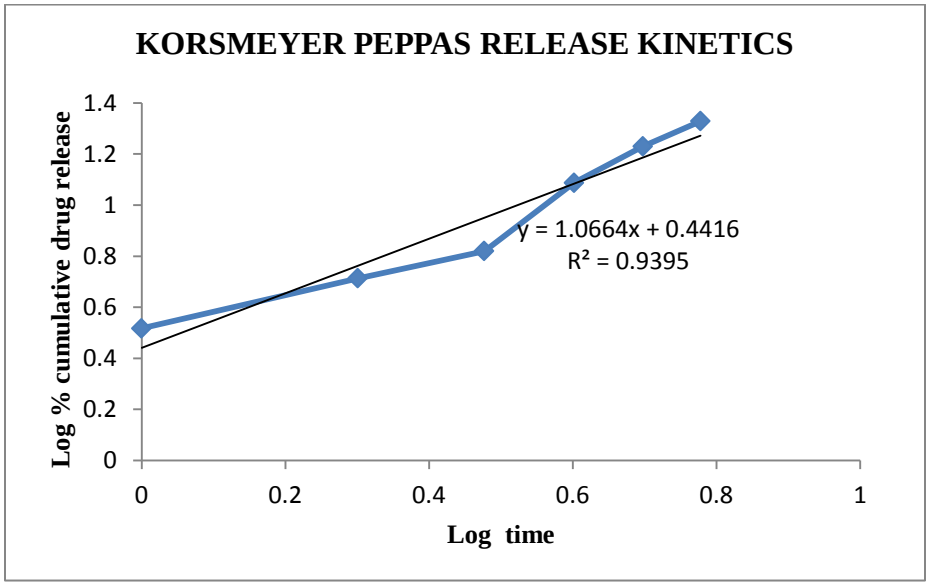


Fig. 35: Korsmeyer Peppas release kinetics

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.

9.6. 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 40: Stability study of Captopril 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 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

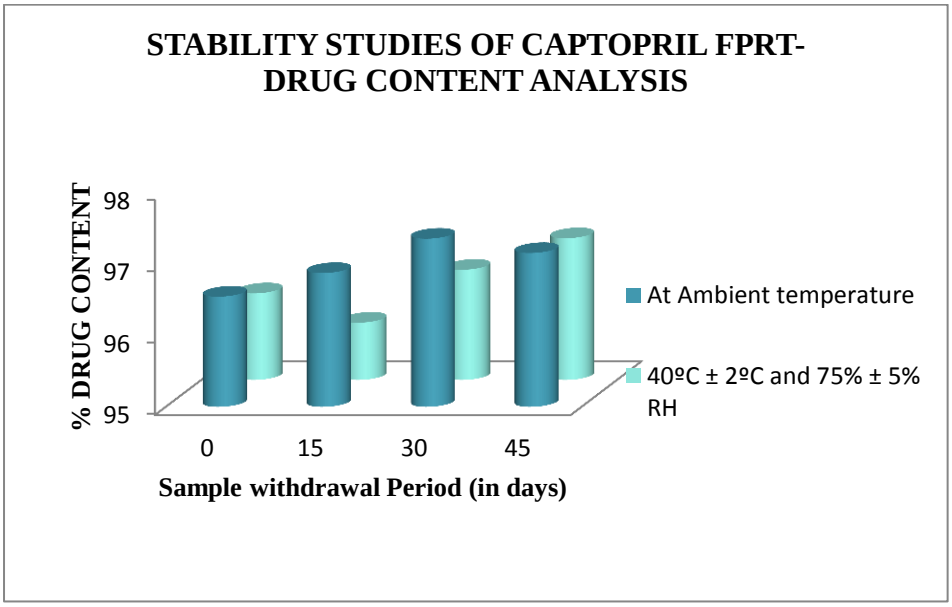


Fig. 36: Stability study of Captopril FPRT – Drug content analysis

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

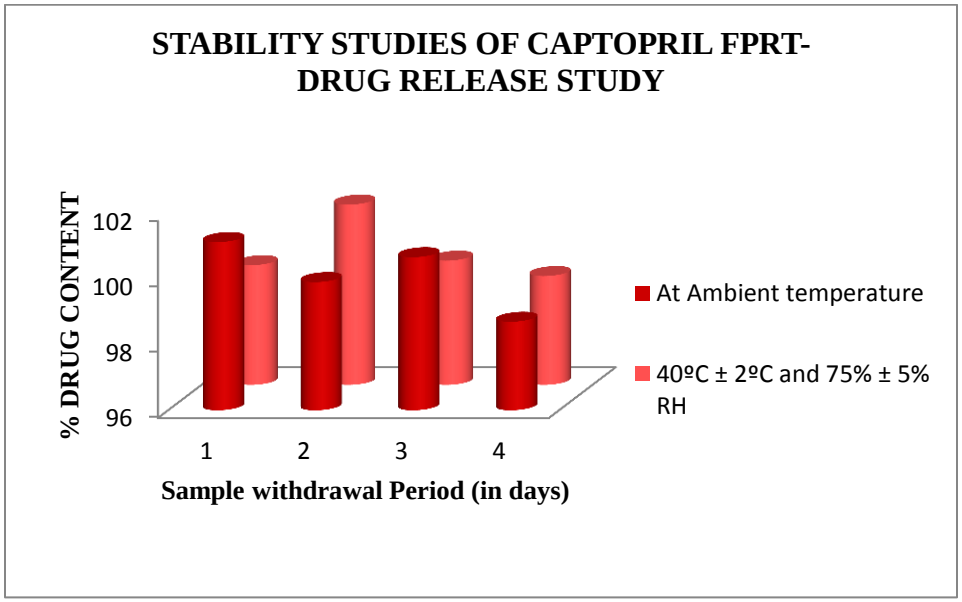


Fig. 37: Stability study of Captopril FPRT – Drug release study

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 Captopril 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 captopril 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 Captopril rapid release Core Tablet (Formulation F3) containing 2% croscarmellose sodium disintegrated quickly (D.T = 21 seconds).

The *in-vitro* dissolution studies of the formulated Captopril 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 captopril 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 Captopril core tablets was done by direct compression technique.

Totally 8 batches of Captopril Floating pulsatile release tablets (FPRT) were prepared using HPMC E15, HPMC K15M, HPMC K4M, Xanthan gum.

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

The drug content of the Captopril 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 Captopril 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 Captopril 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 Captopril 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

BIBLIOGRAPHY

1. Leon Lachman, Herbert A. Lieberman and Joseph L. Kanig. The Theory and practice of Industrial Pharmacy, Varghese publishing house, Mumbai; 3rd edition, 1987: 293-342.
2. Aulton M. Pharmaceutics: The Science of Dosage Form Design; International Student edition: 368, 505-563.
3. Brahmankar DM and Sunil Jaiswal B. Bio pharmaceutics and Pharmaceutics – A Treatise, 2nd edition, vallabh prabakaran; 2009 : 431-435, 453-463.
4. G. Cole, J. Hogan, M. Aulton. Pharmaceutical Coating Technology, Taylor & Francis, Bristol, PA, 1995
5. R. Natarajan, Rohit Vaishnani and NN. Rajendran. Formulation and Evaluation of Immediate Release Tablets of Paroxetine HCl Using Different Superdisintegrants. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2011; Vol. 2 (3):1096-1099.
6. Nyol Sandeep, Dr. M.M. Gupta. Immediate drug release dosage form: A review. Journal of Drug Delivery & Therapeutics. 2013; 3(2): 155-161.
7. Satani R. R, chotaliya M. B, Raval M. K, Sheth N. R. Review On Recent Trends In Press-Coated Pulse Drug Delivery System. International Bulletin of Drug Research. 2014; 4(6): 60-91.
8. Shan-Yang lin, Yoshiaki Kawashima. Current status and approaches to developing press-coated chronodelivery drug systems. Journal of Controlled Release. 2012; 157: 331-353.
9. Alessandra Maroni, Lucia Zema, Maria Doriy Del Curto, Giulia Loreti, Andrea Gazzangia. Oral pulsatile delivery: Rationale and chronopharmaceutical formulations. International Journal of Pharmaceutics. 2010; 398: 1-8.
10. Rajkumar Kotha, Sainath Goud Raghavapally, Suryasri Lavanya Adavi, Sangamesh Taranalli, Dibya Pandey. Current Techniques in Pulsatile drug delivery: A review. International Research Journal of Pharmacy. 2013; 4(3): 77-84.
11. Kakar Satinder, Batra Deepa, Singh Ramandeep, Nautiyal Ujjwal. Review on recent trends in pulsatile drug delivery system. UJP. 2013; 2(1): 21-41.

12. K.P.R. Chowdary, CH. K. L.Chaitanya. Recent Research On Floating Drug Delivery Systems-A Review. Journal of Global Trends in Pharmaceutical Sciences. 2014; 5(1): 1361-1373.
13. Faraz Jamil, Sunil Kumar, Saurabh Sharma, Prabhakar Vishvakarma, Lalit singh. Review on Stomach Specific Drug Delivery Systems: Development and Evaluation. IJRPBS. 2011; 2(4): 1427-1433.
14. Savani Hitesh, Turakhiya Jignesh, Patel Jainish, Goyani Manish, Bhavesh Akbari. Floating Pulsatile Drug Delivery System: A Review. UJP. 2013; 2(1): 6-13.
15. Sachindev Sharma, Nimrata Seth, Naresh Singh Gill. Polymers Employed In Chronomodulated Drug Delivery Systems: A Review. Int J Recent Adv Pharm Res. 2014; 4(4): 5-13.
16. Prevesh Kumara, Sunil Singh, Hemendra Gautam, Ajit Kumar Yadav. A Review On Impact Of Chronopharmaceutics On The Treatment Of Disease. Int J App Pharm. 2013; 5(2): 19-25.
17. Meenu Rajput, Ritika Sharma, Sunil Kumar, Faraz Jamil, Neeraj Sissodia, Saurabh Sharma. Pulsatile Drug Delivery System: A Review. IJRPBS. 2012; 3(1): 118-124.
18. Deepika Jain, Richa Raturi, Vikas Jain, Praveen Bansal, Ranjit Singh. Recent technologies in pulsatile drug delivery systems. Biomatter. 2011; 1(1): 57-65.
19. Hitesh Dalvadi, Jayvadan K Patel. Chronpharmaceutics, pulsatile drug delivery system as current trend. Asian Journal of Pharmaceutical Sciences. 2010; 5(5): 207-230.
20. Mayur Gandhi, Rakesh Chaudhari, Nishant Kulkarni, Snehal Bhusare, Pallavi Kare. Review Article on Pulsatile Drug Delivery System. Int. J. Pharm. Sci. Rev. Res. May – Jun 2014; 26(2): 251-255.
21. 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.
22. 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.

23. 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; Vol. 6(5): 2005-2012.
24. 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.
25. 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.
26. 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; Vol. 4 (5): 549-561.
27. 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. Volume 2014; Article ID 421931:1-13.
28. 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. Volume 2014; Article ID 547212: 1-10.
29. Sunil Patel, Moin K. Modasiya, Vishnu M. Patel, Anand K. Patel. Design and Development of Floating Pulsatile Drug Delivery System using Meloxicam. IJPRBS, 2012: Volume1 (2): 215-235.
30. Hao Zou, Xuetao Jiang, Lingshan Kong, Shen Gao. Design and Evaluation of a Dry coated Drug Delivery system with Floating-Pulsatile Release. J Pharm Sci. 2008; Vol.97: 263-273.
31. Swati C. Jagdale, Monali S. Sali, Ajay L. Barhate, Bhanudas S. Kuchekar, Aniruddha R. Chabukswar. Formulation, Development and Evaluation of Floating Pulsatile Drug Delivery System of Atenolol. PDA Journal of Pharmaceutical Science and Technology. 2013; Vol.67, No. 3: 214-228.

32. Rajendra T. Mogal, Upendra C. Galgatte, Pravin D. Chaudhari. Floating Pulsatile Drug Delivery of Ranitidine Hydrochloride for Nocturnal Acid Breakthrough: Design, Optimization, *In- Vitro* and *In- Vivo* Evaluation. Int J Pharm Pharm Sci. 2013; Vol. 5 (3): 722-727.
33. Pallab Roy, Aliasgar Shahiwala. Statistical optimization of ranitidine HCl floating pulsatile delivery system for chronotherapy of nocturnal acid breakthrough. European Journal of Pharmaceutical Sciences. 2009; 37: 363-369.
34. Piyush Patel, Dinesh Puri, Anil Bhandari, Deepak Choudhary, Rambabu Sharma, Vivek Bhatele. Formulation and Evaluation of Chronomodulated Floating Drug Delivery System of Famotidine. FABAD J. Pharm. Sci. 2011; 36: 167-180.
35. Shinde PV, Mayee RV. Evaluation of floating press-coated pulsatile release of Aceclofenac tablets: A solution for Rheumatoid arthritis. Asian Journal of Biomedical and Pharmaceutical Sciences 2013; 3(17): 16-21.
36. J B Naik, S P Zine. Development of Single Unit Floating-Pulsatile Site Specific Drug Delivery System for Chronotherapeutic Release of Aceclofenac. IJABPT. 2011; Vol. 2 (2): 339-348.
37. N. Tejaswini , M. Sarangapani, G. Sandhyarani. Formulation and Evaluation of Floating Pulsatile Tablet of Eprosartan. Kakatiya Institute of Pharmaceutical Sciences.
38. Asija Rajesh, Patel Jaimin, Asija Sangeeta, Mangukia Dhruv, Chaudhari Bharat, Patel Pinkesh. Formulation and Evaluation of floating pulsatile drug delivery for chronotherapy of hypertension. IJPRBS. 2013; vol. 2(2): 231-242.
39. M.S. Sokar, A.S. Hanafy, A.H. El-Kamel, S.S El-Gamal. Pulsatile core-in-cup valsartan tablet formulations: *in vitro* evaluation. Asian Journal of Pharmaceutical Sciences. 2013; Vol. 8: 234-243.
40. Shaji Jessy, Shinde Amol. Formulation and Optimization of Floating Pulsatile Aceclofenac Microspheres using Response Surface Methodology. IRJP. 2012; 3(1): 166-169.
41. Mayee RV, Shinde PV. Development and Evaluation of Floating Pulsatile Release Tablet of Aceclofenac. IJPT. April-2012; Vol. 4 (1): 3869-3877.

42. Sanjay J Kshirsagar, Shrikant V Patil, Mangesh R Bhalekar. Statistical optimization of floating pulsatile drug delivery system for chronotherapy of hypertension. International Journal of Pharmaceutical Investigation. Oct 2011; Vol.1 (4): 207-213.
43. Shivhare U D, Rathod H D, Mathur V B. Development and Evaluation of Floating Pulsatile Microspheres of Metoprolol Tartrate using Emulsification-Solvent Evaporation Technique. Sch. Acad. J. Pharm. 2013; 2(5): 365-372.
44. Jain Sheetal, Sudhakar CK, Jain Sanjay. Formulation and evaluation of floating pulsatile drug delivery system for chronotherapy of rheumatoid arthritis. Novel Science International Journal of Pharmaceutical Science. 2012; 1 (5): 212-215.
45. Kamat Akshay Ramesh, Shabarya A R, Azharuddin Mohd, Krishnandha Kamath K. Formulation and Evaluation of Pulsatile drug delivery system containing Indomethacin using natural polymers. IRJP. 2013; 4(2): 111-114.
46. Rohitash Kumar, Anvesh MS, Mohammed S Khan, Afrasim Moin, Gowda DV. Formulation and Evaluation of Two-Pulse Drug Delivery System of Amoxicillin Trihydrate. Trop J Pharm Res. October 2014; 13(10): 1593-1600.
47. Vaishali Aggarwal, Ratendra Kumar, Rajiv Sharma, Yogendra Singh, Uday Veer Singh Teotia. Formulation and Optimization of Chronotherapeutic Drug Delivery from Carvedilol Sulphate Compression Coated Tablets by using Design of Experiment Approach. Journal of Applied Pharmaceutical Science 2013; 3 (10): 141-146.
48. Sayantan Mukhopadhyay, Reetika Pant, Laxmi Goswami. Formulation And Evaluation of Pulsatile Drug Delivery System for Sequential Release of Atorvastatin. International Journal of Pharmaceutical and Chemical Sciences. Apr-Jun 2014; Vol.3 (2): 594-604.
49. P Shafi, A Pratyusha, V Uma Maheswar Rao. Formulation and Evaluation of Pulsatile drug delivery system of Lansoprazole by press coated method. IJIPSR. 2014; Vol. 2 (10): 2395-2411.
50. Basawaraj S Patil, Abhishek M Motagi, Upendra Kulkarni, Hariprasanna R C, Shivanand A Patil. Development and evaluation of time controlled pulsatile release Lisinopril tablets. JPSBR. Jan Feb 2012; Volume 2 (1): 30-35.

51. M. Bajpai, D. C. P. Singh, A. Bhattacharya, A. Singh. Design and *in vitro* evaluation of compression-coated pulsatile release tablets of Losartan Potassium. Indian J Pharm Sci. Mar -Apr 2012; 74(2): 101–106.
52. Krishnaveni G, Muthukumaran M, Krishnamoorthy B. Development and Evaluation of Pulsatile Drug Delivery System containing Montelukast Sodium by Press Coated Tablet using natural Polysaccharides. Int J Adv Pharm Gen Res. 2013; 1(2):41-51.
53. Renu Dinkar, Govind Mohan, Kumud Upadhyaya. Development and evaluation of nifidipine loaded tablet formulation for colon drug delivery. Indian J.Pharm.Biol.Res. 2013; 1(4): 64-70.
54. Patel Tejaskumar, Mahantesh Ananthapur, Sabitha J S, Sourav Tribedi, Rinku Mathappan, Prasanth V V. Formulation and Evaluation of Erodible Pulsatile Drug Delivery System of Salbutamol Sulphate for Nocturnal Asthma. IJPI. May- Jun 2013; Vol. 3 (3): 24-35.
55. Amrinder Singh, Naresh Singh Gill, Nimrata Seth. Development and Evaluation of Pulsatile Drug Delivery System of Aceclofenac Sodium. Int J Recent Adv Pharm Res. 2014; 4(4): 123-131.
56. D. Pavani, E. Hari Krishna, Ramesh S. Development and Evaluation of Metoprolol Tartrate Chronotherapeutic Drug Delivery System. JIPBS. 2015; Vol. 2(1): 53-63.
57. Janugade B U, Patil S S, Patil S V, Lade P D. Formulation and Evaluation of Press-Coated Montelukast Sodium Tablets for Pulsatile Drug Delivery System. Int.J. ChemTech Res. 2009; 1(3): 690-695.
58. Rajesh Asija, Sangeeta Asija, Avinash Gupta, Dolly Prakashchand, Gaurav Goyal. Formulation and evaluation of pulsatile tablet of Ramipril. J. Chem. Pharm. Res. 2015; 7(2): 789-797.
59. 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; Vol. 7 (6): 337-341.
60. Sameer Singh, Kalpana Prajapati, A K Pathak, A Mishra. Formulation and Evaluation of Floating Tablet of Captopril. Int.J. PharmTech Res. 2011; 3(1): 333-341.

61. Basawaraj S Patil, Sandeep J Sonawane, Upendra Kulkarni, Hariprasanna R C. Formulation and *in-vitro* Evaluation of Captopril Floating Matrix Tablets using HPMC 50cps. JPSBR. May Jun 2012; Vol.2 (3): 97-102.
62. Mohammad Ali Shahtalebia, Majid Tabbakhiana, Navid Sarbolookzadeh Harandic. Formulation and Evaluation of Orally Disintegrating Tablets of Captopril Using Natural Super Disintegrants. JRPS. 2014; 3(1): 54-64.
63. Archana S Patil, Panchaxari M Dandagi, Vinayak S Masthiholimath, Anand P Gadad, Basavaraj K Najwade. Development and characterization of chronomodulated drug delivery system of captopril. International Journal of Pharmaceutical Investigation. Oct 2011; Vol. 1 (4): 227-233.
64. Ashish Singla, Shakuntla, S K Singh, D N Mishra. Formulation and Evaluation of Floating Matrix Tablets of Captopril. Int J Recent Adv Pharm Res. 2014; 4(3): 63-75.
65. Noushin Bolourtchiana, Naghmeh Hadidia, Seyed Mohsen Foroutana, Bijan Shafaghia. Formulation and Optimization of Captopril Sublingual Tablet Using D-Optimal Design. Iranian Journal of Pharmaceutical Research. 2008; 7 (4): 259-267.
66. Ziyaur Rahman, Mushir Ali, R K Khar. Design and evaluation of bilayer floating tablets of captopril. Acta Pharm. 56 (2006): 49–57.
67. Vijayasankar G R, Naveen Kumar Jakki S, Suresh A G, Packialakshmi M. Formulation and Evaluation of Captopril Gastro retentive Floating Drug Delivery System. Int. J. Pharm & Ind. Res. Jan - Mar 2011; Vol. 1 (1): 11-16.
68. Lingam Meka, Bhaskar Kesavan, Krishna Mohan Chinnala, Venkateswarlu Vobalaboina, Madhusudan Rao Yamsani. Preparation of a Matrix Type Multiple-Unit Gastro Retentive Floating Drug Delivery System for Captopril Based on Gas Formation Technique: *In Vitro* Evaluation. AAPS Pharm.SciTech. June 2008; Vol.9 (2): 612-619.
69. Prasanth V V, Suman Rawat, Sourav Tribed, Rinku Mathappan, Sam T Mathew. Formulation and Evaluation of Floating Microspheres of Captopril. IJPI. Mar-Apr 2013; Vol. 3 (2): 41-51.
70. Lu Xu, Sanming Li, Hisakazu Sunada. Preparation and evaluation in vitro and in vivo of captopril elementary osmotic pump tablets. Asian Journal of Pharmaceutical Sciences. 2006; 1 (3-4): 236-245.

71. Mohammed G Ahmed, Satish K BP, Kiran K GB. Formulation and Evaluation of Gastric- Mucoadhesive Drug Delivery Systems of Captopril. Journal of Current Pharmaceutical Research. 2010; 2(1): 26-32.
72. Harish Gopinath, Koteswararao Pasupuleti, Debjit Bhowmik, Duraivel S. Formulation and Evaluation of Captopril Microencapsules: A Sustained Release Approach. Indian Journal of Research in Pharmacy and Biotechnology. Vol. 1(1): 4-9 ISSN: 2320 – 3471(Online).
73. S Sahu1, A Chourasia, A Toppo, A Asati. Formulation and evaluation of captopril microspheres by ionic gelation technique. IJPLS. Jan 2012; Vol.3 (1): 1377-1379.
74. Hayder Hamed Abed. Accelerated Stability Evaluation of Captopril Tablets. Al-Mustansiriyah J. Sci. 2010; Vol. 23 No.7: 91-98.
75. Harrisons online: Hypertensive vascular disease; chapter 24
76. Tripathi, K D. Essentials of medical pharmacology. New Delhi: Jaypee Brothers Medical Publishers (P) Ltd. 2008; 6:483, 484, 488.
77. Hypertension. Available from: http://www.webmed.com/hypertension/highblood pressure/guide/high-blood-pressure
78. Dr. S L Bodhankar, Dr. N S Vyawahare. Pathophysiology. Pune: Nirali Prakashan. 2008; edition 6: 2.17-2.22
79. Indian Pharmacopoeia, Ministry of Health and Family Welfare. Ghaziabad, India: The Indian Pharmacopoeia commission. 2014; Vol. 2:1264-1266.
80. DrugBank.ca. 'Captopril' Available from: **http://www.drugbank.ca/drugs/DB01197**
81. Y R Sharma. Elementary Organic Spectroscopy. New Delhi: S Chand Publishing Pvt. Ltd. 2013; 5th revised edition: 91-141.
82. Raymond C et al. Hand Book of Pharmaceutical Excipients. London: Pharmaceutical Press and American Pharmacists Association. 2009; edition 6: 129-133, 190-195, 206-210, 326-329, 364-366, 404-406, 629-632, 663-665, 728-730, 782-784.
83. Gurdeep R Chatwal and Sham K Anand. Instrumental methods of Chemical Analysis. Himalaya Publishing House, Mumbai. 2011; 2nd edition: 44-68
84. Indian Pharmacopoeia, Ministry of Health and Family Welfare. Ghaziabad, India: The Indian Pharmacopoeia commission. 2014; 1: 224-226, 251-258, 788.

85. United States Pharmacopoeia, 30th edition NF 25-2007. The Official Compendia of Standards. 242, 643, 674, 728.
86. 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.
87. 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