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Evaluation and Formulation of Pulsatile Drug Delivery System of Ramipril

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ABSTRACT:
Pulsatile Drug Delivery Systems (PDDS) are innovative time-controlled release mechanisms designed to optimize drug delivery by synchronizing it with the body's circadian rhythm. Unlike conventional dosage forms that provide immediate or sustained drug release, PDDS ensures a rapid and targeted release after a predetermined lag phase. This approach enhances therapeutic efficacy while minimizing side effects, particularly for conditions like hypertension, asthma, and cardiovascular diseases.
This study focuses on the development and evaluation of a PDDS for Ramipril, an ACE inhibitor used in hypertension management. A specialized formulation was designed to mitigate first-pass metabolism, enhance bioavailability, and align drug release with the morning surge in blood pressure. The study involved preformulation analysis, core and erodible tablet formulation, capsule coating, and comprehensive in-vitro and ex-vivo evaluations. Key parameters such as drug dissolution, lag time, swelling index, and stability studies were assessed to optimize the release profile.
The results indicate that the developed PDDS effectively regulates the controlled and time-dependent release of Ramipril, improving therapeutic benefits while reducing adverse effects. This formulation provides a promising approach for chronotherapeutic management of hypertension, enhancing patient compliance and treatment efficacy.

Key words: Pulsatile drug delivery system, Ramipril, Chronotherapy, Hypertension, Circadian rhythm, Eudragit S100, Controlled release, Bioavailability, Drug formulation, In-vitro dissolution.

1.INTRODUCTION:

Pulsatile Drug Delivery Systems (PDDS) are time-controlled systems that regulate the lag time for drug release, independent of factors such as pH, enzymes, and gastrointestinal motility. Traditionally, drugs are released either immediately or in an extended manner. However, in recent years, there has been increasing interest in pulsatile drug release systems. These systems are designed to align with the body's circadian rhythm. The term "circadian" comes from Latin, where "circa" means "day" and "dian" means "night." A pulsatile release, where the drug is released rapidly after a specified lag time, offers potential benefits for various drugs or therapies.[1]
Pulsatile systems are designed to ensure that the drug reaches the site of action at the appropriate time and at the correct dosage. Pulsatile drug delivery systems (PDDS) have garnered significant attention due to their numerous advantages over traditional dosage forms. A pulsatile drug delivery system is defined as the rapid and short-term release of a specific amount of drug molecules after a predetermined off-release period, also known as the lag time. These systems are designed to align with the body's circadian rhythm or biological clock. Pulsatile release systems can be classified into multiple-pulse and single-pulse systems. [2&3]

1.1 The PDDS offers several advantages, including:

- It is suitable for both day and night-time therapeutic action.
- It is cost-effective, with fewer side effects due to reduced dose frequency and size.

- It aligns with the body's circadian rhythms.
- Drug targeting is more efficient.
- It protects the gastrointestinal mucosa from the effects of irritating drugs.
- It minimizes first-pass metabolism.
- It helps maintain stable drug levels in the bloodstream.
- Reduces the likelihood of drug resistance and tolerance development.
- Drug release rate is unaffected by pH, food intake, and minimizes the risk of dose dumping.
- Allows the creation of combination dosage forms, facilitating the combination of pellets with different compositions or release patterns.
- Protects mucosal tissues from the irritation caused by certain drugs.
- Delivery profile can be tailored to align with the body's natural circadian rhythm.

1.2 Disadvantages:

- The drug's loading capacity is limited.
- The drug release is lower.
- The uniformity of the coated barrier is crucial to ensure predictable lag times.
- The rupture time may not always be precisely controlled, as it is influenced by the physicochemical properties of the polymer.
- Pulsatile drug delivery systems are expensive, and raw materials are not always easily accessible.
- Designing such dosage forms requires highly skilled professionals.
- The technology and equipment involved are complex.
- The formulation process is complex.
- Reproducibility and efficacy may be inconsistent.
- Manufacturing requires skilled and trained personnel. [1,4&5]

1.3 Circadian rhythm:

Circadian rhythms are self-regulating, internal cycles that follow a roughly 24-hour pattern, governing various bodily functions such as metabolism, sleep, hormone production, and more. Many physiological processes in humans fluctuate rhythmically, in alignment with the body's internal biological clock.

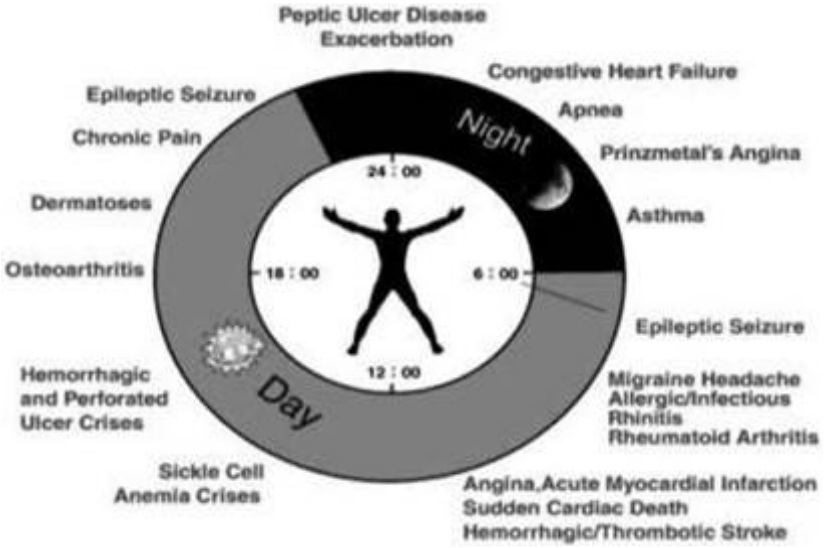


Figure:1.1 The Circadian Pattern of Diseases[6]

1.4 Disease requiring pulsatile drug delivery system:

- Peptic ulcer disease: Acid secretion is high in the afternoon and at night.
- Asthma: Precipitation of attacks during night or at early morning hour

- Cardiovascular disease: Blood pressure reaches its lowest point during sleep and increases sharply in the early morning hours.
- Arthritis: Pain in the morning and more pain at night
- Diabetes mellitus: Increase in the blood sugar level after meal
- Cancer: During each daily phase, the blood flow to tumors is three times greater during the phase of the daily
- Hypercholesterolemia: Cholesterol synthesis is generally higher during night than during day time.[1,2,6&7]

1.5 Mechanism of drug release in PDDS:

The release of drugs from a Pulsatile Drug Delivery System (PDDS) can occur through the following mechanisms:

- Diffusion: When molecules come into contact with aqueous fluids in the gastrointestinal tract, the liquid penetrates the sample, dissolving the drug. The resulting solution then diffuses through the release coating to the external environment.
- Erosion: Certain coatings are designed to gradually break down over time, allowing the drug enclosed within the particle to be released.
- Osmosis: Under suitable conditions, water enters the particle, generating osmotic pressure, which facilitates drug release.[8&7]

1.6 Evaluation parameters for PDDS:

1.6.a Percentage Weight Variation Test

The core tablet's weight is routinely measured to ensure it contains the correct drug dosage. The USP weight variation test involves weighing 20 tablets individually, calculating the average weight, and comparing each tablet's weight to the average. According to USP specifications, no more than two tablets should fall outside the allowed percentage limits, and no tablet should deviate by more than twice the specified limit.

1.6.b Hardness Test

Tablet hardness determines resistance to breaking or damage during storage, transportation, and handling. Each batch's hardness should be assessed using a Monsanto hardness tester as per IP guidelines. The hardness is recorded in kg/cm².

1.6.c Disintegration Test

Disintegration is a crucial step in drug absorption. The test is conducted using the Electro lab USP disintegration test apparatus, which includes six glass tubes, each 3 inches long, open at the top, and fitted with a 10-mesh screen at the bottom. One tablet is placed in each tube, and the basket rack is submerged in a 1-liter beaker containing a phosphate buffer solution (pH 6.8) at 37 ± 1 °C, ensuring the tablets remain 2.5 cm below the liquid surface.

1.6.d Friability Test

To assess friability, 20 core tablets are weighed and recorded, then placed in a Roche friabilator, rotating at 25 rpm for 100 revolutions. Afterward, tablets are removed, dusted to remove loose particles, and reweighed. The friability should not exceed 1%.

1.6.e Thickness Test

Uniform tablet thickness ensures consistency in size. A Vernier caliper is used to measure the thickness of ten tablets from each formulation batch.

1.6.f Determination of lag time

The lag time (t10t {10}t10) in the dissolution profile increases with higher % weight gain, as coating thickness directly influences lag time. The goal was to develop a tablet resistant to the gastric environment, releasing the drug rapidly in the intestine after 5-6 hours. Consequently, lag time varied from 147 to 438 minutes based on coating levels, as determined during the dissolution test.[9]

1.6.g Release Kinetics

Dissolution data from the best formulation are fitted into four widely used release models: zero-order, first-order, Higuchi, and Korsmeyer-Peppas equations. These models describe the drug release kinetics from matrix systems:

- Zero-order kinetics: Q=K0tQ
- First-order kinetics: ln⁡(1−Q) =−K1t
- Higuchi equation: Q=K2t1/2
- Korsmeyer-Peppas equation (Power Law): Mt/M0
- Q = Drug amount released at time t
- K0 = zero-order rate constant
- K1 = first-order rate constant
- K2 = Higuchi rate constant
- Mt is the amount of drug released at time t
- M0 is the amount released at time 0.[10,11&12]

1.6.h Content uniformity:

The API weight is examined to make sure it remains within the Indian Pharmacopoeia's recommended range. Twenty pills were chosen at random and weighed as part of the process. A volumetric flask filled with 0.1 N HCl was then used to dissolve a batch of powdered tablets. A predetermined wavelength was then used to test the absorption.

1.6.i Total floating time:

The duration of time it takes for the tablet to remain afloat on top of the stomach contents at 37 °C, pH 1.2, with paddles turning at 50 rpm, and without pepsin.

1.6.j Dissolution in vitro:

Several USP dissolving instruments will be used to test the several dosage forms that are being considered. A specific medium with a specific pH range will be used for the entire experiment. After samples are routinely collected for analysis, a UV double-beam spectrophotometer is employed.

1.6.k Swelling index:

Before being dissolved in fifty milliliters of double-distilled water, each pill was carefully weighed. After 60 minutes, the tablets were carefully removed, cleaned with filter paper to get rid of any water that had formed on the surface, and then weighed exactly. The percentage swelling index (SI) was computed using the formula SI = (wet weight-dry weight/dry weight) *100.

1.6.l Rupture test:

The USP paddle equipment was used to perform the rupture test on coated tablets. The remaining variables for that procedure were the same as those for the In vitro Dissolution procedure. The amount of time after which the outer coating layer begins to break is known as the lag time.[13&14]

1.7 RAMIPRIL:

- Drug Name: Ramipril
- Drug Class: Angiotensin-Converting Enzyme (ACE) Inhibitor

· Delivery System: Pulsatile Drug Delivery System (PDDS)[15]
· The goal is to maximize the therapeutic benefit of Ramipril while reducing side effects by releasing it in a time-controlled or site-specific manner.

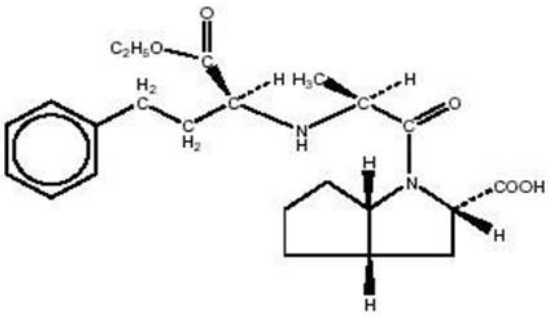


Figure 1.2 Structure of ramipril.[15]

Table.1.1Formulation Ingredients of Ramipril[16]

Component	Function	Examples
Ramipril	Active Pharmaceutical Ingredient (API)	Antihypertensive agent
Superdisintegrant	Facilitates rapid drug release after lag phase	Crospovidone, Sodium starch glycolate
Binder	Provides cohesion	PVP K30, HPMC
Diluents	Improve tablet bulk & flow properties	Lactose, Microcrystalline cellulose (MCC)
Lubricant	Reduces friction	Magnesium stearate
Coating Polymer	Controls lag time before drug release	Eudragit S100, Ethylcellulose, HPMC
Plasticizer	Improves film flexibility	PEG 400, Dibutyl phthalate

1.8 Need for PDDS of ramipril

1. Hypertension Chronotherapy

Circadian Blood Pressure (BP) Rhythm

Blood pressure fluctuates throughout the day according to a circadian rhythm that is regulated by the body's internal clock.

Between 6:00 AM and 12:00 PM, there is a morning spike in blood pressure, which is linked to a higher risk of cardiovascular events like:

Myocardial infarction, or heart attack

stroke

Unexpected cardiac death, Aneurysm.

2. Issue with Instant-Release Ramipril

Traditional immediate-release After being administered, ramipril quickly reduces blood pressure, which may result in:

Quick hypotension (a dip in blood pressure)

Falls, dizziness, and fainting (particularly in older individuals)

Weakness and exhaustion brought on by sudden vasodilation

3. Enhancement of Bioavailability

Problems with the Traditional Formulation of Ramipril

Short Half-Life: Ramipril needs to be used frequently for long-term blood pressure control because of its 13–17 hour half-life.

First-Pass Metabolism: The liver must transform the pro-drug ramipril into its active form, ramiprilat. Before entering the bloodstream, some of the medication is lost as a result of metabolism. [17&18]

1.9 Pharmacokinetics & Pharmacodynamics of Ramipril in Pulsatile Drug Delivery System

1. Absorption: Designed to Help with Peak Blood Pressure Surge Typical Ramipril Absorption Problems: Immediate-release formulations of Ramipril start to absorb quickly, but they don't correspond with the body's normal blood pressure swings.

The stomach breaks down several medications, which lowers their bioavailability.

2. Metabolism: Diminished Impact of the First-Pass Challenges with Conventional Ramipril Metabolism. Being a prodrug, Ramipril must first undergo liver metabolism to become its active form, Ramiprilat, before it may start to work. Overall efficacy is decreased by the first-pass metabolism, which decreases the quantity of active medication that enters circulation.

3. Issues with Conventional Ramipril's Extended Therapeutic Effect and Half-Life: Extension Half-Life Because of its brief half-life (around 13–17 hours), ramipril must be taken often to keep blood pressure under control.

Immediate-release formulations cause plasma concentrations to fluctuate, which raises the possibility of adverse effects and inefficient blood pressure regulation.

4. Excretion: Lower Kidney Burden with Renal Elimination

Traditional Excretion of Ramipril

The kidneys are responsible for 60% of the excretion of Ramipril and its active metabolite, Ramiprilat, with bile (faces) accounting for a little portion.

Formulations with immediate release raise the renal excretion load by causing abruptly elevated plasma concentrations.[13&19]

1.10 Advantages of Pulsatile Drug Delivery for Ramipril:

1. Chronotherapeutic Approach for Better Blood Pressure (BP) Control:

Blood pressure (BP) naturally varies during the day according to a circadian rhythm.

Because the sympathetic nervous system is more active in the early morning (6 AM–12 PM), there is the greatest spike in blood pressure.

An increased risk of heart attacks, strokes, and sudden cardiac death is closely associated with this morning spike in blood pressure. [20&21]

2. Reduced Side Effects (e.g., Sudden Hypotension, Cough)

Unexpectedly low blood pressure: Rapid blood pressure reduction with immediate-release formulations might result in fainting, disorientation, and falls, particularly in older individuals.

Dry Cough: Bradykinin buildup with ACE inhibitors, such as Ramipril, might result in a chronic dry cough.

Renal burden: Particularly in individuals with chronic kidney disease (CKD), a sharp increase in plasma medication levels might put a load on renal function.[22&23]

3. Improved Patient Compliance (Once-Daily or Controlled Dosing)

Instant-release for long-term blood pressure control, Ramipril needs to be taken in the morning and evening.

Poor medicine adherence results from frequent dose schedules, particularly in older patients.

Because patients frequently forget to take their medications in the evening, blood pressure regulation is less effective overnight and in the morning.

4.Minimized Drug Degradation in the Stomach (if pH-Sensitive)

Ramipril is prone to deterioration in the stomach's acidic environment.

Ramipril's bioavailability is further decreased by the liver's first-pass metabolism.

Direct medication interaction with the stomach lining might cause gastric discomfort.[24&25]

2. Aim of the study:

1. To formulate a pulsatile drug delivery system (PDDS) for Ramipril.
2. To evaluate the controlled and timed-release profiles of Ramipril in the PDDS.
3. To assess the influence of formulation parameters on drug release kinetics and stability.
4. To enhance patient compliance by providing a convenient and effective drug delivery system.

3. Methodology:

3.1 Preformulation Studies

a) Identification of Pure Drug:

- Infrared Spectroscopy was used to identify Ramipril.

b) Drug-Excipient Compatibility Studies:

- Compatibility of Ramipril with excipients was assessed using Infrared Spectroscopy.

c) Analytical Methods:

- **Standard Calibration Curve of Ramipril:** Developed in 0.1N HCl, phosphate buffer pH 6.8, and pH 7.4.
- **Preparation of Buffers:** Standard laboratory procedures were followed.
- **Calibration Curve:** Prepared by serial dilution of stock solutions (10 mg drug in 100 ml buffer) and absorbance measured.

3.2 Micrometric Properties

- **Angle of Repose:** Determined by the fixed funnel method.
- **Carr's Compressibility Index:** Evaluates powder compressibility.
- **Hausner's Ratio:** Ratio of tapped density to bulk density.

3.3 Preparation of Core Tablets

- **Method:** Direct Compression.
- **Formulations:** Three types with different diluents (Avicel, Dibasic Calcium Phosphate, Lactose Monohydrate) and Cross PVP (4% & 6%) as superdisintegrants.

3.4 Preparation of Erodible Tablets

- **Method:** Direct Compression.
- **Composition:** Guar gum (50%-75%), talc (2%), magnesium stearate (2%), and lactose.

3.5 Capsule Coating

- **Coating Process:** Hard gelatin capsule bodies coated using a rotatory pan coater at SGSITS-Indore.
- **Coating Solution:** Ethyl cellulose (95%) and dibutyl phthalate (5%) in acetone-propane-2-ol (50:50 v/v).
- **Coating Variables:** 5%, 10%, and 15% coatings tested.

3.6 Assembly of Pulsatile Drug Delivery System

- Precoated capsule body compacted with swelling polymers (129 mg), xanthan gum (136 mg), and guar gum (129 mg).
- Core tablet placed on polymer bed, erodible tablet placed at capsule mouth, and sealed with gelatin cap.

3.7 Evaluation of Pulsatile Drug Delivery System

3.7.1 In-vitro Dissolution Studies:

- **Method:** USP Type I paddle apparatus (Electrolab TDT-60).
- **Procedure:** 0.1N HCl (2h) followed by phosphate buffer (pH 6.8).
- **Analysis:** UV spectrophotometer at 210 nm.

3.7.2 Ex-vivo Studies:

- **Objective:** Assess intestinal drug absorption using chicken intestine model.
- **Procedure:** Drug diffusion measured using UV spectrophotometer.

3.8 Stability Studies

- **Conditions:** 40±2°C/75±5% RH for 45 days.

- **Testing:** Drug content analyzed at 15, 30, and 45days using UV spectrophotometry.

4.RESULTS:

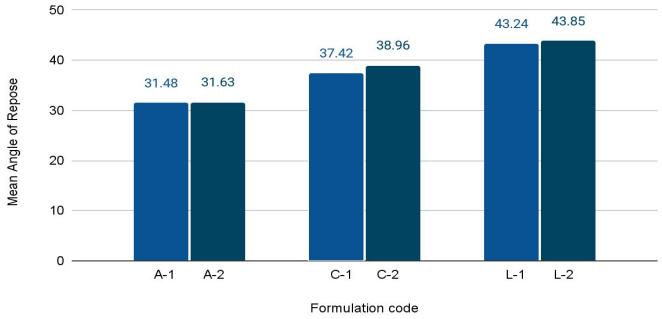
4.1The Angle of Repose of different formulations were evaluated. The results are as follows A-1 (31.48±0.38), A-2 (31.63±0.47) and C-1 (37.42±0.73), C-2 (38.96±0.46) and L-1(43.24±0.38), L-2 (43.85±0.71). 4.2 The Hausner Ratio of different formulations were evaluated. The results are as follows A-1 (1.43±0.013), A-2 (1.57±0.021) and C-1 (1.37±0.034), C-2 (1.41±0.041) and L-1(1.33±0.027), L-2 (1.52±0.03). 4.3 The Carr's Index (CI) of different formulations were evaluated. The results are as follows A-1 (12.16±0.37), A-2 (14.34±0.49) and C-1 (18.34±0.49), C-2 (20.13±0.56) and L-1(23.14±0.72), L-2 (25.45±0.51). 4.4 The Thickness different formulations were evaluated. The results are as follows A-1 (3.41±0.31), A-2 (3.45±0.24) and C-1 (3.78±0.49), C-2 (3.81±0.33) and L-1(3.54±0.75), L-2 (3.58±0.63). 4.5 The Hardness of different formulations were evaluated. The results are as follows A-1 (3.78±0.47), A-2 (3.62±0.41) and C-1 (3.07±0.59), C-2 (3.12±0.46) and L-1(2.73±0.78), L-2 (2.68±0.62). 4.6 The Friability of different formulations were evaluated. The results are as follows A-1 (0.37±0.03), A-2 (0.52±0.17) and C-1 (0.78±0.01), C-2 (0.84±0.96) and L-1(0.96±0.02), L-2 (1.10±0.028). 4.7 The Average weight of one core tablet of different formulations were evaluated. The results are as follows A-1 (100.64±0.68), A-2 (100.52±0.67) and C-1 (100.38±0.61), C-2 (101.1±0.89) and L1(100.28±0.57), L-2 (100.34±0.61). 4.8 The % Drug Content of core tablets of different formulations were evaluated. The results are as follows A-1 (98.76±0.73), A-2 (99.12±1.96) and C-1 (97.13±0.94), C-2 (98.14±1.24) and 1(96.18±0.53), L-2 (97.46±1.32). 4.9 The Disintegration of core tablets of different formulations were evaluated. The results are as follows A-1 (6.3±0.27), A-2 (5.7±0.31) and C-1 (4.5±0.47), C-2 (3.2±0.35) and L-1(3.4±0.15), L-2 (2.7±0.13). 4.10 Calibration Curve of Ramipril at pH 6.8 At the wavelength of 210 nm, the drug's absorbance in 0.1N hydrochloric acid, phosphate buffer pH 6.8 was evaluated. 4.11 Calibration Curve of Ramipril at pH 7.4 At the wavelength of 210 nm, the drug's absorbance in 0.1N hydrochloric acid, phosphate buffer pH 7.4 was evaluated. The percent of drug release A-1 is 0%, 5%, 36%, 40%, 45%, 70%, 82%, 93%; A-2 is 0%, 7%, 30%, 50%, 58%, 75%, 92%, 97%; C-1 is 0%, 5%, 30%, 37%, 45%, 63%, 80%, 85%; C-2 0%, 5%, 30%, 37%,42%, 60%, 75%, 83%; L-1 0%, 5%, 23%, 38%, 44%, 56%, 72%, 80%; L-2 0%, 4%, 25%, 35%, 40%, 57%, 63%, 70% at the time (min) 0, 5, 10,15, 20, 25, 30, 35 respectively. 4.12 In-Vitro Dissolution Study: The dissolution rate of ramipril drug from different core tablet formulations are presented in Figure no.11. Formulation A-2 shows higher release rate of ramipril drug than other core tablet formulations. The sequence of drug release rate as follows: A-2 > A-1 > C-1 > C-2 > L-1 > L-2 Formulation A-2 containing Avicel as the diluent and 6% cross polyvinyl pyrrolidone (PVP) as superdisintegrant showed higher release rate then compared to other formulations. Hence A-2 Formulation is used for the preparation of pulsatile system 5.8 Capsule coating: Water-insoluble ethylcellulose, which creates a semipermeable film with low elongation capacity and low pierce strength, was applied to the capsule bodies. The weights of 50 hard gelatin capsule bodies coated with 5% w/w, 10% w/w, and 15% w/w were 2.1 mg, 2.2 mg, and 2.3 mg, respectively, compared to 1.9 mg for 50 uncoated capsule bodies.9 Evaluation of Pulsatile Drug Delivery system: 5.9.1 In- Vitro Dissolution Studies: Using USP Type I paddle apparatus (Electrolab TDT-60), in-vitro dissolution studies have been conducted for all pulsatile drug delivery system formulations (M-1 to M-12) in 900 ml of 0.1 N HCl for the first two hours and then 900 ml of phosphate buffer (pH 6.8). The release pattern of Ramipril from different pulsatile drug delivery system formulations after every 30 minutes is displayed. Analysis of Pulsatile drug delivery system: The following mathematical model was used to test the in vitro drug release data. The kinetics of drug release were found to be described by the goodness of fit. 5.10.1 Zero Order kinetics Drug release is independent of its concentration as described by Zero order kinetics Systems. According to the equation, time and cumulative drug release are closely correlated. $C = k_0 t$ Where, C = cumulative % of drug release k_0= zero order rate constant t = time First Order Kinetics Systems in which the concentration affects the release rate are described by first order models. The log cumulative proportion of drug remaining vs. time represents the release behavior of the first order equation. $\text{Log } C = \log Co - kt / 2.303$ Where,

C - Cumulative % drug remaining

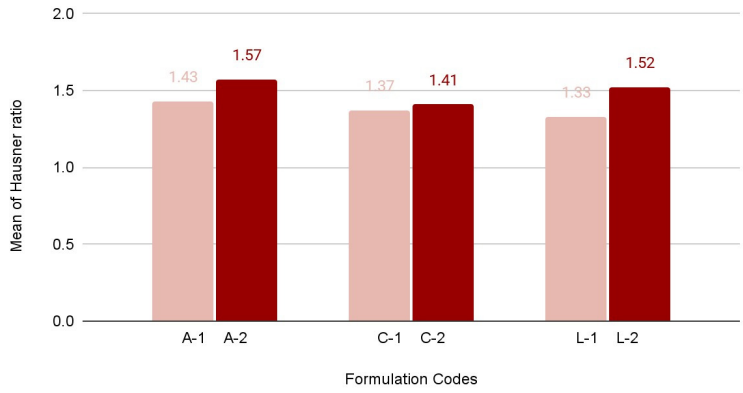
Co – Initial concentration of drug
K – First order constant

Stability Studies of Pulsatile system (M6): Stability studies of formulation code M6 was performed. It is performed for 3 months and the percentage of drug content is evaluated. Initially the % drug content are 99.97%, 99.96% and 99,93%; after a month % drug content are 99.54%, 99.76% and 99.65%; after 2 months the % drug content are 99.37%, 99.56% and 99.52%; after 3 months % drug content are 99.15%, 99.20% and 99.09% for N1, N2 and N3 respectively.

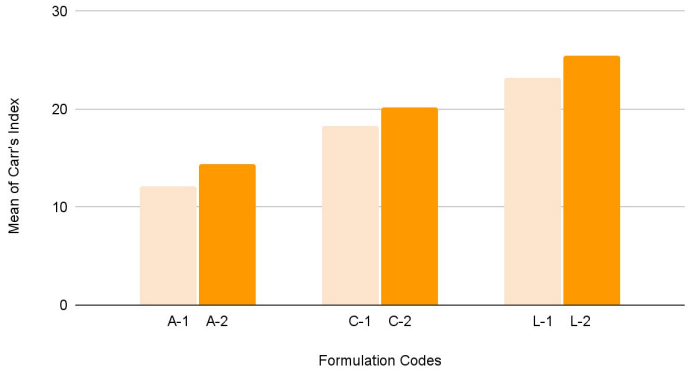
Angle of Repose of core tablets



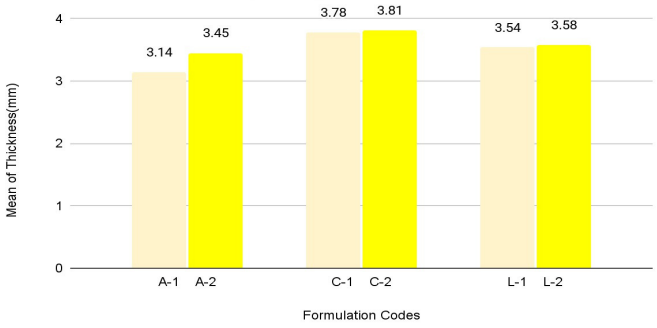
Hausner Ratio of core tablets:



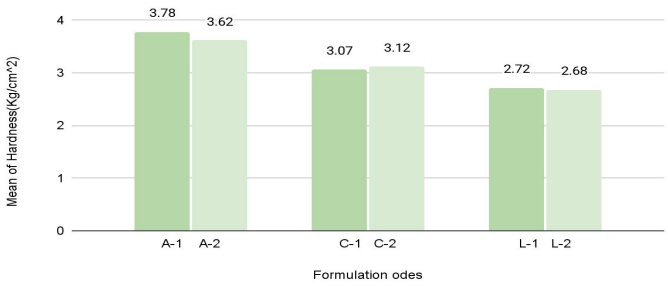
Carr's Index of core tablets:



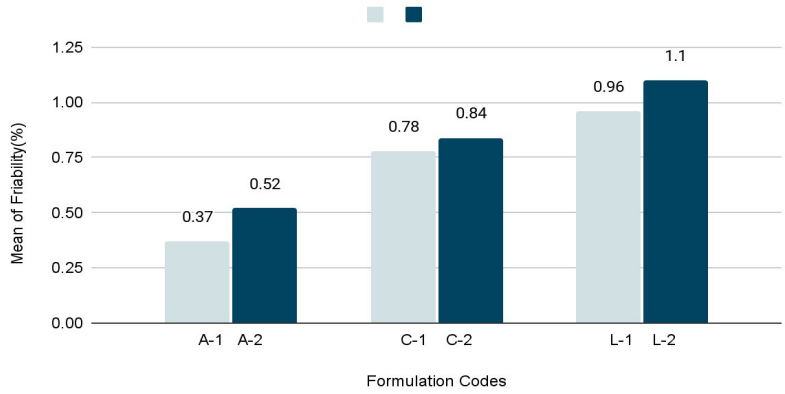
Evaluation of Thickness (in mm) of core tablets:



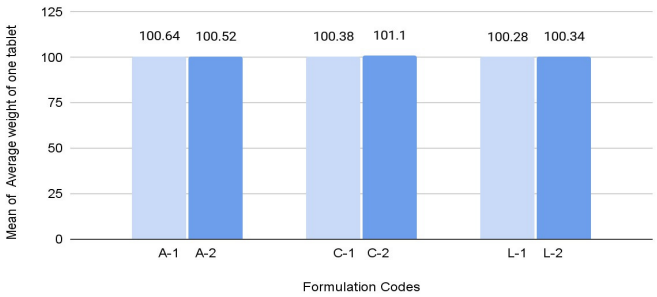
Evaluation of Hardness (kg/cm2) of core tablets:



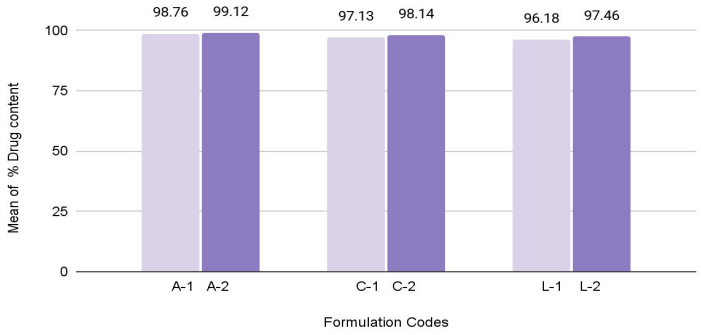
Evaluation of Friability (%) of core tablets:



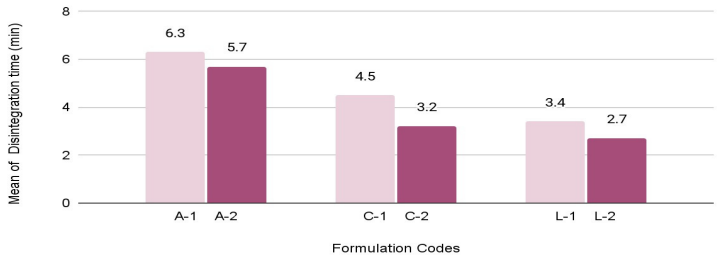
Evaluation of Average weight of one core tablet:



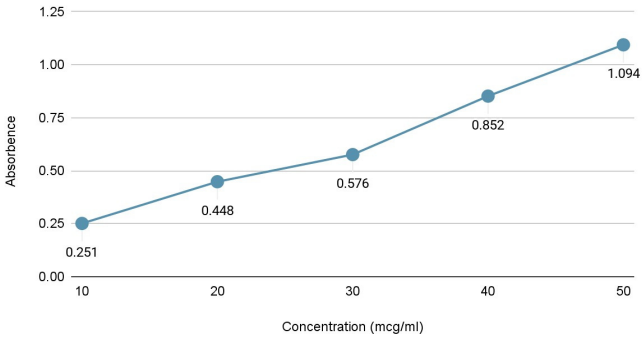
Evaluation of % Drug Content of core tablet:



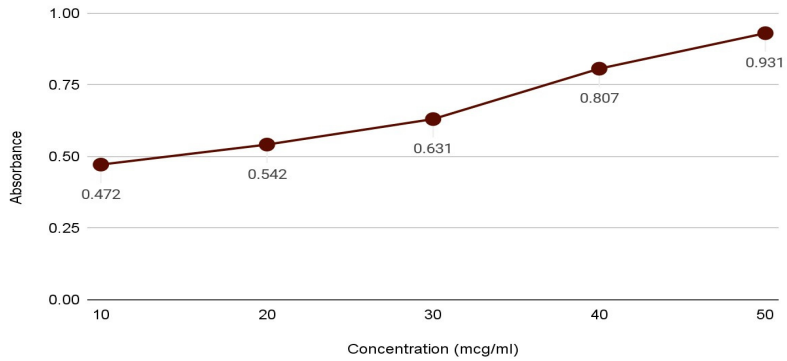
Evaluation of Disintegration time (min) of core tablet:

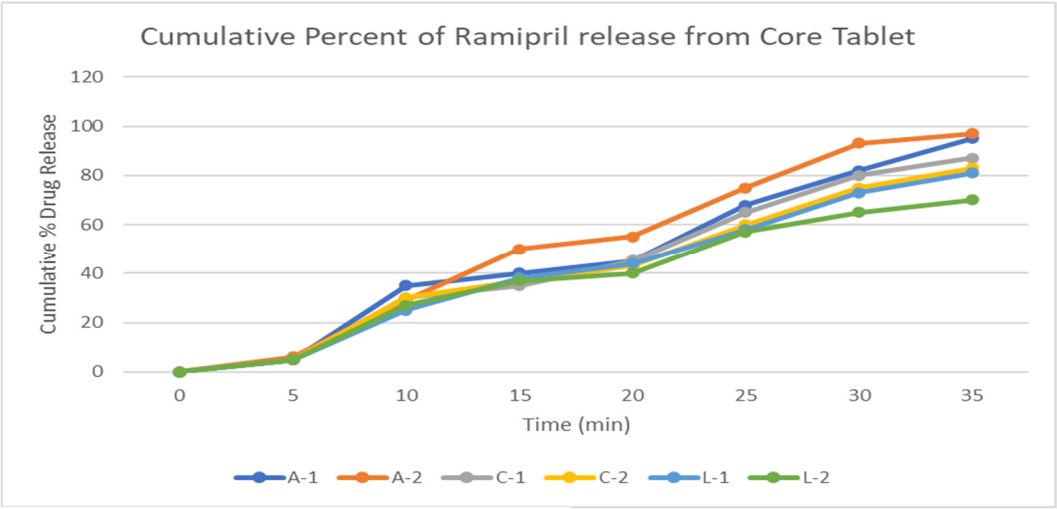


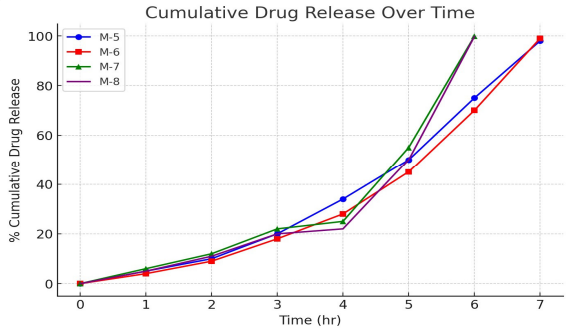
Calibration Curve of Ramipril at pH 6.8

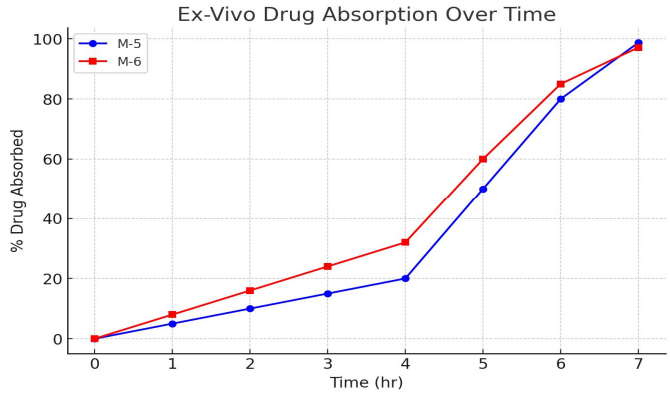


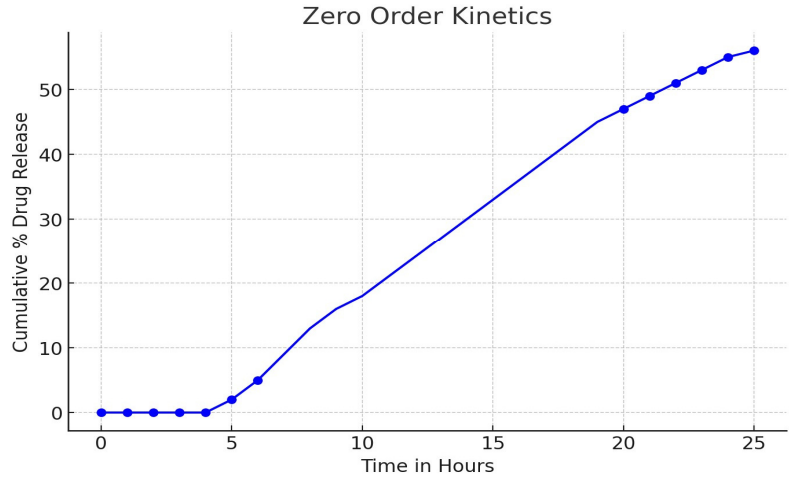
Calibration Curve of Ramipril at pH 7.4











S.no.	Duration	%Drug Content			Mean	SD
		N1	N2	N3		
1	0 month	99.97	99.96	99.93	99.95	±0.011
2	1 month	99.54	99.76	99.65	99.65	±0.019
3	2 months	99.37	99.56	99.51	99.48	±0.049
4	3 months	99.15	99.20	99.09	99.14	±0.032

5.Conclusion

The Aim of this study was to create a pulsatile dosage form in which the drug releases quickly (single pulse). The created formulation allowed for the quick release of the medication following a lag time that complied with the need for chronotherapeutics.

Water-insoluble ethyl cellulose, which creates a semipermeable film with poor elongation capacity and low piercing strength, was applied to the capsule bodies. It is discovered that polymers like xanthan and guar gum are responsible for the release's delay.

Therefore, this method may aid patients with morning blood pressure spikes and offer a practical way to release Ramipril in a pulsatile or programmable manner (with a single pulse).

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