Design Development and Characterization of Gastro-Retentive Bilayer Floating Tablets

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Abstract*—The present study focuses on the design, development, and characterization of gastro-retentive bilayer floating tablets of Lisinopril for improved therapeutic efficacy and controlled drug release. The formulation was developed to achieve a dual-release pattern consisting of an immediate release layer for rapid onset of action and a sustained release floating layer for prolonged drug delivery. The immediate release layer was formulated using super disintegrants such as sodium starch glycolate and croscarmellose sodium, while the sustained release layer was prepared using hydrophilic polymers including HPMC K100M and HPMC K4M along with sodium bicarbonate as a gas-generating agent. Preformulation studies confirmed the purity, compatibility, and suitability of Lisinopril for formulation development. The prepared powder blends exhibited good flow properties, ensuring uniform compression. The bilayer tablets were evaluated for physicochemical parameters such as hardness, friability, weight variation, thickness, drug content, and swelling index, all of which were found to be within acceptable limits. In-vitro dissolution studies demonstrated a biphasic drug release pattern with rapid initial release followed by sustained release up to 12 hours. Among all formulations, the optimized formulation (FE2) showed approximately 94% cumulative drug release with desirable floating and swelling characteristics. Drug release kinetics revealed that the formulation followed zero-order kinetics and Korsmeyer–Peppas model, indicating anomalous (non-Fickian) diffusion mechanism. Stability studies confirmed that the optimized formulation remained stable under accelerated conditions without significant changes in physicochemical properties or drug release profile. Overall, the developed gastro-retentive bilayer floating tablet system of Lisinopril provides an effective approach for enhancing bioavailability, prolonging gastric residence time, and improving patient compliance.

***Index Terms*—Gastro-retentive drug delivery system; Bilayer tablets; Floating drug delivery system; Lisinopril; Sustained release; Immediate release; HPMC; Drug release kinetics; Non Fickian diffusion; Swelling index.**

I. INTRODUCTION

Oral drug delivery remains the most preferred and widely accepted route of administration due to its convenience, patient compliance, cost-effectiveness, and ease of manufacturing. However, conventional oral dosage forms often suffer from limitations such as variable gastric emptying, incomplete drug release, and poor bioavailability, particularly for drugs that are unstable or poorly absorbed in the intestinal environment. These challenges have led to the development of novel drug delivery systems aimed at improving therapeutic efficacy and optimizing drug release profiles.[1-3]

Gastro-retentive drug delivery systems (GRDDS) have emerged as an effective approach to overcome the limitations associated with conventional dosage forms. These systems are designed to prolong the residence time of drugs in the stomach, thereby enhancing drug absorption in the upper gastrointestinal tract. By maintaining the drug at its optimal absorption site, GRDDS can significantly improve bioavailability, reduce dosing frequency, and provide better therapeutic outcomes. Various approaches have been explored for gastric retention, including floating systems, bioadhesive systems, expandable systems, and high-density systems, among which floating drug delivery systems have gained considerable attention due to their simplicity and effectiveness.[4-6]

Floating drug delivery systems (FDDS) are low-

density formulations that remain buoyant in gastric fluids for an extended period without affecting gastric emptying rate. These systems typically incorporate gas-generating agents such as sodium bicarbonate, which produce carbon dioxide upon contact with gastric acid. The generated gas gets entrapped within the hydrated polymer matrix, causing the dosage form to float on the gastric contents. The floating mechanism ensures prolonged gastric residence time and controlled drug release, making FDDS particularly suitable for drugs that exhibit narrow absorption windows in the upper gastrointestinal tract.
In recent years, bilayer tablet technology has gained prominence as a versatile platform for achieving both immediate and sustained drug release within a single dosage form. Bilayer tablets consist of two distinct layers, each designed to deliver drug at different rates. The immediate release layer provides a rapid onset of action, while the sustained release layer maintains drug concentration within the therapeutic window over an extended period. This dual-release system not only enhances therapeutic efficacy but also improves patient compliance by reducing dosing frequency.[7-10]
The combination of gastro-retentive floating systems with bilayer tablet technology offers a promising strategy for achieving both rapid and prolonged drug delivery. Such systems can provide an initial loading dose followed by a maintenance dose, ensuring consistent plasma drug levels. The use of hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC) plays a critical role in controlling drug release by forming a gel barrier upon hydration, while effervescent agents facilitate buoyancy.
Lisinopril, an angiotensin-converting enzyme (ACE) inhibitor widely used in the management of hypertension and heart failure, is a suitable candidate for gastro-retentive delivery due to its physicochemical and pharmacokinetic properties. It exhibits better solubility in acidic environments and is primarily absorbed in the upper gastrointestinal tract. However, its short half-life and variable bioavailability necessitate the development of a controlled release system to improve therapeutic effectiveness and patient adherence.[11-14]
The present study aims to design, develop, and characterize gastro-retentive bilayer floating tablets of Lisinopril. The formulation strategy involves the incorporation of an immediate release layer to achieve rapid drug action and a sustained release floating layer to prolong drug release and gastric retention. Various formulation parameters and excipients were optimized to achieve desired physicochemical properties, drug release behavior, and stability. The developed system is expected to enhance bioavailability, reduce dosing frequency, and improve overall therapeutic outcomes.

II. MATERIALS AND METHODS

Materials and Reagents

Lisinopril was obtained as a gift sample from Lupin Pharmaceuticals Pvt. Ltd., Chhatrapati Sambhajinagar. Hydroxypropyl methylcellulose (HPMC K100M and HPMC K4M) was procured from Research-Lab Fine Chem Industries, Mumbai. Sodium carboxymethyl cellulose and lactose were purchased from Thomas Baker Chem Pvt. Ltd. Talc and sodium bicarbonate were obtained from Research-Lab Fine Chem Industries and Research-Lab Bombay, respectively. Magnesium stearate was supplied by S. Kanth Health Care Ltd. Superdisintegrants such as sodium starch glycolate and croscarmellose sodium were procured from N. B. Enterprises and FMC Corporation (Ireland), respectively. All reagents used were of analytical grade.

Equipment

All experimental work was carried out using standard laboratory equipment including a UV-visible spectrophotometer, Fourier Transform Infrared (FTIR) spectrophotometer, digital balance, mortar and pestle, sieve set (#40 mesh), tablet compression machine equipped with flat-faced punches, and dissolution testing apparatus. The instruments were calibrated prior to use to ensure accuracy and reproducibility.

III. PREFORMULATION STUDIES

Preformulating studies were conducted to evaluate the physicochemical properties of Lisinopril and to ensure its suitability for formulation development. These studies provide essential information regarding drug behavior, compatibility, and stability, which are critical for designing an effective dosage form. The investigation included organoleptic evaluation, melting point determination, solubility profiling, and compatibility studies with excipients. The drug was examined for its physical characteristics such as color,

odor, and taste. The melting point was determined using the open capillary method to assess purity and identity. Solubility analysis was carried out in various solvents including distilled water, phosphate buffer (pH 1.2 and 6.8), methanol, ethanol, and isopropyl alcohol by adding incremental amounts of drug and observing dissolution behavior.[15-22]

Fourier Transform Infrared (FTIR) Analysis

FTIR spectroscopy was employed to confirm the identity of Lisinopril and to investigate possible interactions between the drug and excipients. Samples of pure drug, individual polymers, and physical mixtures were prepared using potassium bromide (KBr) pellet method in a ratio of 1:100. The spectra were recorded over a range of 4000–400 cm^{-1} and analyzed for characteristic peaks. Any significant shift or disappearance of peaks was considered as an indication of possible interaction.[23-38]

UV-Visible Spectroscopic Analysis

Determination of λmax[29-34]

The maximum absorption wavelength (λmax) of Lisinopril was determined using a UV-visible spectrophotometer. A solution of the drug in distilled water (100 µg/mL) was scanned over the range of 200–400 nm, and the wavelength corresponding to maximum absorbance was recorded.

Preparation of Calibration Curve

A standard stock solution of Lisinopril was prepared by dissolving 10 mg of drug in 100 mL of distilled water to obtain a concentration of 100 µg/mL. From this stock solution, aliquots were withdrawn and diluted to obtain working solutions in the concentration range of 2–12 µg/mL. The absorbance of these solutions was measured at the determined λmax, and a calibration curve was plotted between concentration and absorbance. The linearity of the method was confirmed by calculating the correlation coefficient.

Drug–Excipient Compatibility Studies[35-38]

Compatibility studies were performed to assess potential interactions between Lisinopril and selected excipients. Physical mixtures of drug and polymers (HPMC and sodium carboxymethyl cellulose) were prepared and analyzed using FTIR spectroscopy. The spectra of the mixtures were compared with those of the pure drug and excipients to identify any chemical interaction. The absence of significant spectral changes confirmed compatibility, indicating the suitability of excipients for formulation development.

Formulation of Bilayer Floating Tablets[39-47]

Bilayer gastro-retentive floating tablets were formulated comprising an immediate release layer and a sustained release floating layer. The immediate release layer was designed to provide rapid drug release and contained Lisinopril along with superdisintegrants such as sodium starch glycolate and croscarmellose sodium. The sustained release floating layer was formulated to prolong gastric residence time and included gas-generating agent sodium bicarbonate along with polymers such as HPMC K100M, HPMC K4M, and sodium carboxymethyl cellulose.

All ingredients were passed through a #40 mesh sieve, accurately weighed, and blended uniformly. The immediate release layer and floating layer powders were prepared separately. The bilayer tablets were compressed using a tablet compression machine equipped with flat-faced punches. Initially, the floating layer was compressed lightly, followed by the addition of the immediate release layer and final compression to obtain bilayer tablets of desired hardness.

Preparation Method (Direct Compression Technique)

The tablets were prepared by direct compression method. The drug and excipients were mixed thoroughly to ensure uniform distribution. Lubricants such as magnesium stearate and talc were added in the final step to improve flow properties and prevent sticking during compression. The prepared blend was compressed into tablets using appropriate compression force to achieve suitable mechanical strength and floating characteristics.

Table 1: Formulation of Immediate Release Layer (Lisinopril).

INGREDIENTS	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lisinopril (mg)	4	4	4	4	4	4	4	4	4
Sodium Starch Glycolate (mg)	5	7.5	10	5	-	10	5	7.5	10
Cross Carmilose Sodium (mg)	5	5	5	7.5	7.5	7.5	10	10	-

Lactose (mg)	16	13.5	11	13.5	18.5	8.5	11	8.5	16
Talc (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Magnesium Sterate (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Sodium bicarbonate (mg)	20	20	20	20	20	20	20	20	20
Methyl Orange pH Indicator	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Total	51	51	51	51	51	51	51	51	51

Table 2: Formulation of Sustained Release Layer (Lisinopril)

INGREDIENTS	E1	E2	E3	E4	E5	E6	E7	E8	E9
Lisinopril (mg)	16	16	16	16	16	16	16	16	16
HPMC K100M (mg)	13	13	13	19.5	19.5	19.5	26	26	26
HPMC K4M (mg)	13	19.5	26	13	19.5	26	13	19.5	26
Sodium Carboxy Methyl Cellulose (mg)	14	14	14	14	14	14	14	14	14
Lactose (mg)	70	63.5	57	63.5	57	50.5	57	50.5	44
Talc (mg)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium Sterate (mg)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Total	129	129	129	129	129	129	129	129	129

Pre-Compression Evaluation of Powder Blend[48-60]

- Bulk Density

Bulk density of the powder blend was determined to evaluate packing properties. A known quantity of powder was carefully introduced into a graduated cylinder, and the volume occupied without tapping was recorded. The bulk density was calculated as the ratio of mass of powder to its bulk volume. This parameter helps in understanding the initial packing arrangement of particles and flow characteristics.

- Tapped Density

Tapped density was measured by mechanically tapping the graduated cylinder containing the powder blend until a constant volume was achieved. The reduction in volume after tapping reflects the ability of particles to rearrange themselves under applied stress. The tapped density was calculated as the ratio of mass of powder to tapped volume.

- Compressibility Index and Hausner Ratio

The compressibility index and Hausner ratio were determined from bulk and tapped density values to assess flow properties of the powder blend. These parameters indicate the degree of interparticle interaction and cohesiveness. Lower values represent better flowability, while higher values suggest poor flow behavior, which may affect tablet uniformity during compression.

- Angle of Repose

The angle of repose was measured using the fixed funnel method to evaluate flow characteristics of the powder. The powder was allowed to flow through a funnel to form a conical heap, and the angle formed between the surface of the pile and horizontal plane was calculated. This parameter provides insight into frictional forces between particles and helps predict handling properties.

Post-Compression Evaluation of Bilayer Tablets

- Hardness Test

The mechanical strength of the compressed tablets was evaluated using a Monsanto hardness tester. The force required to break the tablet diametrically was recorded, and the average of multiple readings was calculated. Adequate hardness ensures that tablets can withstand mechanical stress during handling, packaging, and transportation.

- Friability Test

Friability testing was carried out using a Roche friabilator to assess the resistance of tablets to abrasion and shock. A pre-weighed sample of tablets was subjected to rotational stress, after which tablets were reweighed. The percentage weight loss was calculated, and values below acceptable limits indicated good mechanical integrity.

- Weight Variation Test

Uniformity of tablet weight was evaluated by weighing individual tablets and comparing them with the average weight. This test ensures dose consistency across the batch and compliance with pharmacopeial standards.

- Thickness Measurement

The thickness of tablets was measured using a Vernier

caliper. Consistent thickness indicates uniform die filling and compression, which is important for maintaining tablet quality and packaging requirements.

- Swelling Index

The swelling behavior of bilayer tablets was studied by placing tablets in acidic buffer (pH 1.2) and measuring weight gain at regular time intervals. The swelling index was calculated as the percentage increase in weight relative to the initial weight. This parameter is crucial for evaluating the hydration and gel-forming ability of polymers, which directly influences floating and drug release behavior.

- Drug Content Uniformity

Drug content uniformity was determined by crushing tablets and dissolving an accurately weighed quantity equivalent to a known dose in buffer solution. The solution was filtered, diluted appropriately, and analyzed using a UV-visible spectrophotometer. This test ensures uniform distribution of drug within the formulation.

- Disintegration Test

The disintegration time of tablets was evaluated using a standard disintegration apparatus maintained at physiological temperature. Tablets were placed in the apparatus, and the time required for complete disintegration into smaller particles was recorded. This test is particularly important for the immediate release layer of bilayer tablets.

In-Vitro Dissolution Study[58-61]

In-vitro drug release studies were performed using USP dissolution apparatus type II (paddle method). The dissolution medium consisted of simulated gastric fluid (pH 1.2), maintained at 37 ± 0.5°C. Tablets were rotated at a constant speed, and samples were withdrawn at predetermined time intervals. The withdrawn samples were filtered and analyzed spectrophotometrically. The amount of drug released was calculated using a calibration curve, and cumulative percentage drug release was determined.

Drug Release Kinetics and Model Fitting[62-64]

To understand the mechanism of drug release, dissolution data were fitted to various kinetic models including zero-order, first-order, Higuchi, and Korsmeyer–Peppas models. The best-fit model was selected based on correlation coefficient (R^2) values. The release exponent (n) obtained from the Korsmeyer–Peppas model was used to characterize the release mechanism, such as Fickian diffusion, anomalous transport, or case II transport.

Stability Studies

Stability studies were conducted on the optimized formulation to evaluate its physical and chemical stability under accelerated conditions. Tablets were stored at 40°C and 75% relative humidity for a period of three months. Samples were withdrawn at specified intervals and analyzed for parameters such as hardness, drug content, and in-vitro drug release. These studies help predict shelf life and ensure formulation stability over time.

IV. RESULTS AND DISCUSSION

Characterization of Lisinopril

- Organoleptic Properties and Melting Point

The organoleptic properties of Lisinopril were evaluated and found to be consistent with standard specifications. The drug appeared as a white to off-white crystalline powder with a characteristic pungent odor and a complex taste profile. The melting point was observed in the range of 146–148°C, which falls within the official pharmacopeial limits. These results confirm the identity and purity of the drug, indicating its suitability for formulation development.

- Solubility Analysis

The solubility behavior of Lisinopril was studied in different solvents to understand its dissolution characteristics. The drug exhibited good solubility in water and 0.1 N HCl, while it was sparingly soluble in methanol and practically insoluble in ethanol. This solubility pattern indicates that Lisinopril is more soluble in aqueous acidic environments, which supports its suitability for gastro-retentive drug delivery systems. The enhanced solubility in acidic pH is advantageous for floating tablets designed to remain in the stomach.

- UV Spectroscopic Analysis (λmax Determination)

The UV absorption spectrum of Lisinopril in 0.1 N HCl showed a distinct maximum absorbance at 205 nm. This wavelength was selected for further quantitative analysis. The clear and sharp peak

obtained indicates that the drug exhibits good absorbance characteristics in acidic medium, making it suitable for spectrophotometric estimation during dissolution studies.

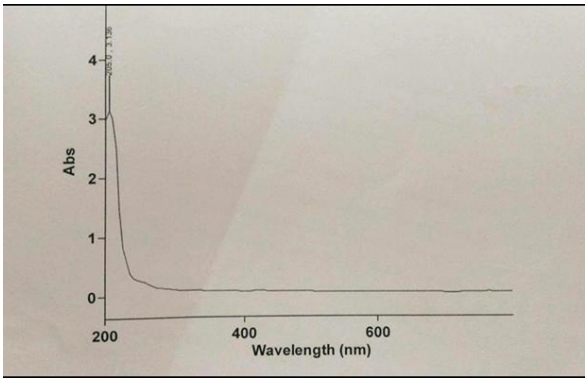

Figure 1: UV Light absorption spectrum of Lisinopril in 0.1 N HCl

- FTIR Compatibility Studies

FTIR analysis was carried out to evaluate possible interactions between Lisinopril and selected excipients such as HPMC K100M, HPMC K4M, sodium starch glycolate, and croscarmellose sodium. The spectra of the pure drug showed characteristic peaks corresponding to its functional groups. These peaks were retained in the spectra of drug-excipient mixtures without significant shifting or disappearance.

This observation confirms the absence of chemical interaction between Lisinopril and the polymers used. The compatibility of drug and excipients suggests that the formulation is stable and suitable for further development of bilayer tablets.

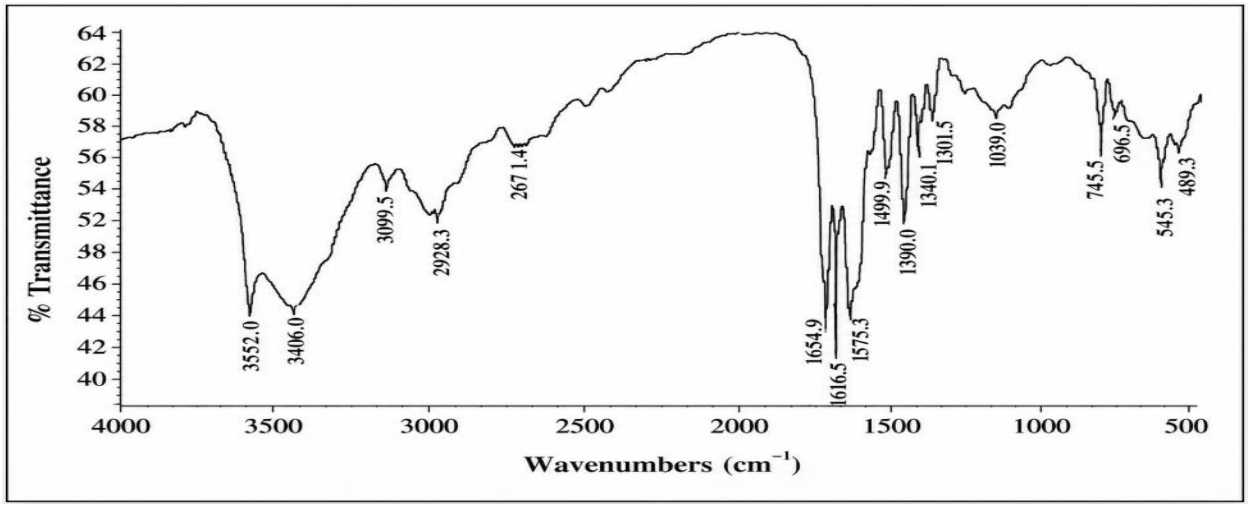

Figure 2: FTIR study of Lisinopril

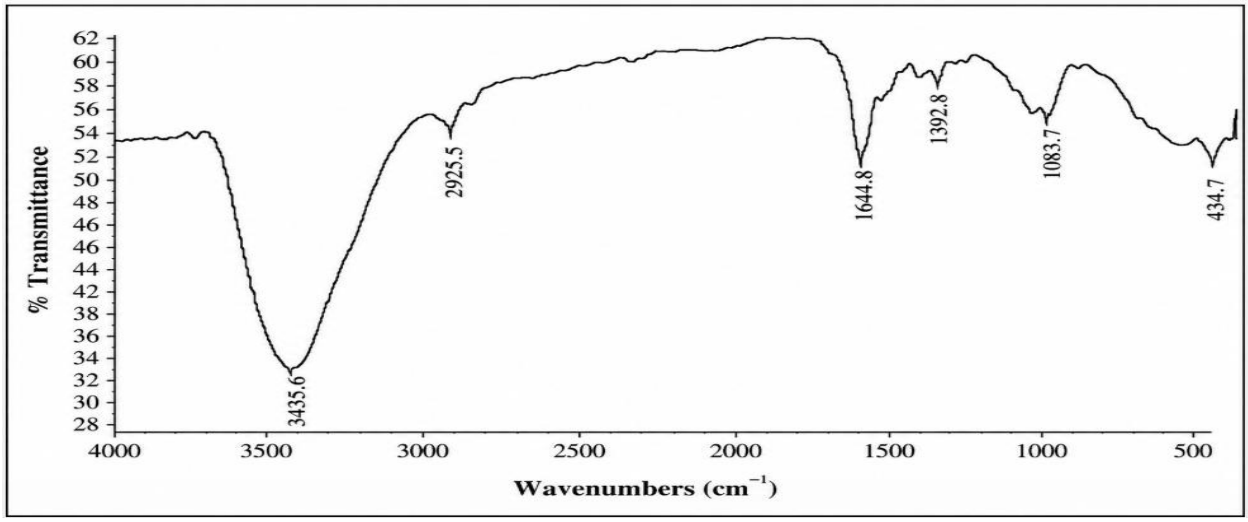

Figure 3: FTIR study of Lisinopril with excipients

- Calibration Curve of Lisinopril

The calibration curve of Lisinopril in 0.1 N HCl was constructed in the concentration range of 2–12 µg/mL. The absorbance values increased linearly with concentration, demonstrating good adherence to Beer-Lambert's law. The correlation coefficient was found to be close to unity, indicating excellent linearity of the method. This confirms that the developed UV spectrophotometric method is reliable, accurate, and suitable for quantification of Lisinopril in dissolution and content uniformity studies.

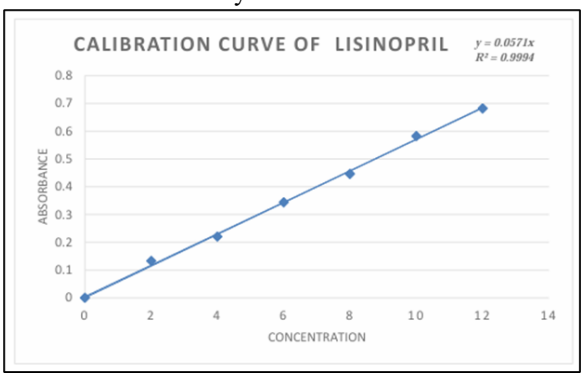

Figure 4: Calibration Curve of Lisinopril

Formulation and Development of Bilayer Tablets

- Immediate Release Layer

The immediate release layer of Lisinopril was successfully formulated using lactose as a diluent and superdisintegrants such as sodium starch glycolate and croscarmellose sodium at varying concentrations. The increase in superdisintegrant concentration from 10% to 20% significantly improved the disintegration behavior of tablets. Formulations with higher levels of superdisintegrants exhibited faster drug release due to rapid water uptake and swelling action. The inclusion of sodium bicarbonate contributed to effervescence, which further enhanced tablet disintegration and initial drug release. Lubricants such as magnesium stearate and talc ensured smooth compression and improved flow properties.

- Sustained Release Layer

The sustained release layer was formulated using hydrophilic polymers HPMC K100M and HPMC K4M in varying ratios. These polymers formed a gel barrier upon contact with gastric fluid, thereby controlling the release of Lisinopril over an extended period. An increase in polymer concentration resulted in a more robust gel layer, which slowed down drug diffusion and prolonged release. HPMC K100M, being of higher viscosity grade, showed stronger retardation effect compared to HPMC K4M. The combination of both polymers provided a balanced release profile.

- Bilayer Tablet Formulation

Bilayer tablets were successfully prepared by sequential compression of sustained release and immediate release layers. The initial light compression of the sustained layer ensured proper adhesion between the two layers, followed by final compression with the immediate release layer. The use of colorant in the immediate release layer allowed easy identification of the bilayer structure. The tablets exhibited good mechanical strength, uniformity, and clear layer separation without delamination. This confirms that the adopted formulation and compression technique were appropriate for bilayer tablet preparation.

Evaluation of Powder Blend (Pre-Compression Parameters)

- Immediate Release Layer

The powder blends prepared for the immediate release layer (F1–F9) were evaluated for flow and compressibility characteristics. The angle of repose values for all formulations were found to be below 33°, indicating good flow properties of the granules. This was further supported by Carr's index values ranging approximately between 10–13%, suggesting good compressibility and flowability.

The bulk density and tapped density values showed minimal variation among formulations, indicating uniform particle size distribution and packing ability. The Hausner ratio values were close to 1.1–1.14, which further confirmed good flow behavior. Overall, these results demonstrated that the prepared blends possessed suitable flow characteristics for direct compression without the need for additional flow enhancers.

- Sustained Release Layer

The powder blends for the sustained release layer (E1–E9) were also evaluated for pre-compression parameters. Most formulations exhibited angle of repose values in the range of approximately 31°–35°, indicating acceptable to good flow properties. However, formulations E5 and E8 showed relatively higher angles of repose and Carr's index values,

suggesting comparatively poor flow due to higher polymer concentration. Bulk density values were found within acceptable limits, indicating good packing characteristics. The compressibility index values for most formulations were below 20%, confirming acceptable flow properties. Hausner ratio values ranged between 1.12 and 1.19, which indicates good to fair flow behavior. Overall, the results suggest that most sustained release blends were suitable for compression, although slight variations were observed due to differences in polymer composition.

Evaluation of Immediate Release Layer Tablets

The immediate release tablets were evaluated for disintegration time and drug content. The disintegration time varied among formulations depending on the concentration of superdisintegrants. Formulations containing higher concentrations of sodium starch glycolate and croscarmellose sodium showed faster disintegration. Among all formulations, F6 exhibited the fastest disintegration time (approximately 5 minutes), indicating effective action of superdisintegrants. Drug content across all batches ranged from approximately 93% to 99%, confirming uniform distribution of drug within the formulations. The results indicate that the immediate release layer was successfully optimized to provide rapid drug release.

Table 3: Precompression evaluation parameters for immediate release layer of Lisinopril. (Each sample was analyzed in triplicate (n=3)

Formulation	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner Ratio
F1	0.536±0.02	0.525±0.01	29.1±0.02	10.0%	1.11
F2	0.520±0.02	0.552±0.02	29.8±0.01	12.2%	1.14
F3	0.510±0.04	0.567±0.04	30.5±0.01	12.1%	1.14
F4	0.507±0.04	0.559±0.03	31.6±0.03	12.4%	1.13
F5	0.518±0.03	0.579±0.05	31.2±0.03	13.5%	1.14
F6	0.520±0.01	0.590±0.02	33.5±0.02	12.5%	1.14
F7	0.504±0.04	0.560±0.03	31.7±0.03	12.4%	1.13
F8	0.519±0.03	0.580±0.05	31.3±0.03	13.5%	1.14
F9	0.521±0.01	0.591±0.02	33.6±0.02	12.5%	1.14

Table 4: Blend properties of Lisinopril sustained release layer.

Formulation	Bulk density	Tapped density	Angle of repose	Carr's index	Hausner Ratio
E1	0.379±0.01	0.422±0.02	33.4±0.01	10.2%	1.12
E2	0.408±0.01	0.472±0.01	31.5±0.02	13.5%	1.16
E3	0.399±0.02	o.462±0.02	34.7±0.01	13.6%	1.16
E4	0.389±0.03	0.457±0.03	32.6±0.02	14.8%	1.17
E5	0.346±0.02	0.476±0.02	48.4±0.0.3	27.3%	1.38
E6	0.405±0.01	0.468±0.01	31.0±0.01	13.4%	1.16
E7	0.396±0.03	0.458±0.03	34.6±0.02	15.8%	1.19
E8	0.358±0.02	0.478±0.02	47.4±0.0.3	28.3%	1.42
E9	0.421±0.01	0.470±0.01	34.0±0.01	14.4%	1.18

Each sample was analyzed in triplicate (n=3)

Post-Compression Evaluation of Bilayer Tablets

- Thickness

The thickness of bilayer tablets was found to be consistent across all formulations, ranging approximately between 5.2 mm and 5.4 mm. This uniformity indicates proper die filling and consistent compression during tablet manufacturing.

- Hardness

The hardness of tablets ranged from approximately 5.3 to 6.3 kg/cm², indicating adequate mechanical strength. These values suggest that the tablets are sufficiently robust to withstand handling, packaging, and transportation without breakage.

- Friability

Friability values for all formulations were found to be less than 1%, which is within acceptable pharmacopeial limits. This indicates that the tablets possess good resistance to abrasion and mechanical stress.

- Weight Variation

All formulations passed the weight variation test as the percentage deviation was within the acceptable limits specified for tablets. This confirms uniformity in tablet weight and ensures dose consistency.

- Drug Content Uniformity

The drug content of all formulations was found to be within acceptable limits, ranging approximately between 98% and 100%. This indicates uniform distribution of Lisinopril in the bilayer tablets and confirms the reliability of the formulation process.

Table 5: Post compression evaluation of Lisinopril bilayer floating tablet

Formulation	Thickness (mm)±S.D	Hardness (kg/cm2)±S.D	Friability (%)±S.D	Weight Variation(gm) ±S.D	Drug content (%w/w)±S.D
FE1	5.2±0.006	5.72±0.360	0.40	178±3.79	98.78±0.54
FE2	5.2±0.010	5.70±0.288	0.18	180±3.54	99.77±0.32
FE3	5.2±0.009	6.01±0.154	0.25	175±4.01	98.46±1.22
FE4	5.2±0.001	6.25±0.152	0.27	180±3.58	98.71±0.95
FE5	5.4±0.010	6.30±0.100	0.34	177±3.91	99.02±0.82
FE6	5.4±0.011	5.49±0.058	0.26	176±3.97	98.65±0.96
FE7	5.3±0.010	5.35±0.210	0.20	180±3.30	99.52±0.57
FE8	5.3±0.006	6.05±0.156	0.21	176±3.98	98.73±0.83
FE9	5.3±0.008	5.91±0.018	0.22	178±3.76	98.12±1.36

All the values represent mean ± standard deviation (n=3)

In-Vitro Floating Studies:

The in vitro floating characteristics of the formulated bilayer floating tablets is given in Table.

Table 6: In-vitro floating characteristics of the formulated bilayer floating tablets

Formulation	Floating Lag Time (Min.)	Floating Duration (Hrs.)
FE1	2min, 24sec	>12
FE2	2min, 56sec	>12
FE3	2min, 12sec	>12
FE4	3min, 02sec	>12
FE5	3min, 12sec	>12
FE6	3min, 24sec	>12
FE7	2min, 39sec	>12
FE8	3min, 03sec	>12
FE9	2min, 07sec	>12

In-Vitro Drug Release Studies

The in-vitro dissolution study of Lisinopril bilayer floating tablets (FE1–FE9) was carried out using USP type II dissolution apparatus in 0.1 N HCl. The results demonstrated a biphasic release pattern consisting of an initial rapid release followed by a sustained release phase.

The immediate release layer showed rapid drug release within the first 30 minutes, which is essential for achieving prompt therapeutic action. Among all formulations, FE6, FE7, and FE8 exhibited comparatively higher initial drug release due to higher concentrations of superdisintegrants and effervescent agents, which enhanced tablet disintegration and drug dissolution.

The sustained release phase extended up to 12 hours, indicating effective control of drug release by hydrophilic polymers. Among all formulations, FE2 showed an optimal release profile with approximately 94% drug release at 12 hours, demonstrating a balanced combination of immediate and sustained release characteristics. Formulations with higher polymer concentrations (such as FE5 and FE8) exhibited slower drug release due to the formation of a thicker gel barrier, which restricted drug diffusion. Conversely, formulations with lower polymer content showed relatively faster drug release.

Table 7: In vitro dissolution profile for bilayer floating tablet. (All batches)

Formulation	FE1	FE2	FE3	FE4	FE5	FE6	FE7	FE8	FE9
Time(min/hr)	%Cumulative Drug Release								
0	0	0	0	0	0	0	0	0	0
5 min	16.04	14.91	16.98	14.95	15.71	39.16	30.21	33.60	24.26
10	18.14	15.61	17.55	15.35	17.09	40.86	32.21	37.33	25.13
15	19.03	16.32	19.69	16.10	18.03	42.48	34.35	41.10	27.12
20	20.32	17.06	20.46	18.58	20.04	44.60	36.12	44.57	29.84
25	24.01	19.14	20.59	20.12	23.61	48.38	38.61	49.89	30.92
30	28.92	20.03	21.82	22.13	26.12	49.41	69.12	53.42	34.12
1 hr.	34.16	22.15	27.91	24.59	32.59	50.70	40.21	55.14	36.19
2	41.38	28.69	39.72	29.64	35.14	53.07	42.21	58.67	44.54
3	49.85	35.45	43.14	34.72	42.34	56.13	44.36	60.67	49.23
4	55.02	40.14	48.35	38.60	49.65	57.04	47.32	64.33	57.78
5	62.16	44.33	52.33	41.27	57.45	58.23	51.84	66.80	62.14
6	69.64	51.02	55.56	47.64	63.46	59.23	56.10	72.41	70.15
7	77.16	70.47	66.37	66.97	76.21	69.59	69.14	78.07	76.61
8	79.62	75.94	66.45	74.70	79.14	73.06	71.03	80.78	79.17
9	81.39	81.04	66.83	78.69	82.31	77.12	74.96	81.29	81.05
10	81.74	85.36	67.90	82.48	85.73	80.52	77.88	82.19	81.74
11	82.55	89.12	68.73	84.75	89.39	85.23	80.28	85.85	82.35
12	86.70	94.12	71.25	87.84	91.74	91.84	86.36	89.02	84.90

Comparative Dissolution Behavior of Formulations

The dissolution profiles of different formulation groups (F1–F3, F4–F6, and F7–F9) revealed that increasing the concentration of superdisintegrants significantly enhanced the initial drug release. Formulation F6 showed the highest drug release within 30 minutes, confirming its superior immediate release behavior. Similarly, sustained release formulations (E1–E9) demonstrated controlled drug release over an extended period. Among these, E2 exhibited a more uniform and prolonged release pattern compared to others, indicating optimal polymer composition and matrix integrity. Overall, the combination of optimized immediate release (F6) and sustained release (E2) layers resulted in the best-performing bilayer formulation (FE2).

Drug Release Kinetics and Mechanism

To understand the mechanism of drug release, dissolution data of all formulations were fitted to various kinetic models including zero-order, first-order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas models.

The optimized formulation FE2 showed a high correlation coefficient (R^2 = 0.973) for zero-order kinetics, indicating a constant drug release rate over time. Additionally, the Korsmeyer–Peppas model showed a correlation coefficient close to unity (R^2 = 0.993), suggesting that the drug release mechanism follows anomalous (non-Fickian) diffusion.

The value of the diffusion exponent (n) indicated that drug release was governed by a combination of diffusion and polymer relaxation mechanisms. The Higuchi model also showed good correlation, confirming that drug release was diffusion-controlled through a hydrated matrix. These findings indicate that the developed formulation successfully achieved controlled drug release through a combination of swelling, diffusion, and erosion mechanisms.

Table 8: Kinetic modeling data of batches

Formulation Code	Zero Order	First order	Hixon Crowell	Peppas Model	Higuchi Model
FE1	0.803	0.388	0.942	0.956	0.963
FE2	0.973	0.546	0.981	0.993	0.980
FE3	0.773	0.380	0.927	0.954	0.950
FE4	0.964	0.581	0.971	0.985	0.970

FE5	0.900	0.446	0.992	0.972	0.991
FE6	0.744	0.328	0.912	0.902	0.875
FE7	0.858	0.390	0.982	0.940	0.961
FE8	0.647	0.295	0.894	0.895	0.854
FE9	0.782	0.372	0.936	0.948	0.954

Swelling Index Study

The swelling behavior of the optimized formulation (FE2) was evaluated over a period of 12 hours. The results showed a gradual increase in swelling index with time, reaching approximately 85% at the end of 12 hours. This behavior is attributed to the hydrophilic nature of polymers such as HPMC, which absorb water and form a gel layer around the tablet. The gel layer acts as a barrier, controlling drug release and maintaining tablet integrity during dissolution.

The continuous swelling and gel formation ensure prolonged gastric retention and sustained drug release, which are essential characteristics of gastro-retentive floating drug delivery systems.

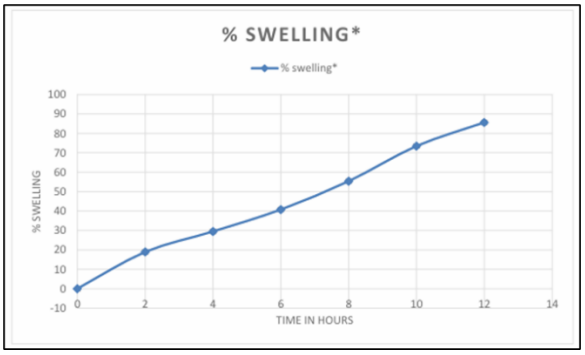

Figure 5: %Swelling Index

Accelerated Stability Studies

Accelerated stability studies of the optimized formulation (FE2) were conducted at 40°C ± 2°C and 75% ± 5% relative humidity for a period of three months. The formulation was evaluated at regular intervals for physical and chemical parameters. The results indicated no significant changes in tablet thickness, hardness, or drug content during the study period. The drug content remained within acceptable limits, demonstrating chemical stability of the formulation. Furthermore, the in-vitro dissolution profile of the formulation before and after stability studies showed negligible variation, indicating that the release characteristics were maintained over time. These findings confirm that the optimized formulation is stable under accelerated conditions and is expected to have a satisfactory shelf life.

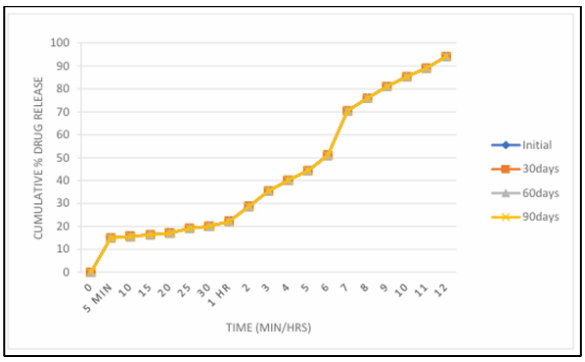

Figure 6: In-Vitro drug release study of optimized formulation FE2 Before and after accelerated stability study

The results obtained from formulation development, evaluation, and in-vitro studies demonstrate that the developed gastro-retentive bilayer floating tablets of Lisinopril successfully achieved the intended objectives. The formulation provided a rapid initial release followed by sustained drug release for up to 12 hours. The optimized formulation (FE2) exhibited desirable physicochemical properties, excellent drug release behavior, and stability under accelerated conditions. The use of hydrophilic polymers and effervescent agents played a crucial role in controlling drug release and maintaining buoyancy. The combination of immediate and sustained release layers ensures improved therapeutic efficacy and patient compliance. Overall, the developed bilayer floating tablet system represents a promising approach for enhancing the bioavailability and therapeutic performance of Lisinopril.

V. CONCLUSION

The present study successfully developed gastro-retentive bilayer floating tablets of Lisinopril with desirable physicochemical and drug release characteristics. The formulation strategy combining immediate release and sustained release layers proved effective in achieving a biphasic drug release profile, ensuring rapid onset of action followed by prolonged therapeutic effect.

Preformulation and compatibility studies confirmed the stability and suitability of the drug with selected excipients. The prepared tablets exhibited acceptable mechanical strength, uniformity, and low friability, indicating robustness of the formulation. In-vitro dissolution studies demonstrated controlled drug release for up to 12 hours, with the optimized formulation (FE2) showing the best performance. Kinetic analysis revealed that drug release followed zero-order kinetics with anomalous diffusion mechanism, indicating the combined effect of diffusion and polymer relaxation. The swelling behavior of the formulation contributed to sustained drug release and prolonged gastric retention. Stability studies further confirmed that the formulation remained stable under accelerated conditions. Thus, the developed gastro-retentive bilayer floating tablet system of Lisinopril represents a promising approach for enhancing therapeutic efficacy, improving bioavailability, and increasing patient compliance in the management of hypertension.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interest regarding the publication of this research work.

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