Research Paper

Design And *In-Vivo* Evaluation Of Cilostazole Sustained Release Swellable, Floating Gastroretentive Tablet- Pharmacokinetic Investigations

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Running Title- Pharmacokinetics of Cilostazol, Sustained-Release Floating Tablets

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Abstract

Aim: This research focuses on designing and assessing a gastroretentive drug delivery system for cilostazol, with the goal of prolonging gastric residence time and controlling drug release. Method: The wet granulation technique was used to prepare floating tablets with Hydroxypropyl Methylcellulose (HPMC) of different grades, Carbopol 934P, and sodium bicarbonate. The tablets were evaluated for parameters such as hardness, friability, weight variation, swelling index, buoyancy, and in vitro drug release. In-vivo studies were performed on rabbits to examine gastric retention time and pharmacokinetics. Results: The optimized formulation (F4) demonstrated sustained drug release for up to 24 hours and good floating ability in vitro. In vivo, the study confirmed a prolonged gastric residence time of about 24 hours. The tablets improved bioavailability over conventional immediate-release forms, indicating potential therapeutic advantages. A strong correlation between in-vitro and in-vivo results (r2=0.9462) was established, highlighting the predictive power of the in-vitro dissolution study for in-vivo performance. Conclusion: Pharmacokinetic data showed a significant increase in Cmax and AUC0-∞, along with a delayed Tmax for the F4 swellable and floating tablet compared to marketed tablets. These findings suggest that the developed cilostazol swellable and floating tablets could be a promising approach for sustained drug release and enhanced therapeutic effectiveness. Further clinical studies in humans are necessary to confirm these outcomes.

Keywords: Cilostazole, Swellable, floating gastroretentive tablet, *In-vivo* Evaluation, *In-vitro* evaluation, Correlation

Cilostazol is a drug used to treat symptoms of intermittent claudication, a condition characterized by pain and cramping in the legs during physical activity due to reduced blood flow [1,2]. It is classified under the Biopharmaceutics Classification System (BCS) Class II. The BCS is a system used to categorize drugs based on their solubility and permeability. It helps in predicting their behavior in the human body and their potential for bioavailability and efficacy. Cilostazol falls into BCS Class II because it has high permeability but low solubility [3, 4]. This classification implies that the drug's absorption can be influenced by its dissolution rate, and certain factors affecting its solubility could impact its overall bioavailability. To address this issue, pharmaceutical manufacturers may use different formulation strategies to enhance the drug's solubility and ensure consistent therapeutic effects.

The oral route is one of the most commonly used routes for medication administration. It involves the ingestion of medications through the mouth, where they are absorbed into the bloodstream through the gastrointestinal tract [4]. This route offers several advantages and disadvantages, which should be considered when choosing the most appropriate method of drug delivery. One of the primary advantages of the oral route is its ease of administration. Oral medications are generally well accepted by patients, as they are easy to swallow and do not involve discomfort or pain. This leads to improved patient compliance, as individuals are more likely to adhere to prescribed treatment regimens. This convenience enhances patient autonomy and contributes to a better quality of life. The oral route is generally considered safe, with a well-established safety profile for many medications [5]. The gastrointestinal tract acts as a barrier, preventing direct contact between drugs and vital organs. This reduces the risk of infections, tissue damage, and adverse effects associated with other routes of administration. The oral route offers versatility in drug delivery. Medications can be formulated in various oral forms, such as tablets, capsules, liquids, or suspensions. This allows for different dosage strengths and formulations tailored to individual patient needs. Furthermore, certain drugs can be formulated as sustained-release formulations, providing prolonged therapeutic effects.

Multi-unit drug delivery systems like tablets are preferred over single-unit systems, highlighting their performance as floating drug delivery systems. Unlike single-unit systems that can sometimes release the entire drug dose at once, multi-unit systems tablets offer a more gradual release [6]. This is because they distribute the drug throughout the digestive tract, avoiding an all-or-nothing emptying scenario. Due to their gradual and distributed release of medication, tablets can reduce the risk of localized mucosal damage, a potential issue when high concentrations of a drug come into contact with the gut wall.

A floating drug delivery system (FDDS) is an advanced method of drug administration that helps improve the bioavailability and therapeutic effectiveness of drugs [7]. It operates on a mechanism where the system remains buoyant in the stomach after oral administration, enhancing the duration of drug release [8]. This system is particularly beneficial for drugs absorbed primarily in the stomach or upper intestine. FDDSs can maintain a consistent drug concentration in the bloodstream, minimizing side effects and reducing dosing frequency. They are often used in treatment plans for diseases requiring prolonged medication, like peptic ulcers and diabetes [9].

The controlled release provided by these multi-unit systems allows for more predictable drug absorption, which can help maintain a steady and therapeutic drug level in the body [10]. Multiple-unit systems offer the possibility of having units with different drug release profiles in the same dosage [11]. This can allow for complex and tailored medication release schedules, which can be beneficial for various disease conditions.

A Gastro Retentive Drug Delivery System (GRDDS) is an advanced approach to controlled drug release, designed to improve the efficacy of medications. The system works by retaining the drug in the stomach for an extended period, allowing prolonged and localized drug release in the upper gastrointestinal tract. GRDDS utilizes various methods like bioadhesive systems, floating systems, swelling or expanding systems, and magnetic systems. This targeted delivery system can be highly beneficial for drugs with narrow absorption windows, poor solubility at alkaline pH, or local action in the stomach, thus optimizing drug absorption, improving bioavailability, and minimizing side effects [12].

Material And Methods

Materials

Cilostazol solid dispersion, Carbopol 934P, Talc, Lactose, Sodium bicarbonate, Citric acid, Magnesium stearate, PVP K30, HPMC K4 M, HPMC K15M, HPMC K100M, all reagents used in the laboratory are laboratory grades.

Compatibility Study

Infrared (IR) Spectra were obtained for a mixture containing Cilostazol, HPMC K4 M, HPMC K15M, and Carbopol 934 P.

A blend of Cilostazol, HPMC K4 M, HPMC K15M, and Carbopol 934 P was combined to create sample mixtures.[101] These mixtures were then incorporated into KBr discs, each containing 1 mg of the sample and 100 mg of KBr. Then, a small portion of the triturated sample was placed into a pellet maker and compressed at 10 kg/cm² pressure. The infrared (IR) spectra were recorded in a range spanning from 4000 to 400 cm^{-1}, with a resolution set at 4 cm^{-1}.[139]

Preparation of swellable and floating gastroretentive tablet

Tablets were prepared by the wet granulation method using HPMC K4 M, HPMC K15M, and HPMC K100M as a release retardant, Carbopol as swelling agents' sodium bicarbonate and citric acid as a gas generating agent, citric acid provides sufficiently acidic medium for sodium bicarbonate react and maintain buoyancy (Table 1). All ingredients were passed through sieve no 60 and mixed in a polybag for 10 minutes, and granulated using PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through a sieve. 14. Thereafter, the drug solid dispersion cilostazol (SD3) was added to the wet granules and mixed thoroughly in a plastic bag. The granules were then dried in a hot air oven at 50°c for 2hr. The dried granules were mixed with magnesium stearate as a lubricant and talc as a glidant. Tablets were compressed using a single-station tablet punch machine.

Table 1: Swellable and floating gastroretentive tablet

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
Solid dispersion of cilostazol	200	200	200	200	200	200
HPMC K100M	25	50	-	-	-	-
HPMC K15M	-	-	25	50	-	-
HPMC K4M	-	-	-	-	25	50
Carbopol 934P	70	45	70	45	70	45
Sodium bicarbonate	15	15	15	15	15	15
Citric acid	10	10	10	10	10	10
Magnesium stearate	3	3	3	3	3	3
PVPK30	10	10	10	10	10	10
Talc	2	2	2	2	2	2
Lactose	15	15	15	15	15	15
Total weight	350	350	350	350	350	350

Optimization of the Formulation Parameters and the Processing
Swellable and Floating gastroretentive tablet

The optimisation study was conducted using the design expert software 13 model. Concentrations of HPMC (X1) and Carbopol 940 P (X2) were chosen as independent variables, while parameters related to gastroretentive behaviour, such as floating lag time (Y1) and % Drug release at 24 hours (Y2), were designated as dependent variables, as illustrated in Table 9. A 2-3 level (32) Box-Behnken design was employed to attain the desired responses. [145,111]

Table 2: Layout of batches by 3^2 full factorial designs

Batch No.	X1	X2
F1	-1	+1
F2	-1	-1
F3	-1	0
F4	+1	-1
F5	+1	-1
F6	+1	0

Table 3: Translation of coded value in an actual unit

Coded value	HPMC	Carbopol 940 P(X2)
+1	25	45
-1	50	70

Table 4: *In-vitro* buoyancy study of optimized batches

Formulation codes	Floating lag time (min)	Total FLT hours
F1	3:10	24
F2	2:41	23
F3	2:45	22
F4	2:49	24
F5	1:17	20
F6	2:10	20

Determination of tablet parameters

To assure the uniformity and mechanical integrity of the tablets, the following parameters were measured: weight variation, hardness, friability, and drug content.

X-RD Analysis of Tablets

XRD is a common technique used in pharmaceutical research and quality control to determine the crystalline structure of the active pharmaceutical ingredient (API) and excipients within a tablet. The prepared tablets were crushed into a fine powder using a mortar and pestle. The sample was homogeneous and free from lumps or aggregates. Place a small amount of the powdered sample onto a flat sample holder. Ensure that the sample is evenly spread and leveled to obtain accurate results. Instrument to the appropriate parameters, such as the X-ray source, wavelength, and scanning range. The typical X-ray source used is copper (Cu Kα) radiation. The XRD instrument will generate a diffraction pattern, which is a plot of intensity versus angle (2θ). This pattern provides information about the crystalline structure of the sample. Analyze the diffraction pattern to identify the peaks and calculate their 2θ values. Compare the obtained diffraction pattern with reference patterns of known compounds to identify the crystalline phases present in the tablet. Interpret the results to determine the type and quantity of crystalline and amorphous phases in the tablet.[143]

Differential Scanning Calorimetry (DSC) Analysis of tablets

Crush the tablet into a fine powder using a mortar and pestle. The sample was homogeneous and free from lumps or aggregates. A small amount of powdered sample (usually a few milligrams) was accurately weighed using an analytical balance. The weights of the samples were recorded. The weighed sample was placed in a DSC pan was sealed carefully to prevent any air from entering, as this can affect the analysis. Typically, a hermetic seal or crimp is used. DSC instrument and allowed it to stabilize. Instrument parameters, including the heating rate and temperature range, were set. The typical heating rate was 10°C/min, and the temperature range depended on the expected thermal events in the sample. The sample and reference pans were placed in the DSC instrument. This involved heating the sample and reference pans simultaneously at a specified heating rate. The heat flow difference (ΔH) between the sample and reference pans was monitored as a function of the temperature. The data were recorded using a DSC thermogram. The DSC thermogram was analyzed to identify thermal events such as melting peaks, crystallization, glass transitions, and other phase transitions. The onset temperature, peak temperature, and enthalpy change associated with each thermal event are measured. Melting points, heat of fusion, and any interactions between components were measure**.**[146,147]

***In-vitro* drug release studies**

Study on *in-vitro* dissolution, the United States Pharmacopeia (USP) type II (paddle) apparatus was used for the in vitro dissolution investigation, and a rotational speed of 100 rpm was used. The tablet was put inside a vessel that contained 900 ml of 0.1N HCl as the dissolution media, keeping the temperature at 37±0.5 °C. For 24 hours, 5 ml of the sample was taken out at predetermined intervals and replaced with new dissolving media. A UV spectrophotometer was used to test the samples' absorbance at 258 nm. Three tablets were used in the release studies, and the mean values obtained were plotted against time

Stability studies

Stability application of the enhanced preparation remains conceded out as conforming to the ICH recommendations, at 40˚C/75% RH stability chambers for 3 months. The carried remain observed for drug content, floating behavior and *in vitro* drug release profile The optimized F4 formulation was subjected to accelerated stability conditions for 3 months at 40˚C/75% RH stability chamber, at the interval of 1-month tablets were taken and evaluated for various parameters like thickness, diameter, weight variation, hardness, content uniformity and dissolution. The tablets had shown slight variation in the tested parameters, and the results were within the limits. Comparison of physical parameters for optimized formulation F4.

***In-vivo* studies**

In-vivo studies were conducted in New Zealand male rabbits weighing 2 kg and obtained approval from the Institutional Animal Ethical Committee (P.Col/48/2022/IAEC/VMCP).

***In-vivo* buoyancy studies**

An x-ray imaging study was conducted to investigate the in vivo buoyancy of prepared floating tablets in the stomach, utilizing three New Zealand rabbits as test subjects. To enable the observation of the exact position and condition of the floating tablets, barium sulfate was incorporated into the F4 formulation. Before the x-ray imaging studies, the rabbits underwent a fasting period of 36 hours, during which they had free access to water. After this fasting period, each rabbit was orally administered a floating tablet containing barium sulfate, along with an adequate quantity of water. Subsequently, abdominal radiographs were taken at specific time intervals: 0 hr, 2 hr, 4 hr, 6 h, 8hr, 10h, 12hr and 24 hrs after tablet administration. The use of barium sulfate in the tablet formulation allowed researchers to visualize and track the movement of the floating tablets within the rabbits' stomachs over time, providing valuable insights into their buoyancy properties and behavior in the gastric environment.

***In-vivo* pharmacokinetics-study**

In this study, the researchers aimed to compare the performance of two different formulations of the drug Cilostazol. The formulations under investigation were compression floating bioadhesive tablets and immediate-release marketed tablets. To conduct this comparison. The study involved the use of New Zealand male rabbits, which were divided into two groups, each containing 6 animals. In the first phase of the study, group I animals were administered immediate-release marketed with a 100 mg dose of cilostazol, while group II received (F4) compression floating tablets with the same 200 mg dose. In the second phase of the study, the administration was switched, so group I received the compressed floating tablets while group II received the immediate-release marketed tablets. The blood samples were collected from the rabbits' marginal ear veins at specific time points after the oral administration of the respective formulations. The sampling time points were at 2, 4, 6, 8, 12, and 24 hours post-oral dose. The blood samples were collected in EDTA-coated Eppendorf tubes to prevent clotting. After collection, the blood samples were centrifuged at 4000 rpm for 15 minutes to separate the plasma, which was then stored at -20°C until further analysis.

HPLC analysis of Cilostazol in plasma

The plasma concentration of Cilostazol from the provided samples was assessed via a slightly modified version of the High-Performance Liquid Chromatography (HPLC) method as suggested by Chella and colleagues. 1 ml of acetonitrile was introduced to 1 ml of the plasma sample, which was then centrifuged at a speed of 3000 rotations per minute for 10 min. After centrifugation, the supernatant was extracted, filtered using a 0.2 µm filter, and 20 µl of this filtered liquid was injected into the Shimadzu HPLC system for analysis. This HPLC device, manufactured by the Shimadzu Corporation based in Kyoto, Japan, is fitted with a C18 column and an ultraviolet (UV) detector. For the mobile phase, we used a combination of acetonitrile and water at a ratio of 55:45 (v/v). This mixture's pH was regulated to approximately 3.2 with diluted ortho-phosphoric acid. The resultant eluents were inspected at a wavelength of 250 nm and a flow rate of 0.8 ml per minute.

Pharmacokinetic analysis

The pharmacokinetic parameters were determined using Kinetica software. The peak plasma concentration (Cmax) and the time taken to reach this peak (Tmax) were directly obtained from the graph of time versus plasma concentration. The area under the concentration versus time curve (AUC) and the area under the first moment curve (AUMC) were calculated using the trapezoidal rule. Mean residence time (MRT) and relative bioavailability were also determined. Both the immediate release and floating tablets were analyzed using analysis of variance (ANOVA) to compare their pharmacokinetic parameters. A statistically significant difference was considered if the p-value was less than 0.05. To assess the correlation between in vitro and in vivo performance, the in vitro cumulative percent of drug release of F4 compression floating tablets was compared with the extent of absorption, represented by cumulative AUC values of the same formulation. This comparison was made to demonstrate the in vitro and in-vivo correlation (IVIVC).

Results And Discussion

Infrared (IR) Spectra were obtained for a mixture containing Cilostazol, HPMC K4M, HPMC K15M, and Carbopol 934 P

Peaks in an IR spectrum correspond to specific vibrational modes of chemical bonds, aiding in the identification of functional groups. The fingerprint region, typically ranging from 1500 to 400 cm^{-1}, features distinctive peak patterns crucial for compound identification. Cilostazol therapeutic agent, HPMC K4M, and HPMC K15M, polymer, as well as Carbopol 934 P, a polymer not showing any interaction (Figure 7.5.1).[101]

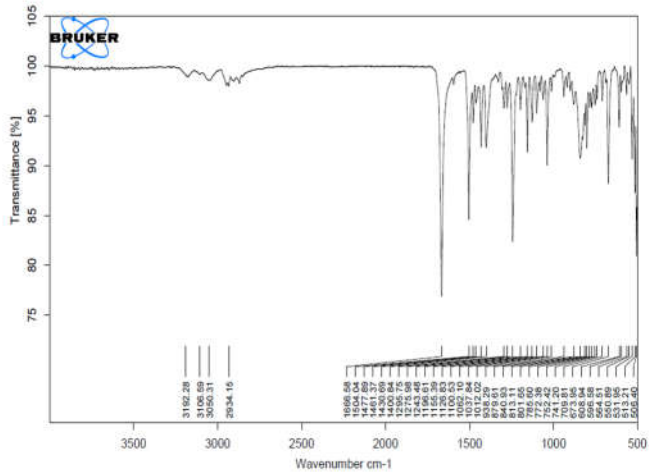

Figure 1: Infrared (IR) Spectra were obtained for a mixture containing Cilostazol, HPMC K4M, HPMC K15M and Carbopol 934 P.

Evaluation of Swellable, floating gastroretentive tablet

Table 2 displays the comprehensive evaluation of physical parameters for the prepared floating tablets. The results indicate that all the tablets exhibited uniformity in weight variation and drug content.

Table 5. Hardness, thickness, avg wt. variation, friability, floating lag, and floating duration for different formulations of cilostazol tablets

Formulation code	Hardness (kg/cm2)	Thickness (mm)	Avg weight variation (mg)	Friability	Floating Lag time (Min: Sec)	Floating duration (hrs.)	Drug content
F1	4.4	3.2	349.8±0.2	0.61	3:10	24	97.12
F2	4.2	3.6	349.6±0.4	0.61	2:41	23	98.10
F3	4.1	3.3	350.4±0.4	0.52	2:45	22	98.21
F4	3.9	3.5	350.6±0.6	0.62	2:49	24	99.43
F5	4.2	3.1	349.6±0.4	0.67	1:17	20	99.33
F6	3.9	3.3	350.2±0.2	0.63	2:10	20	99.21

Optimization of Swellable and Floating Gastroretentive tablets

Data analysis for the optimization of floating gastroretentive swellable tablets involved fitting the responses observed from six different formulations software design Expert 13. The outcomes, including r^2 values, degrees of freedom, and coefficients of variance (%), have been presented in Table 7.6.2. The ANOVA results

displayed in Table 14 indicate that the models significance extended to all three response variables, affirming its relevance in the context of the dependent variables.

Table 6: Result of ANOVA

Response model	Sum of square	Degree of freedom	Mean square	F value	P value	R square	Ade. precision
Floating Lag time	17.71	6	2.95	0.238	0.0026	0.2806	4.442
% Drug release	970.01	1	769.20	2.18	0.0046	0.9721	5.212

Tablet floating log time and various variables design, expert software was used. Significant p-value (0.0045) plot of surface and contour plot is cited in Figure 7.6.2.1 to 7.6.2.4. it can be observed that both HPMC(X1) and Carbopol 940 P (X2) have a good floating. Moreover, importance of the polymer Carbopol 940 P had non-significant effect of lag time tablet float means increase Carbopol 940 amount (X2) will be accompanied by significant reduction in nature of floating due to the hydrophilic nature of Carbopol 940P produces faster medium penetration rate, and thus, shorter time for gel layer formation. Mathematical relationship of polynomial equation for the measured response lag time of tablet surface ness obtained and given in equation 3 below. Positive sign of X in the regression equation indicated agonistic effect and negative sign of X in the regression equation indicated antagonistic various variables on response.[145]

F-value model of 2.15 implies the model no any relations to polymer variation. 16.30% F-values due to polymer changes.

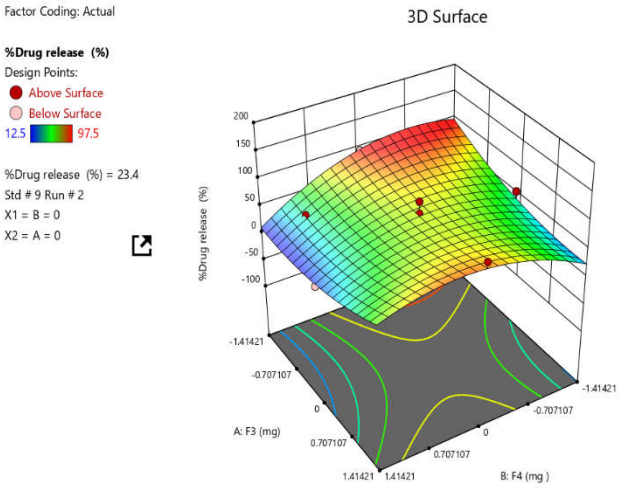

Figure 2: A counter levels of independent variables to gain a fixed value of % drug release, floating lag time

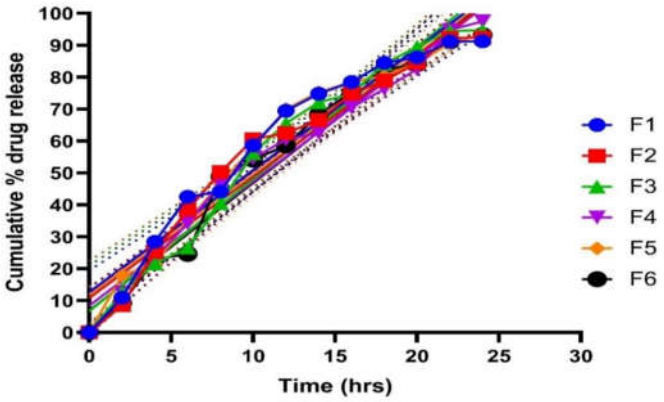

Figure 3: Cumulative % drug released of F1 to F6 (Swellable)

A one-way ANOVA was conducted to analyze the data, with three different formulations being evaluated. The values presented in the results represent the mean standard deviations (SD). Significance was observed within each formulation, as indicated by p-values < 0.05, while there was no significant difference observed between the different formulations.

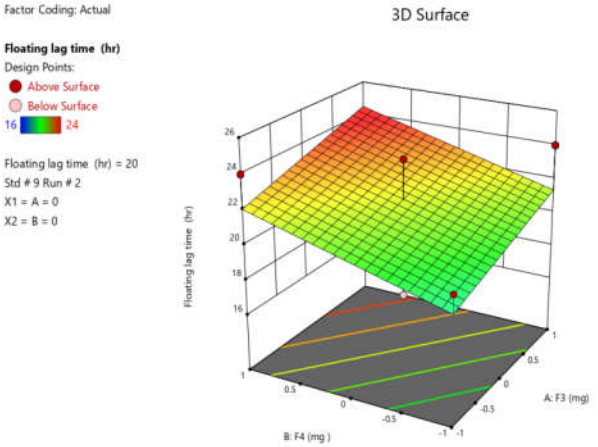

Figure 4: A plot illustrating the link between multiple layers of independent variables to obtain a fixed value of floating lag time.

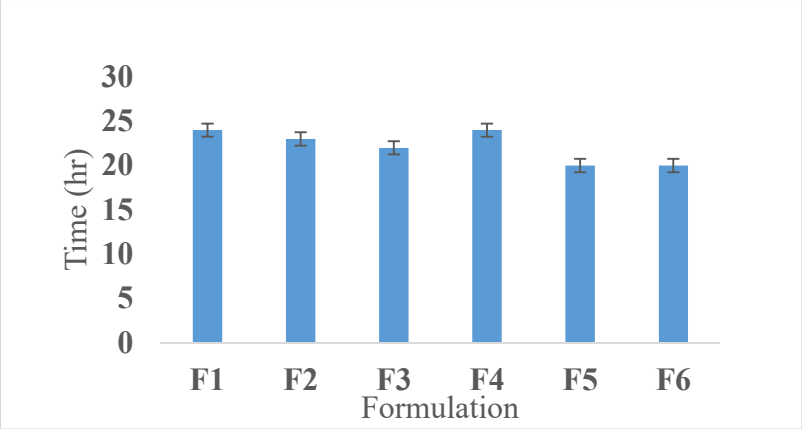

Figure 5: *In-vitro* buoyancy test

A one-way ANOVA was conducted data, with six different formulations being evaluated. The values presented in the results represent the mean standard deviations (SD). Significance was observed within each formulation, as indicated by p-values < 0.05, while there was no significant difference observed between the different formulations.

XRD Analysis

The X-ray diffraction (XRD) patterns of the tablets closely matched those calculated from their respective single crystal structures, providing strong confirmation of the crystalline nature of the tablets. In the case of DES, the slight displacement of experimental peaks towards lower 2θ angles was attributed to the thermal expansion of the unit cell. This was a result of the experimental PXRD data being obtained at 298 K, while the crystal structure had been determined at 100 K (46). When tablets were compressed at 300 MPa, a significant number of diffraction peaks were evident in their XRD patterns. The variations in peak intensities were explained by the preferential orientation of crystals within the samples. Notably, distinct XRD peaks, characteristic of the tablets, were prominently visible in the patterns of the compressed tablets, without any extraneous peaks being detected. This observation indicated that the crystals within the tablets remained stable in phase even under the compression conditions (Figure 6.).

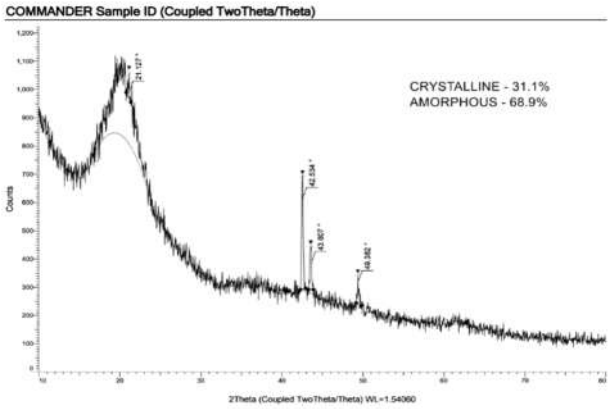

Figure 6: X-ray diffraction pattern of Optimized tablet (F4)

7.7.7. DSC analysis of Pure Cilostazol and formulation F4

The DSC thermograms of both the pure therapeutic molecule and the formulated drug showed melting points of 170°C and 169°C, respectively. The minimal difference in melting points between the drug's isolated form and its form within the formulation suggests that the drug likely maintains its pure state within the formulation, without undergoing significant interactions with the polymers (Figure 7 and 8).

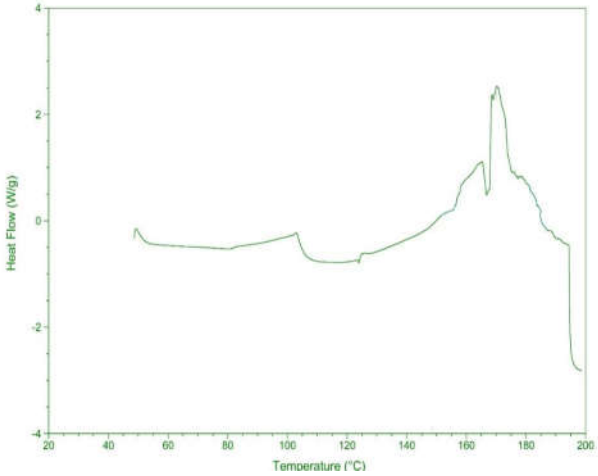

Figure 7: DSC spectrum of pure drug

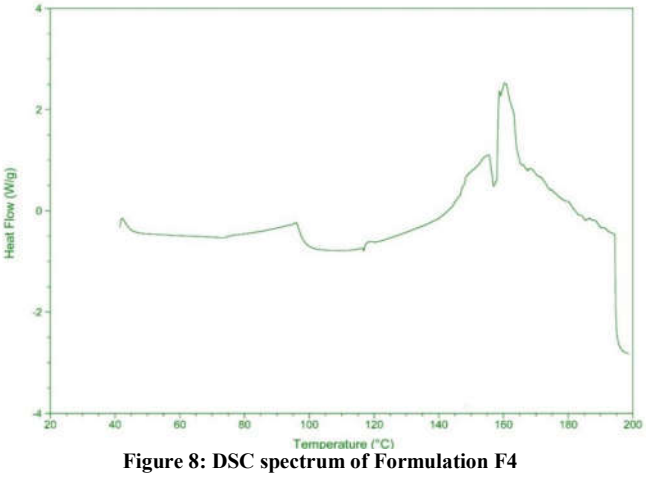

Figure 8: DSC spectrum of Formulation F4

The *In-Vitro* Drug Release Profile for the formulation

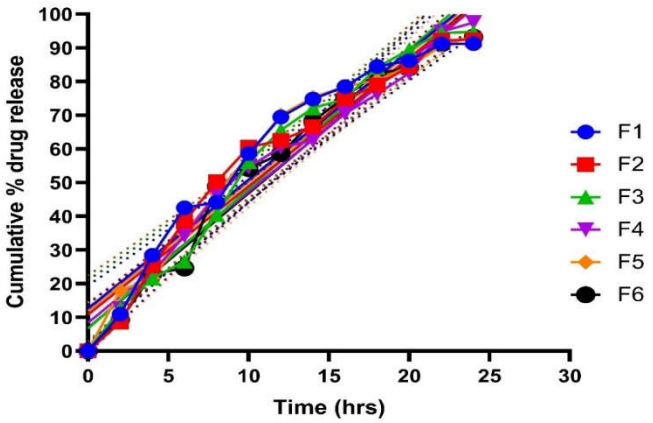

Figure 9: Cumulative % drug released of F1 to F6 (Swellable)

A one-way ANOVA was conducted to analyze the data, with six different formulations being evaluated. The values presented in the results represent the mean standard deviations (SD). Significance was observed within each formulation, as indicated by p-values < 0.05, while there was no significant difference observed between the different formulations

Stability studies

The optimized F4 formulation was subjected to accelerated stability conditions for 3 months at 40 °C/75% RH stability chamber. at the interval of 1 month, tablets were taken and evaluated for various parameters like thickness, diameter, weight variation, hardness, content uniformity, and dissolution. The tablets had shown slight variation in the tested parameters, and the results were within the limits (Table 7).

Table 7: Comparison of physical parameters for optimized formulation F4

Parameter	F4	40 °C/75% RH		
		At the end of 1st month	At the end of 2nd month	At the end of 3rd month
Thickness (mm)	3.5±0.3	3.5±0.31	3.7±0.32	3.6±0.31
Hardness (kg/cm^2)	3.9±0.2	3.9±0.11	3.8±0.20	3.7±0.22
Friability (%)	0.62±0.14	0.61±0.12	0.60±0.10	0.62±0.13
Weight Variation (mg)	350.6±0.6	351.6±0.12	350.8±0.18	350.7±0.18
Content Uniformity	99.43±0.21	99.20±0.17	99.11±0.11	99.38±0.12

Table 8: Dissolution data of F4 batch at 40 °C/75% RH comparison of physical parameters for optimized formulation F4

Time (hr)	Cumulative % Drug Release		
	At the end of 1st month	At the end of 2nd month	At the end of 3rd month
2	12.5±0.2	12.2±0.2	12.1±0.2
4	23.4±0.1	22.7±0.1	22.9±0.1
6	34.25±0.3	32.1±0.3	33.9±0.3
8	46.5±0.2	44.2±0.2	46.1±0.2
10	54.6±0.4	52.3±0.4	51.9±0.4
12	60.54±0.2	58.5±0.2	59.2±0.2
14	62.5±0.2	60.4±0.2	61.8±0.2
16	70.5±0.5	71.9±0.5	69.9±0.5
18	76.32±0.2	74.7±0.2	78.2±0.2
20	82.5±0.3	85.5±0.3	86.7±0.3
22	94.8±0.4	93.8±0.4	91.2±0.4
24	97.50.1	96.3±0.1	94.4±0.1

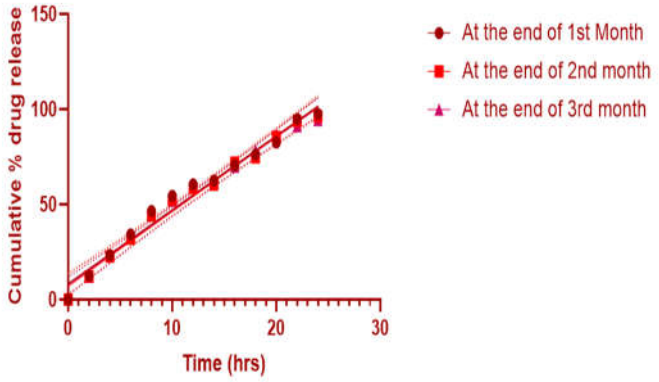

Figure.10. Dissolution data of F4 batch at 40 °C/75% RH Comparison of physical parameters for optimized formulation F4.

The *In-Vivo* Drug Release profile for the Swellable and Floating Gastro-retentive tablet formulation

In-vivo, the research identified all useful and possible pharmacokinetic parameters for the F4 tablet. Figure.11. shows the plasma drug concentration-time profile of a Swellable floating tablet.

Table 9: *In-vivo* drug release profile for the swellable & floating gastroretentive tablet formulation

Time (hr)	Plasma concentration (ng/ml)
0	0
2	125
4	345
6	523
8	645
10	341
12	256
24	25

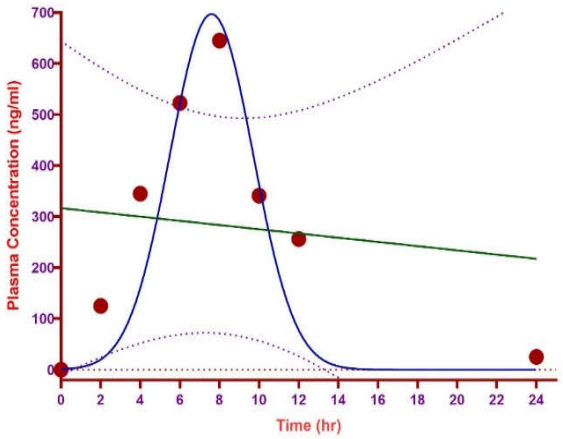

Figure 11: Plasma drug concentration-time- time profile of F4 tablet

7.17. *In-Vivo* Buoyancy Studies

In-vivo buoyancy studies play a pivotal role in the assessment of floating drug delivery systems, particularly those designed for prolonged gastric retention. These studies provide critical insights into how these specialized formulations behave within the complex physiological environment of living organisms. In-vitro studies can provide initial insights into buoyancy, but they cannot replicate the dynamic conditions and physiological responses of the living body. In-vivo studies bridge this gap, offering a comprehensive understanding of how formulations interact with gastric fluids, adapt to peristaltic movements, and maintain their buoyant properties over time. Any discrepancies between in-vitro and in-vivo observations can guide further refinement of the formulations. Additionally, the correlation between gastric retention time and drug absorption kinetics can provide valuable insights into the therapeutic benefits of the formulation. In-vivo buoyancy studies represent a critical stage in the development of floating drug delivery systems. These studies offer a dynamic perspective on how formulations interact with the gastrointestinal environment within living organisms.

Utilizing X-ray imaging, barium sulphate was employed as a tracer to explore the tablets performance within the stomach.[97,98] The X-ray images distinctly showcased the tablets structural integrity, with no indications of deterioration or compromise.Moreover, these images provided unequivocal evidence of the tablets' buoyancy, as they maintained their position and floated seamlessly within the stomach environment for an extensive duration of around 24 hours (Figure 12).

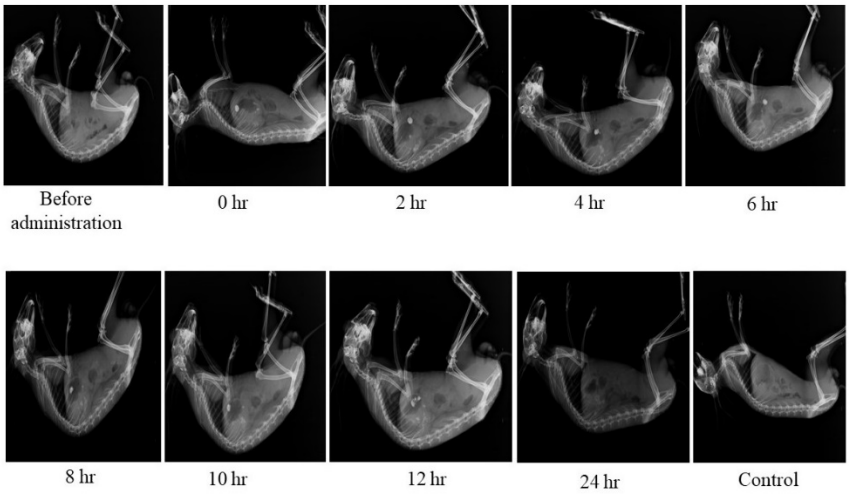

Figure 12: *In-vivo* buoyancy test of Cilostazol floating tablet

In-Vitro and *In-Vivo* Correlation

F4 floating tablets, a meticulous evaluation of *in vivo* and *In vivo* correlations was undertaken. The graphical representation yielded a correlation coefficient (r^2) of 0.9598 indicative of a robust association between the *in vitro* and *in vivo* attributes.

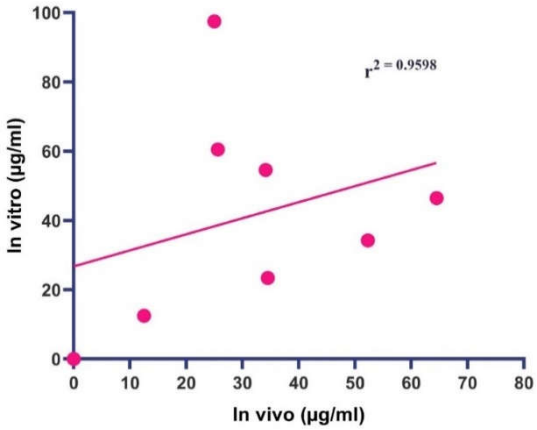

Figure 13: *In-vitro* and *In-vivo* correlation of F4

Comparison of Pharmacokinetic Profiles of Oral administration of Swellable and Floating Cilostazol tablet (F4) and Marketed Cilostazol tablet

The pharmacokinetic parameters of F4 tablets (swellable and floating tablets) and marketed tablet (Cilodoc) are presented in Table 7.19 and in Figure 7.19.1. The drug content in plasma was analysed by HPLC method.

Table 10: Plasma Drug Concentration Time Profile (F4 and Marketed Tablet)

Time (hr)	Plasma Drug Concentration (µg/ml) F4	Plasma Drug Concentration (µg/ml) Marketed Tablet-CILODOC
0	0	0
2	12.5	11
4	34.5	48.9
6	52.3	24.5

8	64.5	5
10	34.1	2
12	25.6	
24	2.5	

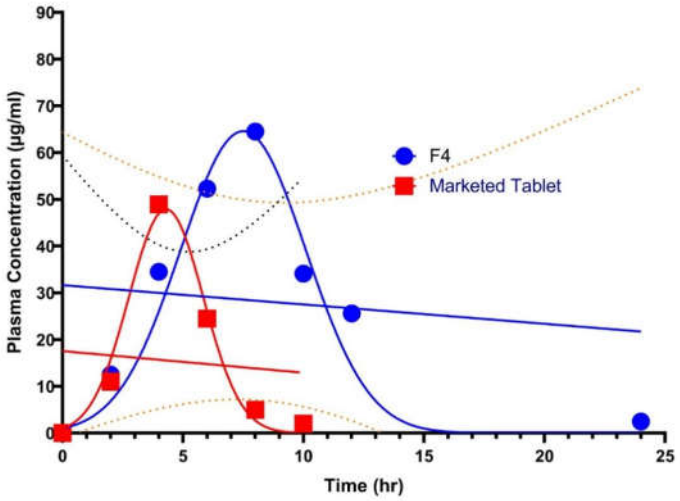

Figure 14: Comparison of pharmacokinetic profiles of oral administration of Swellable and floating tablets F4 and marketed Cilostazol tablet.

Table 11: Pharmacokinetic Profile of Cilostazol Swellable and Floating tablet and Marketed tablet

Parameters	F4 -Optimized tablets	Marketed tablets	P<
C_{max} (µg/ml)	64.5 ± 2.1	48.9 ± 2. 68	0.05
T max (hrs.)	8.09 ± 0.01	4.01 ± 0.01	0.05
$AUC_{0-\infty}$ (µg.h^2/ml)	577.5 ± 1.12	169.8± 2.2	0.05
MRT (hrs.)	9.19± 0.03	5.34± 0.02	0.05
$AUMC_{0-\infty}$ (µg.h^2/ml)	5309.92 ± 3.02	908± 01.12	0.05

+

Discussion

In the physical parameter evaluations, all tablets demonstrated consistency in weight variation and drug content, indicating successful formulation.[153] The formulations also displayed varying levels of hardness, thickness, friability, floating lag time, and floating duration, all of which are important factors in the design and performance of drug delivery systems. Stability studies demonstrated that the F4 formulation remained stable under 40 °C temperature and humidity conditions for three months, with minimal changes in physical parameters. In vivo buoyancy studies using X-ray imaging confirmed the tablets' ability to float in the stomach for approximately 24 h, which is crucial for their gastroretentive properties.

In the pharmacokinetic study, a significant increase in C_{max} and $AUC_{0-\infty}$ and a delay in T_{max} were observed with the F4 floating tablet compared with the marketed tablets. This suggests that floating tablets can maintain higher plasma concentrations of Cilostazol for a longer duration, which may result in improved efficacy. A good correlation (r^2=0.9598) was found between the in vitro drug release and in vivo absorption of the drug, implying a strong in vitro-in vivo correlation. This is significant, as it indicates that *in-vitro* tests can be reliable predictors of in vivo behaviour. One-way ANOVA was conducted to analyse the data with the F4 and marketed formulation. No significance was observed between the F4 and marketed formulation, as indicated by p-values <0.05. The results also showed no significant differences between the different formulations. Overall, these results indicate that the F4 floating tablet formulation was successful in achieving the intended objectives for a gastroretentive drug delivery system. However, before moving forward, these results should be confirmed in further preclinical and clinical studies.

Conclusion

The present study successfully demonstrated the preparation and evaluation of a swellable and floating gastroretentive tablet of cilostazol. The incorporation of different grades of HPMC, along with Carbopol 934P and sodium bicarbonate, allowed the formulation to maintain buoyancy and modulate the drug release effectively. The in vitro studies confirmed the controlled drug release up to 24 hours and a good floating ability of the tablets, which is crucial for the gastroretentive drug delivery system. The stability studies proved that the optimized formulation F4 retained its key attributes and complied with the pharmacopoeial standards even after exposure to various stress conditions. The in-vivo studies in rabbits showed that the tablets remained buoyant in the stomach for approximately 24 hours, which confirmed the in vitro findings. The pharmacokinetic studies indicated that the prepared floating tablets improved the bioavailability of cilostazol, showing a clear advantage over the conventional immediate-release tablets. Finally, the in-vivo and in-vitro correlation study demonstrated a high degree of correlation, affirming that the in-vitro dissolution study can be a predictive tool for in-vivo performance. The overall results suggest that the prepared floating tablets of cilostazol using the wet granulation method may be a promising approach for prolonging the gastric residence time and achieving controlled drug release, which could potentially enhance the therapeutic efficacy and patient compliance. However, additional clinical studies in humans are required to further substantiate these findings.

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