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PREPARATION AND *IN-VITRO* CHARACTERIZATION OF SOLID DISPERSION TABLETS OF CILOSTAZOL TO IMPROVE RELEASE APPROACHES BY FLOATING SYSTEMS

ANJANA MN[1*], KUMAR M[2] AND MATHEWS SM[3]

1: Department of Pharmaceutics, Pushpagiri College of Pharmacy, Thiruvalla, 689101 Kerala, India

2: Department of Chemistry, Vinayaka Mission's College of Pharmacy, Vinayaka Mission's Research Foundation, (Deemed to be University) Salem, Tamil Nadu, 636008, India

3: Department of Pharmaceutics, Pushpagiri College of Pharmacy, Thiruvalla, 689101, Kerala, India

***Corresponding Author: Dr. Anjana M N: E Mail: anjanamn81@gmail.com**

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ABSTRACT

The research focused on improving the floating capabilities of Cilostazol, a drug used for its antiplatelet and vasodilatory effects, through the preparation of solid dispersion (SD) tablets using three different approaches: effervescent, sublimation, and effervescent with swelling system control release. First prepared SDs of Cilostazol using hydroxypropyl methylcellulose (HPMC) as a carrier in various ratios. These SDs were then characterized in vitro to assess their solubility, drug content percentage, and dissolution studies. It was observed that the dissolution rate significantly increased with the use of entirely SDs, indicating the effectiveness of this approach. Tablets were formulated using the optimized SD products, and various parameters were evaluated to determine the quality of the formulations. Among all the tablet formulations, the F4 formulation exhibited the best results in terms of pre-compression and post-compression parameters. It possessed the desired qualities of a good swellable and floating gastroretentive tablet, which led to its selection as the best formulation. The release data obtained from the in vitro studies were fitted into several kinetic models to elucidate the release

mechanism. The F4 formulation demonstrated zero-order release, indicating a consistent and controlled drug release profile. From the findings, it can be concluded that the use of swellable and floating gastroretentive tablets containing SDs of Cilostazol can effectively achieve the desired therapeutic objective. By improving the drug's dissolution rate and controlling its release, these formulations offer potential benefits for enhancing the drug's efficacy and therapeutic outcomes.

Keywords: Solid dispersion, Sublimation, Effervescent, Swelling, Floating Capability, Tablet

INTRODUCTION

The main objective of the work is to increase the solubility of Cilostazol **[1]**, a drug with low solubility and higher permeability, a biopharmaceutical classification system (BCS class-II drug) **[2]**. This is important because poor drug solubility can lead to low bioavailability and challenges in dosage form development. By increasing the solubility of Cilostazol, its bioavailability can be improved, resulting in more effective and reliable treatment **[3-5]**. This is particularly crucial for long-term treatment of conditions like ischemic stroke, where Cilostazol is a safer and more effective medication compared to aspirin. The half-life of Cilostazol, which is approximately 11 hours, also plays a role in its effectiveness. By enhancing the solubility of the drug, its therapeutic concentration can be maintained for a longer duration, leading to sustained efficacy and desired pharmacological effects **[6]**. Development of novel formulations or modification of existing formulations to enhance drug solubility. This can involve the selection of suitable excipients, solubilizers, or co-solvents that improve the drug's solubility and dissolution rate—formulation of Cilostazol as solid dispersions with hydrophilic carriers or polymers **[7]**. Solid dispersions can improve drug solubility by dispersing the drug molecule in a hydrophilic matrix, facilitating its dissolution upon administration **[8]**. Cyclodextrins, such as hydroxypropyl-β-cyclodextrin, are utilized to form inclusion complexes with Cilostazol. Cyclodextrins can encapsulate the drug molecule, enhancing its solubility and stability, and designing and synthesizing prodrugs of Cilostazol that possess improved solubility properties.

MATERIAL AND METHODS

Materials

Cilostazol, HPMC K4 M, HPMC K15M, and HPMC K100M, all reagents used in the laboratory, are laboratory grades.

Preparation of Cilostazol Solid Dispersion

A conventional fusion method was used to prepare the solid dispersion (SD) of Cilostazol and PVPK30. The 1:1, 1:2, 1:3 and 1:4 (Code: SD1, SD2, SD3 and SD4)

W/W Cilostazol and PVPK30 ratio were selected for the preparation of SD. Cilostazol and PVPK30 were dissolved in an adequate amount of methanol. The methanol solvent was then rapidly evaporated using mild heat and surface airflow while vigorously stirring to form a uniform solid mass. The co-precipitate was crushed into fine particles and removed moisture stored in a vacuum desiccator for 24 hr. Solid particles sieved (sieved: 80) and stored in a desiccator until further use.

Formulation of gastroretentive floating tablets using three different approaches

Preparation of gastroretentive tablets by using an effervescent approach

Tablets were prepared by the wet granulation method using HPMC K4 M, HPMC K15M, and HPMC K100M as a release retardant, sodium bicarbonate and citric acid as a gas generating agent, citric acid provides a sufficiently acidic medium for sodium bicarbonate reactant, and maintains buoyancy. The composition of various formulations is given in Table 1. All ingredients were passed through sieve no 60 and mixed in a polybag for 10 min and granulated using PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through sieve no 40. 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, talc as a glidant tablets were compressed using a single-station tablet punch machine.

Table 1: Preparation of gastroretentive tablets by using an effervescent approach

Ingredients	Formulation code					
	A1	A2	A3	A4	A5	A6
SD3 (solid dispersion of cilostazol)	200	200	200	200	200	200
HPMC K100M	75	50	-	-	-	-
HPMC K15M	-	-	25	50	-	-
HPMC K4M	-	-	-	-	25	50
Sodium bicarbonate	30	55	80	55	80	55
Citric acid	10	10	10	10	10	10
Magnesium stearate	5	5	5	5	5	5
PVPK30 in isopropyl alcohol	10	10	10	10	10	10
Talc	5	5	5	5	5	5
Lactose	15	15	15	15	15	15
Total weight	350	350	350	350	350	350

Preparation of a swellable and floating gastroretentive tablet

Tablets were prepared by the wet granulation method using HPMC K4 M, HPMC K15M, and HPMC K100M as release retardants, Carbopol as swelling agents, sodium bicarbonate and citric acid as gas-generating agents, citric acid provides a sufficiently acidic medium for sodium bicarbonate to react and maintain buoyancy. The composition of various formulations is given in Table 2. 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 no. 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, talc as a glidant. Tablets were compressed using a single-station tablet punch machine.

Table 2: Swellable and floating gastroretentive tablet

Ingredients	Formulation code					
	F1	F2	F3	F4	F5	F6
SD3 (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 in isopropyl alcohol	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

Preparation of gastroretentive tablets by the sublimation method

Floating tablets were prepared by the wet granulation method. The composition of various formulations is given in Table 3. HPMC K4 M, HPMC K15M, and HPMC K100M as a release retardant. MCC and Lactose as glidant, 100 mg camphor was mixed with the mixture was then mixed in a polybag, and the mixture was passed through mesh (No.40). Granulation was done using a solution of PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through mesh No. 16. 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 at 50ºC for about 2 h with a residual moisture content of 2 to 3% w/w. The dried granules were then mixed with magnesium stearate and talc for 2 min. Tablets were compressed at 200 mg weight. The hardness was kept constant and measured with a hardness tester (Monsanto hardness tester). The diameter and thickness of prepared tablets were maintained between 10 mm and 7 mm. The tablets were sublimated in a 60°C Hot air oven, and the weight of the tablets was measured at regular time intervals. Tablets with a final weight equal to the theoretical weight after complete sublimation were selected for further experiments. In this study, camphor was completely sublimated within 24 hrs.

Table 3: Sublimation method

Ingredients	Formulation code					
	B1	B2	B3	B4	B5	B6
SD3(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 in isopropyl alcohol	10	10	10	10	10	10
Talc	2	2	2	2	2	2
Lactose	15	15	15	15	15	15
Camphor	100	100	100	100	100	100
Before Sublimation	400	400	400	400	400	400
After sublimation total weight	350	350	350	350	350	350

Preparation of a standard calibration curve of Cilostazol.

Preparation of simulated gastric fluid P^H 1.2

Before performing the test for floating tablets, a standard curve of cilostazol in simulated gastric fluid P^H 1.2 was constructed.

Preparation of simulated gastric fluid P^H 1.2

The simulated gastric fluid was prepared by dissolving sodium chloride 3 grams in about 1450 ml of deionized water and then adjusting p^H to 1.2±0.1 with diluted hydrochloric acid.

Determination of absorption maxima (λ max) for cilostazol

A 1ml aliquot of solution standard solution stock solution-II was diluted to 10ml to give 10 µg/ml standard solutions of simulated gastric fluid, pH 1.2. This solution was scanned on a UV-Visible spectrophotometer against the respective media blank. An absorption maximum (λ max) of 258nm was obtained for all solutions and was selected to prepare the standard curve.

Preparation of calibration curve of cilostazol in simulated gastric fluid pH 1.2

50 mg of drug (Cilostazol) was accurately weighed and dissolved in 100 ml of simulated gastric fluid pH 1.2 to yield a 500 µg/ml solution, which was used as a standard solution. From this solution, 10 ml was taken and diluted to 100 ml with simulated gastric fluid pH 1.2 to obtain a solution with a concentration of 50 µg/ml, which was used as the standard solution. Aliquots of standard solution (0.4, 0.8, 1.2, 1.6, 2.0 ml) were added to a series of 10 ml volumetric flasks and made up to 10 ml using simulated gastric fluid pH 1.2. At 258 nm, the absorbance of these solutions was measured in comparison to a reagent blank **(table)**. A standard curve was drawn between concentration and absorbance

(Figure 3). A straight line through the origin is obtained.

Characterization of granules, Drug-polymer interaction studies

To study the interaction between drug and polymer, an interaction study was performed. drug drug-polymer study was carried out according to the following procedure. The drug and polymer were mixed in a 1:1 ratio and put into the glass vials. The glass vials were sealed and placed in the stability chamber at 40°C and 75% RH for 21 days. The sample was analysed for colour change, liquification, and bad odours after 7, 15, and 21 days. The IR spectra were taken after 21 days and analysed for any shift in major peaks. No shift was observed in the IR spectrum, and no additional peak was observed, indicating no interaction between the drug and polymer.

Evaluation of granules' properties, pre-compression parameters, and Angle of repose

It is defined as the maximum angle possible between the surface of the pile of powder and the horizontal plane. The fixed funnel method was used. A funnel was fixed to its tip at a given height 'h, above a flat horizontal surface to which a graph paper was placed. The powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using the following equation

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

Where, h=height of the pile, r=radius of the pile, θ=angle of repose.

Bulk density

It is a ratio of the mass of powder to bulk volume. The bulk density depends on particle size distribution, shape, and the cohesiveness of particles.

$$\text{Bulk density} = \frac{\text{mass of the powder}}{\text{bulk volume of the powder}}$$

Tapped density

10gm of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height, and the tapped volume was read. It is expressed in g/mL and is given by.

$$\text{Tapped Density} = \frac{\text{mass of the powder}}{\text{Final tapping volume of the powder}}$$

Compressibility index (Carr's index)

The compressibility index is used as an important parameter to determine the flow behavior of the powder. It is indirectly related to the relative flow property rate, cohesiveness, and particle size. It is a Simple, fast, and popular method for predicting flow characteristics. Carr's index can be represented.

$$\text{Carr's Index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} X100$$

Hausner's Ratio

It is the ratio of tapped density to bulk density. It is given by

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post-compression parameters

Weight variation

Twenty (20) tablets from each batch were individually weighed in grams on an analytical balance. The average weight and standard deviation were calculated, individual weight of each tablet was also calculated using the same method and compared with the average weight.

Hardness

Hardness or tablet crushing strength, the force required to break a tablet in a diametric compression) was measured using a Monsanto tablet hardness tester. It is expressed in kg/cm^2.

Thickness

The thickness of the tablets was measured using a vernier caliper. It is expressed in mm.

Friability (F)

Twenty (20) tablets were selected from each batch and weighed. Each group of tablets was rotated at 25 rpm for 4 minutes (100 rotations) in the Roche Friabilator. The tablets were then dusted and re-weighed to determine the loss in weight. Friability was then calculated as per weight loss from the original tablets. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} X100$$

Swelling index or water-uptake studies

The individual tablets were weighted accurately and kept in 50 ml of water. Tablets were taken out carefully after 60 minutes, blotted with filter paper to remove the water present on the surface and weighed accurately. Percentage swelling (swelling index) was calculated by using the formula.

$$\text{Swelling index} = \frac{W_{wet} - W_{dry}}{W_{dry}} X100$$

Floating lag time

The floating abilities of single tablets were determined in 500 ml pre-warmed 0.1 N HCl, and shaken at 70 rpm, 37 ± 0.5°C for 24 hrs, using a shaker apparatus. The floating lag time and duration were measured by visual observation. The time taken for the dosage form to emerge on the surface of the medium is called the floating Lag Time (FLT) or total duration of time (TFT).

***In vitro* buoyancy studies**

The *in vitro* buoyancy was determined by the floating lag time. The tablets were placed in a 100 ml beaker containing simulated gastric fluid, pH 1.2. The time required for the tablet to rise to the surface and float was determined as the floating lag time**.** The duration of time for which the dosage form constantly remained on the surface of the medium was determined as the total floating time.

***In vitro* drug release studies**

Study on an *in vitro* dissolution study, 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.

Drug release kinetics

To determine the mechanism of drug release from the produced tablets, the following graphs were created: a) Zero-order kinetic model -% Qt Vs t; b) First-order kinetic model -log (100 -% Qt) Vs t; c) Higuchi's model -% Qt Vs t1/2; and d) Equation of Korsmeyer and Peppas: log% Qt versus log t. The drug release kinetics from the formulations were interpreted using a variety of kinetic models, including zero order (percentage cumulative drug release vs. time), first order (log cumulative percentage of drug vs. time), Higuchi model (percentage cumulative drug release vs. square root of time), and Korsemeyer-Peppas model (log percentage cumulative drug release vs. log t). The best-fit model was chosen based on the formulations' greatest regression values for correlation coefficients.

Stability studies

Stability application of the enhanced preparation remains conceded out as conferring to the ICH recommendations, at 25˚C/60% RH, 30˚C/75% RH, 40˚C/75% RH stability chamber for 3 months. The carried remain observed for drug content, floating behaviour and *in vitro* drug release profile The optimized F4 formulation was subjected to accelerated stability conditions for 3 months at 25˚C/60% RH, 30˚C/75% RH 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.

RESULTS AND DISCUSSION

Gastroretentive tablets by various approaches:

Identification of drug and drug-polymer compatibility study

Fourier Transform Infrared spectroscopy (FT-IR) is a commonly used technique to identify drugs and study drug-polymer compatibility **[9]**. Compare the individual

drug and polymer spectra with the drug-polymer mixture spectra. Shifts, new peaks, overlapping peaks, or changes in intensity in the mixture spectra compared to the individual spectra. There are no changes it indicating no interactions and compatibility between the drug and polymer **(Figures 1 and 2)**.

I-R spectra for SD3 with HPMC K4M + HPMC K15M and Carbopol 934P

A sample mixture of diclofenac sodium with HPMC K4 M + HPMC K15M and carbopol 934P was prepared in KBr discs (1 mg sample in 100 mg KBr). A small amount of triturated sample was taken into a pellet maker and compressed at 10 kg/cm2. The scanning range was 4000–400 cm_1, and the resolution was 4 cm-1.

Determination of Absorption Maxima (λ max) for cilostazol

The Cilostazol absorbance was obtained using a UV-visible spectrophotometer. By plotting the concentration of cilostazol on the x-axis and the corresponding signal (absorbance) on the y-axis, a calibration curve can be generated. The curve would typically exhibit a linear relationship, allowing the determination of the concentration of cilostazol in unknown samples by measuring their signals and comparing them to the calibration curve **(Figure 3)**.

Gastroretentive tablets by using an effervescent approach

Gastroretentive tablets are designed to remain in the stomach for an extended period, allowing for controlled drug release and enhanced therapeutic effects. One approach to achieving gastroretention is using effervescent systems. Effervescent tablets release gas when in contact with gastric fluid, which helps to float or swell the tablet and prolong its gastric residence time **(Tables 4, 5, 6, and Figure 4)**.

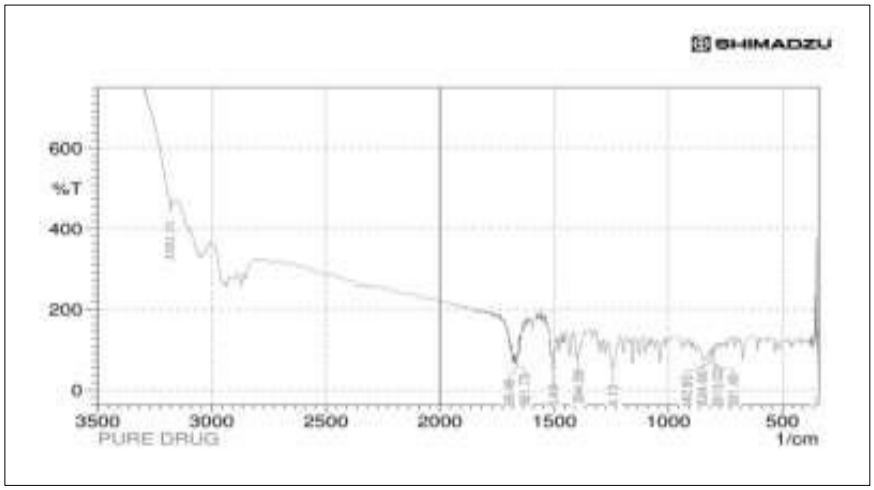

Figure 1: IR spectrum of the pure drug

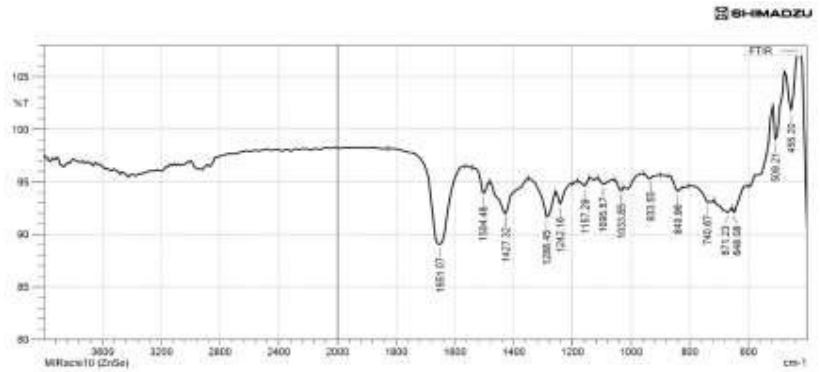

Figure 2: IR spectra for SD3 with HPMC K4M + HPMC K15M and Carbopol 934P

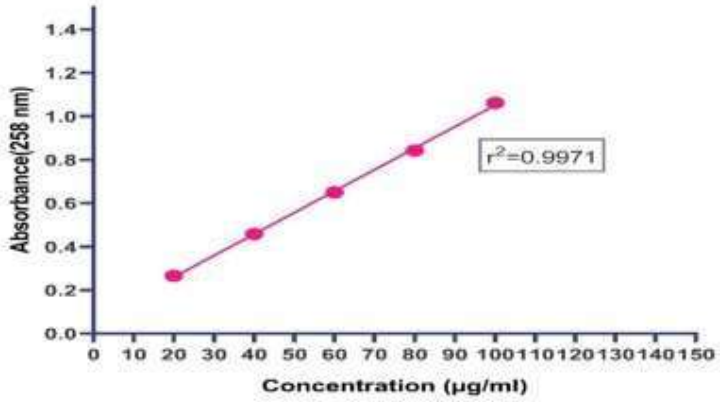

Figure 3: Calibration curve of Cilostazol

Pre-compression parameters

Table 4: Angle of repose, bulk density, tapped density, carr's index hausners ratio for different formulations of cilostazol granules

Formulation code	Angle of repose	Bulk density	Tapped density	Carr's index	Hausners ratio
A1	26.8	0.47	0.53	0.11	1.12
A2	26.5	0.54	0.63	0.14	1.16
A3	28.3	0.56	0.64	0.12	1.14
A4	26.2	0.55	0.64	0.14	1.16
A5	24.9	0.49	0.58	0.15	1.18
A6	27.8	0.57	0.68	0.16	1.19

Post-compression parameters

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 wt. variation (mg)	Friability	Floating Lag (Sec)	Floating Duration (hrs.)	Drug content
A1	4	3.1	350	0.47	42	> 12	98.13
A2	4.1	3	348	0.51	50	> 12	98.12
A3	3.9	3.2	349	0.46	51	> 12	97.21
A4	3.8	3.4	351	0.58	58	> 12	99.31
A5	4	3	350	0.47	57	> 12	98
A6	4	3.1	350	0.47	75	> 12	97.43

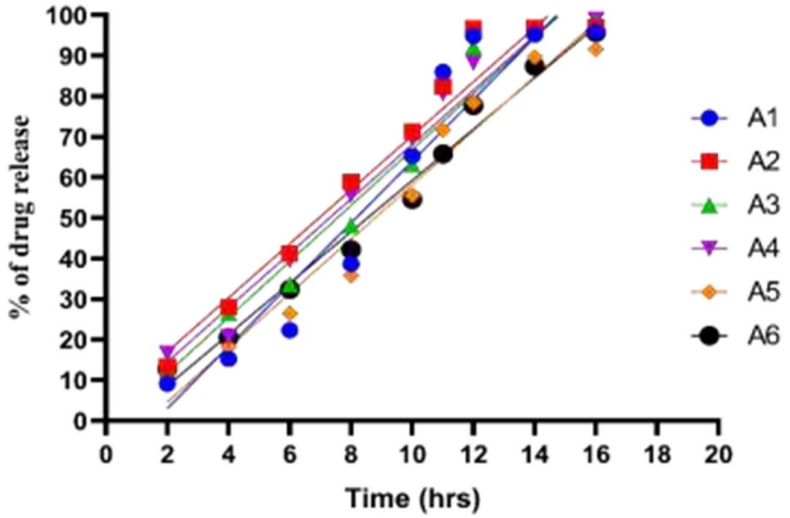

Figure 4: Cumulative % of drug release

Table 6: Kinetic parameters for drug release of cilostazol Gastroretentive tablet

Formulation code	Zero order	First order	Higuchi model	Korsmeyer peppas model	
	r^2	r^2	r^2	r2	n
A1	0.9276	0.8040	0.8105	0.9757	0.662
A2	0.9647	0.9233	0.9165	0.9970	0.445
A3	0.9673	0.8785	0.8837	0.9924	0.477
A4	0.9724	0.9059	0.9102	0.9828	0.591
A5	0.9674	0.8351	0.8472	0.9886	0.592
A6	0.9880	0.8641	0.8807	0.9893	0.477

2. Swellable and floating gastroretentive tablet

Swellable and floating gastroretentive tablets are specific types of oral dosage forms designed to prolong gastric residence time, thereby improving drug delivery and bioavailability **[10]**. These tablets are designed to swell or expand upon contact with gastric fluids and float on the gastric contents, ensuring that the drug remains in the stomach for an extended period **(Tables 7, 8, 9, 10, and Figure 5)**.

Pre compression parameters

Table 7: Angle of repose, bulk density, tapped density, carr's index hausners ratio for different formulations of cilostazol granules Swellable and floating gastroretentive tablet

Formulation code	Angle of repose	Bulk density	Tapped density	Carr's index	Hausners ratio
F1	25.32	0.68	0.75	9.4	1.102
F2	25.21	0.69	0.70	4.1	1.014
F3	26.90	0.72	0.81	11.11	1.125
F4	24.90	0.64	0.71	9.85	1.10
F5	25.19	0.69	0.73	5.4	1.05
F6	24.20	0.71	0.79	10.12	1.11

Post compression parameters

Table 8: Hardness, thickness, avg wt. variation, friability, floating lag, 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

In-vitro buoyancy test

Table 9: *In-vitro* buoyancy test

Formulation	Floating Lag time (Min: Sec)	Total floating time (Min: Sec)
F1	3:10	24
F2	2:41	23
F3	2:45	22
F4	2:49	24
F5	1:17	20
F6	2:10	20

The *In-vitro* drug release profile for the swellable and floating gastroretentive tablet formulation

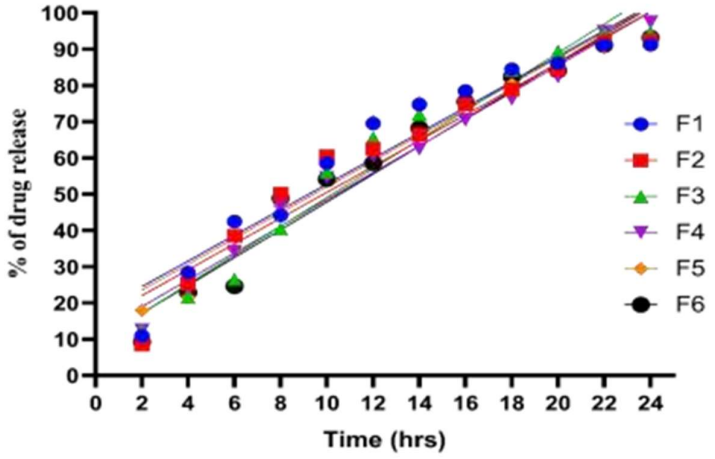

Figure 5: Cumulative % drug released of F1 to F6 (Swellable)

Table 10: Kinetic parameters for drug release of cilostazol gastroretentive swelling tablet

Formulation code	Zero order	First order	Higuchi model	Korsmeyer peppas model	
	r^2	r^2	r^2	KKP	n
F1	0.8802	0.8581	0.6602	0.9862	0.413
F2	0.9069	0.8319	0.6495	0.9736	0.452
F3	0.9535	0.8683	0.5918	0.9778	0.414
F4	0.9540	0.8795	0.6218	0.9822	0.597
F5	0.8943	0.8599	0.6508	0.9358	0.541
F6	0.9473	0.8351	0.5978	0.9713	0.542

Gastroretentive tablets by the sublimation method

Gastroretentive tablets are dosage forms designed to remain in the stomach for an extended period, allowing for controlled drug release and increased bioavailability. One method of preparing gastroretentive tablets is the sublimation method, which involves the use of subliming agents to create porous structures within the tablet matrix **(Tables 11, 12, 13 and Figure 6)**.

Pre-compression parameters

Table 11: Angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio for different formulations of cilostazol granules.

Formulation code	Angle of repose	Bulk density	Tapped density	Carr's index	Hausners ratio
B1	24.34	0.56	0.60	0.066	1.071
B2	23.67	0.51	0.64	0.20	1.254
B3	26.54	0.58	0.67	0.134	1.15
B4	23.89	0.54	0.62	0.12	1.14
B5	22.56	0.52	0.61	0.145	1.17
B6	23.30	0.50	0.66	0.266	1.32

Post-compression parameters

Table 12: Hardness, Thickness, Avg wt. variation, Friability, Floating Lag, Floating Duration for different formulations of cilostazol tablets

Formulation code	Avg wt variation (mg)		Hardness (kg/cm2)		Thickness (mm)	Friability	Floating Lag time (Sec)	Drug content
	Before Sublimation	After Sublimation	Before Sublimation	After Sublimation				
B1	400	350	4.1	3.1	4.4	0.51	45	95
B2	402	345	4.6	3.8	4.3	0.52	33	93.86
B3	400	348	4.5	3.8	4.2	0.72	48	99.68
B4	410	351	5.1	4.1	4	0.62	49	97.23
B5	400	354	5.4	4.2	4	0.61	60	98.62
B6	420	350	5.2	4.2	4.1	0.57	52	99.65

The *In-vitro* drug release profile for the formulation

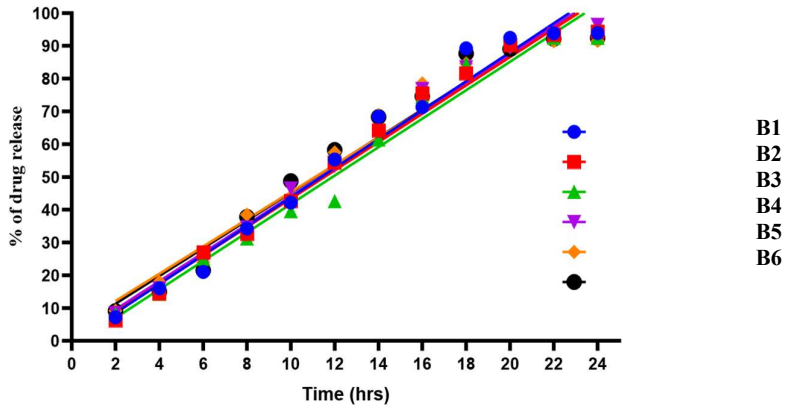

Figure 6: Cumulative *In-vitro* drug release profile for the Gastroretentive tablets by Sublimation formulation

Table 13: Kinetic parameters for drug release of cilostazol gastroretentive tablets by the Sublimation method

Formulation code	Zero order	First order	Higuchi model	Korsmeyer peppas model	
	r^2	r^2	r^2	r^2	n
F1	0.9690	0.9290	0.5137	0.9854	0.611
F2	0.9816	0.9165	0.5247	0.9954	0.628
F3	0.9700	0.9458	0.4772	0.9753	0.592
F4	0.9840	0.9366	0.5294	0.9855	0.566
F5	0.9590	0.9270	0.5466	0.9805	0.530
F6	0.9906	0.9244	0.5402	0.9705	0.561

Effect of gastroretentive tablets in different grades of polymer and different concentrations of polymer on percentage drug release

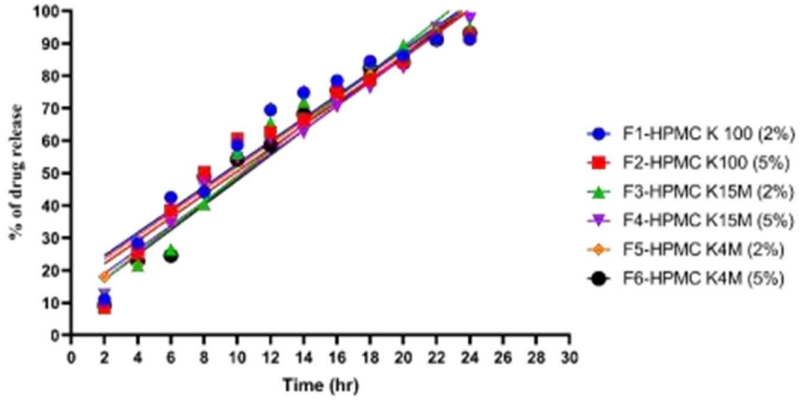

Figure 7: Effect of gastroretentive tablets in different grades of polymer and different concentrations of polymer on percentage drug release

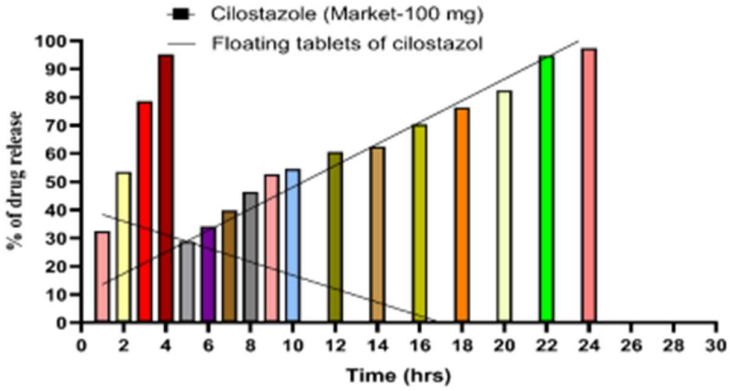

Figure 8: Comparison of marketed tablets and floating tablets of Cilostazol solid dispersion

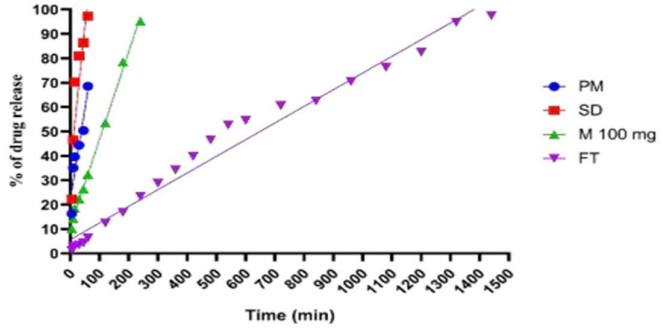

Figure 9: Comparative in vitro release study of marketed tablet, physical mixture, solid dispersion of cilostazol, and floating tablets of cilostazol solid dispersion

Effect of HPMC grade on lag time of tablets

HPMC (Hydroxypropyl Methylcellulose) is a hydrophilic polymer that can swell and form a gel-like matrix when in contact with water, contributing to its functionality in drug delivery. The choice of HPMC grade can indeed impact the floating lag time of tablets. The floating lag time refers to the time it takes for a tablet to start floating in the gastric fluid after oral administration. The lag time is influenced by various factors, including the viscosity and gel-forming properties of the polymer **(Table 14)**.

Stability studies

The optimized F4 formulation was subjected to accelerated stability conditions for 3 months at 25 °C/60% RH, 30 °C/75% RH 40 °C/75% RH stability chambers. 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 **(Tables 15, 16, 17, 18, 19, and 20)**.

Table 14: Different grades of HPMC used in the formulation have an impact on the floating lag time of the tablets. The lag time of HPMC K15 M is slightly higher compared to HPMC K4 M tablet

Quantity of different grades HPMC	Floating lag time (Min: sec)
25(HPMC K100M)	2:10
50(HPMC K100M)	2:41
25(HPMC K15M)	2:45
50(HPMC K15M)	2:49
25(HPMC K4M)	1:17
50(HPMC K4M)	2:10

Table 15: Comparison of physical parameters for optimized formulation F4

Parameter	F4	25°C / 60% 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±0.3	3.5±0.3	3.5±0.3
Hardness (kg/cm^2)	3.9±0.2	3.9±0.2	3.9±0.2	3.9±0.2
Friability (%)	0.62±0.14	0.62±0.14	0.62±0.14	0.62±0.14
Weight Variation (mg)	350.6±0.6	350.6±0.6	350.6±0.6	350.6±0.6
Content Uniformity	99.43±0.21	99.43±0.21	99.43±0.21	99.43±0.21

Table 16: Dissolution data of F4 batch at 25 °C / 60 % RH

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	12.5	12.5
4	23.4	23.5	23.1
6	34.25	34.5	35
8	46.5	46	47.3
10	54.6	54.3	54.8
12	60.54	59.7	58.9
14	62.5	60.8	61.9
16	70.5	71.6	71.9
18	76.32	75.7	76.2
20	82.5	81.5	81.7
22	94.8	93.8	94.2
24	97.5	97.3	97.4

Table 17: Comparison of physical parameters for optimized formulation F4 (30˚C/75% RH)

Parameter	F4	30 °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	3.6±0.31	3.6±0.32	3.5±0.31
Hardness (kg/cm^2)	3.9±0.2	3.8±0.1	3.7±0.22	3.7±0.21
Friability (%)	0.62±0.14	0.65±0.13	0.61±0.12	0.62±0.14
Weight variation (mg)	350.6±0.6	350±0.1	350.4±0.4	350.5±0.5
Content uniformity	99.43±0.21	99.56±0.22	99.21±0.14	99.31±0.16

Table 18: Dissolution data of the F4 batch at 30 ˚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	12	12.4
4	23.4	22.5	23.6
6	34.25	34.2	33.8
8	46.5	46.8	46.9
10	54.6	53.7	52.5
12	60.54	58.4	55.2
14	62.5	61.8	64.8
16	70.5	73.6	74.9
18	76.32	77.7	73.2
20	82.5	80.6	87.7
22	94.8	93.8	92.4
24	97.5	95.9	94.9

Table 19: 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 20: 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	12.2	12.1
4	23.4	22.7	22.9
6	34.25	32.1	33.9
8	46.5	44.2	46.1
10	54.6	52.3	51.9
12	60.54	58.5	59.2
14	62.5	60.4	61.8
16	70.5	71.9	69.9
18	76.32	74.7	78.2
20	82.5	85.5	86.7
22	94.8	93.8	91.2
24	97.5	96.3	94.4

CONCLUSION

The bulk density of granules is used for the determination of the compressibility index and Hausner ratio. The compressibility index of all formulations shows less than 10% limits, which indicates an excellent flow property. Hausner ratio of all formulations shows 1 to 1.11, indicating an excellent flow property. The angle of repose of all formulations ranges from 25 to 30 respectively indicate the excellent flow property. The percentage of the drug released from the formulations F1, F2 and F3, F5, and F6 was found to be 91.25,92.4,94.7,93.5,93.2 respectively. The percentage of the drug released from the formulation F4 was found to be 97.5% in 24 hours, respectively. The percentage of the drug released from formulations A1 to A6 was found to be 91 to 98% in 16 hours, respectively. The percentage of the drug released from formulations B1 to B6 was found to be 91 to 96% in 24 hrs, respectively. In the 3 methods, f4 is the best formulation for sustained release formulation indicating 97.5% drug was released in 24 hrs. Combination of Carbopol 934 with HPMC K15M shows good sustained release properties. The results of dissolution data were fitted to various drug release kinetic equations. The best-fitting model for the three methods using all formulations was calculated. The different ratios of polymer batches, the best fitted models were found to be zero order and Korsmeyer-Peppas release. The batch F4 followed zero order and Korsmeyer-Peppas release, shown in **Table 5**. The values of n as estimated by linear regression of log (Mo / Mt) vs. log (t) of formulations indicated Fickian release behavior, which is indicative of drug release mechanisms involving a combination of both diffusion and chain relaxation mechanisms. Thus, the release of the drug from the prepared tablets is sustained by swelling of the polymer, followed by drug diffusion through the swelled polymer, and slow erosion of the polymer.

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CONFLICT OF INTEREST

Nil

FUNDING

Nil

ABBREVIATIONS

SD: Solid Dispersion

PEG: Polyethylene glycol

PVPK: Polyvinyl Pyrrolidone

FT-IR: Fourier Transform infrared

PM: Physical Mixture

BCS: Biopharmaceutical classification system.

HPMC: Hydroxypropyl Methylcellulose

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