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Formulation and Evaluation of a Gastric Retentive Drug Delivery System to Improve the Oral Bioavailability and Therapeutic Efficacy of Clopidogrel

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Abstract

Clopidogrel, a widely prescribed antiplatelet agent, exhibits poor oral bioavailability due to limited solubility at alkaline pH and a narrow absorption window. Gastric retentive drug delivery systems (GRDDS), particularly floating drug delivery systems (FDDS), have emerged as promising strategies by prolonging gastric residence time and enhancing drug absorption. This study aimed to formulate and evaluate a gastroretentive floating tablet of Clopidogrel Bisulphate to improve its bioavailability through sustained drug release and extended gastric retention. Tablets were developed using compression techniques with polymers (hydroxypropyl methylcellulose) and effervescent agents. The formulations underwent pre- and post-compression evaluations, including hardness, friability, weight variation, floating lag time (FLT), total floating time (TFT), drug content uniformity, and in vitro dissolution behavior. Compatibility studies used UV-visible spectroscopy, FTIR spectroscopy, and differential scanning calorimetry. Among six formulations, F6 showed superior performance with favorable physicochemical properties, minimal floating lag time (7.29 ± 0.055 seconds), extended floating duration (>24 hours), and sustained drug release (98.97% over 24 hours). The drug release kinetics followed the Korsmeyer-Peppas model (R^2 = 0.977; n = 0.499), indicating non-Fickian diffusion. The optimized formulation demonstrated rapid buoyancy and sustained floating over 12 hours, with controlled drug release. Stability studies under ICH guidelines for three months showed consistent physical integrity, floating characteristics, and drug content. The developed gastroretentive floating tablet successfully prolonged gastric residence and achieved sustained drug release, suggesting potential enhancement of oral bioavailability and therapeutic performance. This approach may apply to drugs with similar absorption profiles.

Keywords: Clopidogrel Bisulphate, Gastroretentive Drug Delivery System (GRDDS), Floating Drug Delivery System (FDDS), Gastric Residence Time, Controlled Release

Introduction

Clopidogrel bisulphate is an extensively prescribed oral antiplatelet agent, primarily indicated for the prevention of atherothrombotic events such as myocardial infarction, ischemic stroke, and peripheral arterial disease (Squizzato et al., 2017). It exerts its pharmacological effect by irreversibly inhibiting the $P2Y_{12}$ subtype of adenosine diphosphate (ADP) receptors located on the platelet surface, thereby impeding platelet aggregation and thrombus formation (Cattaneo, 2011). Despite its well-established clinical efficacy, the therapeutic utility of Clopidogrel is limited by several pharmacokinetic and physiological challenges (Jiang et al., 2015).

A major concern associated with Clopidogrel therapy is its poor and highly variable oral bioavailability, typically reported to be in the range of 50–60%. This suboptimal bioavailability is primarily attributable to its limited solubility in alkaline pH environments, extensive first-pass hepatic metabolism, and a narrow absorption window that is confined to the upper gastrointestinal (GI) tract (Squizzato et al., 2017). Furthermore, Clopidogrel is a prodrug that requires biotransformation via the cytochrome P450 enzyme system, predominantly CYP2C19, to yield its active metabolite. The efficiency of this metabolic conversion is influenced by genetic polymorphisms and concomitant drug interactions, contributing to substantial inter-individual variability in therapeutic response. This variability often necessitates dose escalation or frequent administration, increasing the risk of adverse effects, particularly bleeding complications(Dean & Kane, 2012).

Conventional immediate-release formulations of Clopidogrel are often associated with premature gastric emptying, leading to incomplete drug absorption and fluctuating plasma concentrations(Choursiya et al., 2024). To overcome these limitations, the development of a gastric retentive floating drug delivery system (GRFDDS) has emerged as a promising strategy. Such systems are designed to prolong the gastric residence time of the dosage form by maintaining buoyancy in the stomach, thereby facilitating sustained drug release at the site of optimal absorption(Reddy et al., 2021).

The underlying mechanism of floating drug delivery systems (FDDS) is based on the reduction of the dosage form's density below that of gastric fluids, which enables the system to remain afloat on the gastric contents. This localized delivery within the acidic gastric environment is particularly advantageous for Clopidogrel, whose solubility and stability are enhanced at lower pH. Moreover, extended gastric retention promotes more uniform plasma drug levels, reduces dosing frequency, and minimizes drug loss due to premature gastrointestinal transit(Razavi et al., 2021).

However, the design and development of an effective GRFDDS for Clopidogrel present several formulation and physiological challenges. Key considerations include the selection of appropriate hydrophilic polymers and effervescent agents to achieve sufficient buoyancy and controlled drug release, as well as accounting for patient-specific variables such as gastric motility, fed or fasted state, posture, age, gender, and the influence of co-administered medications. Additionally, critical formulation parameters—such as tablet density, size, shape, and polymer viscosity—must be optimized to ensure favorable in vivo performance while mitigating the risk of dose dumping and

associated toxicity (Vrettos et al., 2021).

The present research seeks to address these challenges by formulating and evaluating a gastric retentive floating drug delivery system for Clopidogrel bisulphate. The primary objective is to enhance the oral bioavailability and therapeutic efficacy of the drug through sustained gastric retention and improved pharmacokinetic consistency.

Materials & Methodology

The materials utilized in the present study were selected based on their pharmaceutical functionality and compatibility with Clopidogrel Bisulphate for the development of a gastric retentive floating drug delivery system (GRFDDS). All excipients employed were of analytical or pharmaceutical grade and were used as received without any further purification.

Clopidogrel Bisulphate, the active pharmaceutical ingredient (API), was obtained from *Aarti Drugs*. **Avicel pH 112** (microcrystalline cellulose), procured from *FMC Biopolymer*, functioned as a direct compression binder and filler, contributing to tablet integrity and compressibility. **Lactose anhydrous**, supplied by *DMB Fontera*, served as a diluent to enhance tablet bulk and improve flow properties.

Hydrophilic matrix-forming polymers, **Hydroxypropyl Methylcellulose (HPMC) K4M** and **HPMC K100LV**, both obtained from *Dow Chemicals*, were employed to modulate drug release and provide the necessary gel-forming properties to support buoyancy upon hydration. **Sodium bicarbonate**, sourced from *Merk Chemicals*, was incorporated as a gas-generating agent to ensure flotation of the dosage form by generating carbon dioxide in the acidic gastric environment.

Colloidal silicon dioxide, procured from *Cobot Chemicals*, was included as a glidant to enhance powder flowability. **Polyethylene glycol (PEG) 6000**, obtained from *Clarint Pharma*, acted as a hydrophilic plasticizer and matrix modifier to improve drug diffusion and tablet integrity. **Talc**, sourced from *Prachin Chemicals*, was utilized as an anti-adherent and lubricant to prevent sticking during compression. **Magnesium stearate**, supplied by *Vasa Pharmaceuticals*, functioned as a lubricant to facilitate tablet ejection and minimize friction during the manufacturing process.

Additionally, **hydrogenated castor oil**, also obtained from *Clarint Pharma*, was incorporated to further sustain drug release and modify matrix properties.

All excipients were selected following pre-formulation compatibility studies and were systematically optimized through factorial experimental design to achieve desirable physicochemical characteristics of the floating dosage forms, including adequate buoyancy, sustained release profile, mechanical robustness, and reproducibility.

Identification of Drug

Physical Characterization: Clopidogrel bisulphate was observed as a white crystalline powder with a characteristic odour and palatable taste.

Melting Point Determination: The melting point was determined using Thiel's tube method with liquid paraffin, under atmospheric pressure.

Solubility Characteristics

Solubility studies were conducted by preparing saturated solutions in various solvents (e.g., 0.1N HCl, acetate buffer, phosphate buffer, methanol, water, DMSO). The solutions were stirred at 25 °C for 24 hours, centrifuged, filtered, and analyzed at 220 nm using a UV spectrophotometer.

UV-Spectrophotometric Study: A stock solution of Clopidogrel bisulphate was prepared in methanol and further diluted in pH 1 water. The solution was scanned between 200-400 nm using a UV/Visible spectrophotometer to determine the absorption maxima.

FTIR Study: FTIR analysis was carried out using the KBr pellet method. Spectra were recorded from 4000 to 400 cm^{-1} to identify characteristic functional groups.

Compatibility Study

Drug-Excipient Interaction Using DSC: Differential Scanning Calorimetry was employed to assess possible interactions between Clopidogrel and selected excipients. Samples were scanned from 50–300°C under a nitrogen atmosphere.

Compatibility with Excipients: Physical mixtures of drug and excipients (1:1 ratio) were stored at 25°C and 40°C for one month. Samples were analyzed weekly to evaluate physical stability and detect any degradation.

Calibration Curve Development: A stock solution of 1000 µg/ml was prepared and diluted to concentrations ranging from 10–45 µg/ml using distilled water (pH 1). Absorbance at 220 nm was recorded and plotted to obtain a calibration curve.

Characterization of Powder Blend

Angle of Repose: Used to assess flowability of powder blend. Calculated using standard formula.

Bulk Density: Bulk density was determined by measuring the mass and volume of the powder in a graduated cylinder.

Tapped Density: Determined using a mechanical tapper with 100 taps. Tapped volume recorded to compute tapped density.

Carr's Index: Carr's Index was calculated from bulk and tapped densities to assess compressibility.

Tablet Formulation

Floating tablets of Clopidogrel were prepared by compression using HPMC K4M/K100LV, sodium bicarbonate, PEG 6000, hydrogenated castor oil, lactose, and Avicel PH112. Blends were passed through mesh ≤40, mixed thoroughly, and compressed using a 16-station rotary tablet press (average tablet weight: 280 mg).

Evaluation of Tablets

Physical Parameters

- *Thickness:* Measured using Vernier calipers.
- *Hardness:* Evaluated using Erweka Hardness Tester (n = 6).
- *Friability:* Tested using Roche Friabilator for 100 revolutions; % loss calculated.

- *Weight Variation:* 20 tablets weighed individually, and % deviation from average weight was determined.

In-Vitro Floating Behavior: Tablets were tested in 100 ml of 0.1N HCl (pH 1.2) at 37°C. Floating lag time and total floating duration were recorded.

Swelling Study: Individual tablets were immersed in 0.1N HCl. At predetermined intervals up to 24 h, tablets were weighed, and swelling index (SI) was calculated.

In-Vitro Drug Release: Dissolution studies were conducted using USP Type II apparatus in 900 ml of 0.1N HCl at 50 rpm and 37°C. Samples were withdrawn at intervals, filtered, and analyzed at 220 nm.

Drug Release Kinetics: Release data were fitted to Zero-order, First-order, Higuchi, and Korsmeyer-Peppas models to determine the release mechanism.

Stability Studies: Stability of the optimized formulation was assessed under ICH conditions. Tablets were stored at controlled temperatures and monitored for changes in physical appearance, drug content, and dissolution profile over time.

Results & Discussion

Identification of Drug

Physical characterization

Clopidogrel Bisulphate was evaluated for its physical properties and it was observed that Clopidogrel Bisulphate was a white or off-white crystalline powder and the melting point was observed as 178 °C.

Solubility characteristics

Table 1: Solubility of Clopidogrel Bisulphate in different Solvents

Sr. no.	Solvent	Solubility(mg/ml)
1	0.1N HCl	99.38
2	pH 2.0 HCl Buffer	24.67
3	pH 4.5 Acetate Buffer	4.82
4	pH 6.8 Phosphate Buffer	15.49
5	pH 7.2 Phosphate Buffer	0.056
6	Methanol	182.83
7	Water	163.95
8	Dimethyl Sulphoxide	96.54

Clopidogrel Bisulphate was found to be very soluble in various Solvents. The highest solubility of clopidogrel bisulphate was 182.83 mg/ml in Methanol.

UV- Spectrophotometric study

UV-Spectrophotometric study was carried out in order to determine the λ_{max} and observed λ_{max}(220nm) was found to similar with literature value.

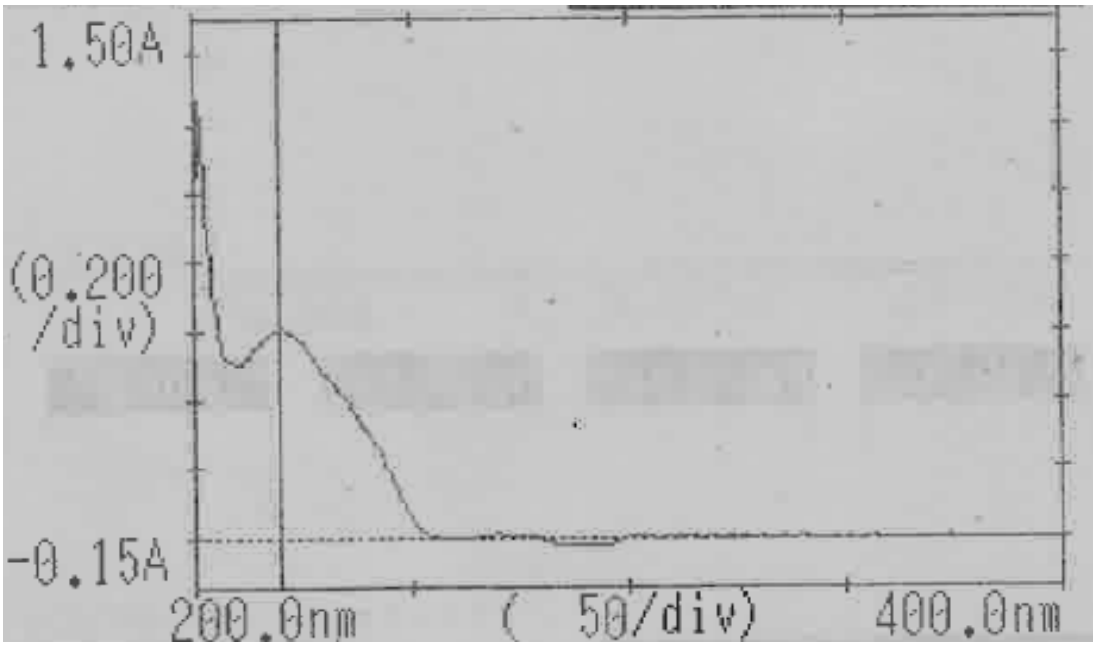

Figure 1: U.V. Spectrum of Clopidogrel Bisulphate

FTIR Spectra of Drug

The FTIR spectra were recorded on a FTIR multiscope spectrophotometer (Shimadzu® 8400-S) equipped with spectrum v3.02 software. KBr pellets were prepared so as to contain approximately 3% of polymorph powder. The spectrum for each sample (an average of 16 co-added scans) was recorded over the 450 to 4000cm^{-1} spectral region with a resolution of 4 cm^{-1}.

It is reported that clopidogrel moiety, which acts as a cation in CLP, shows band due to aromatic C–H stretching vibrations was present at 3121 cm^{-1}. It also showed a broad absorbance band at about 2500–2550 cm^{-1} associated with stretching vibrations of bonded N^+–H occurring due to salt formation between the qua- ternary nitrogen of clopidogrel and –OH of hydrogen sulphate. IR spectra also showed a strong absorbance band due to C=O stretching vibrations at 1752 cm–1 and due to O–H stretching of the hydrogen sulphate moiety around 3300 cm^{-1}. The band associated with C–O stretching appeared at 1175 cm^{-1}. It was found from the structure that Cl and O (of –OCH_3 group) are in close proximity, creating electron repulsion between the lone pair electron of Cl and O and thus making the C–O bond stronger. Also, IR spectra exhibited unique absorption bands at 841 and 1029 cm^{-1}, respectively.

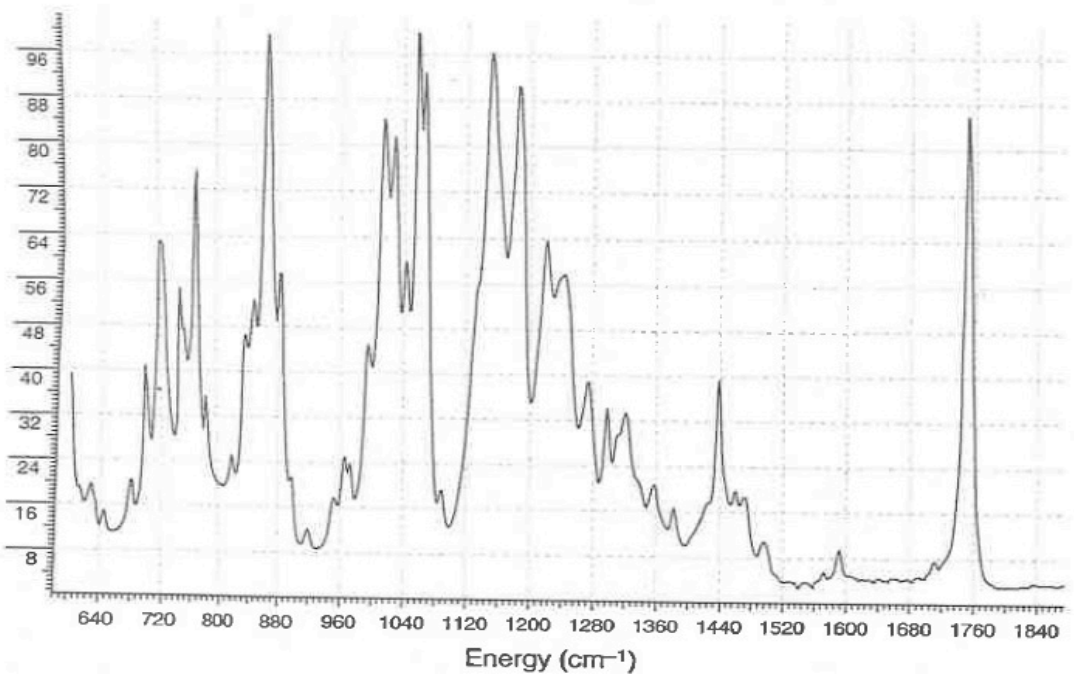

Figure 2: Reference FTIR Spectra of Clopidogrel Bisulphate

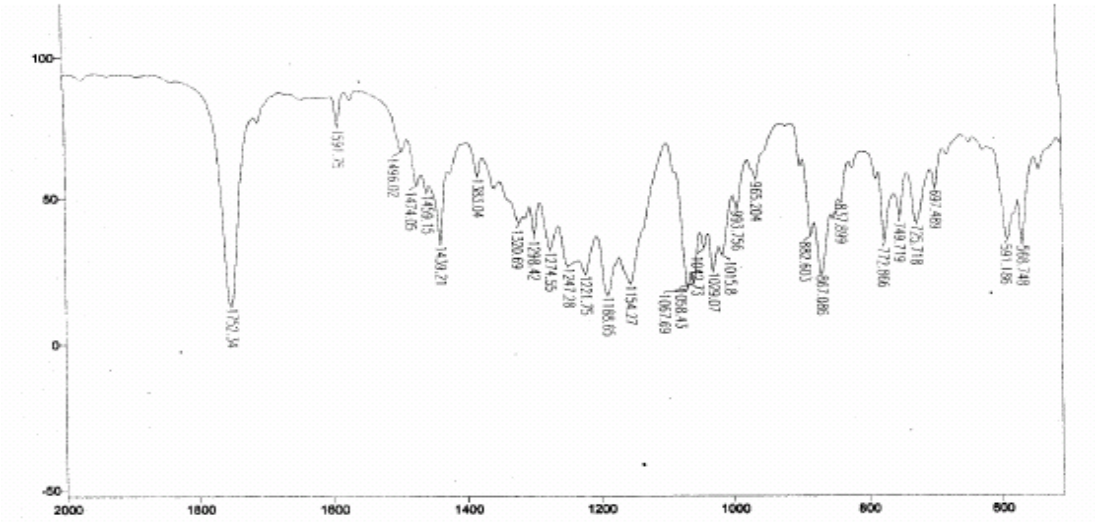

Figure 3: FTIR Spectra of Clopidogrel Bisulphate

Table 2: Interpretation of infrared spectrum bands of Clopidogrel sample

Sr. no.	Wave No. (cm^{-1})	Interpretations
1.	1752.34	C=O stretching
2.	1651.18	C=C stretching
3.	1154.27	C-O stretching

4.	2924.96	C-H stretching

The FTIR spectrum of Clopidogrel have identical peaks as reported in references spectra of Clopidogrel Bisulphate.

Compatibility Study

Drug-Excipient interaction study using DSC

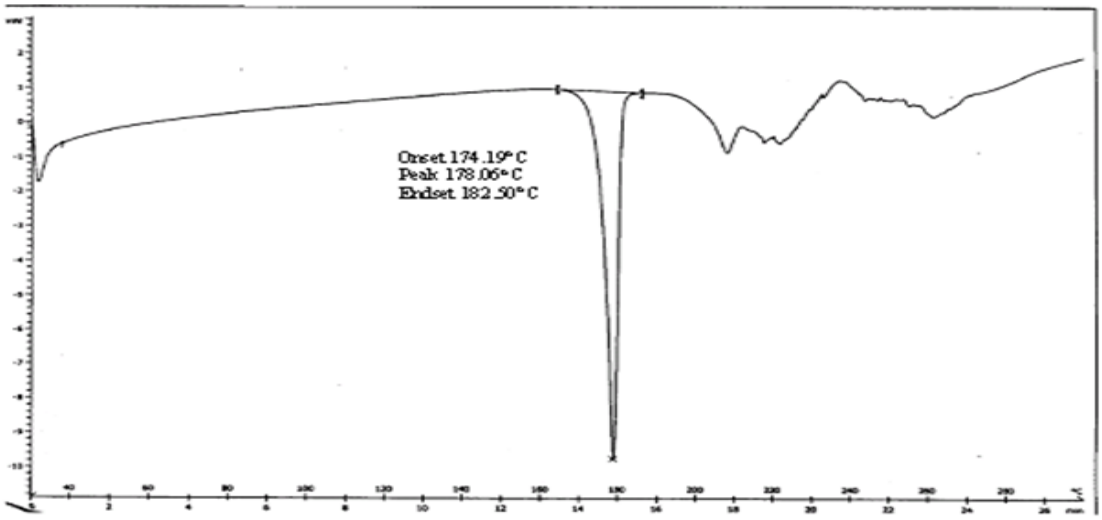

Figure 4: DSC spectra of Clopidogrel Bisulphate (API)

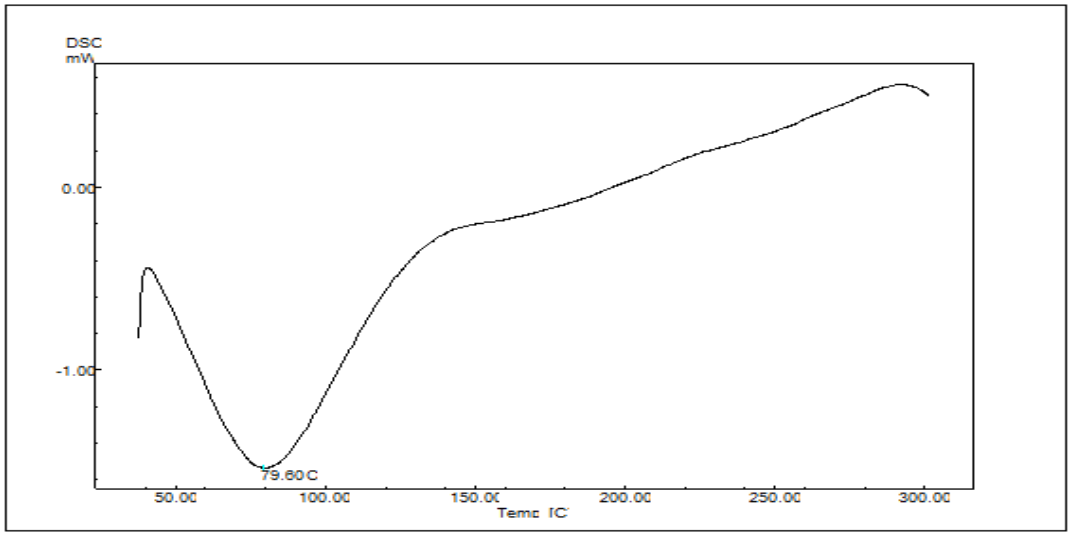

Figure 5: DSC spectra of Avicel pH 112

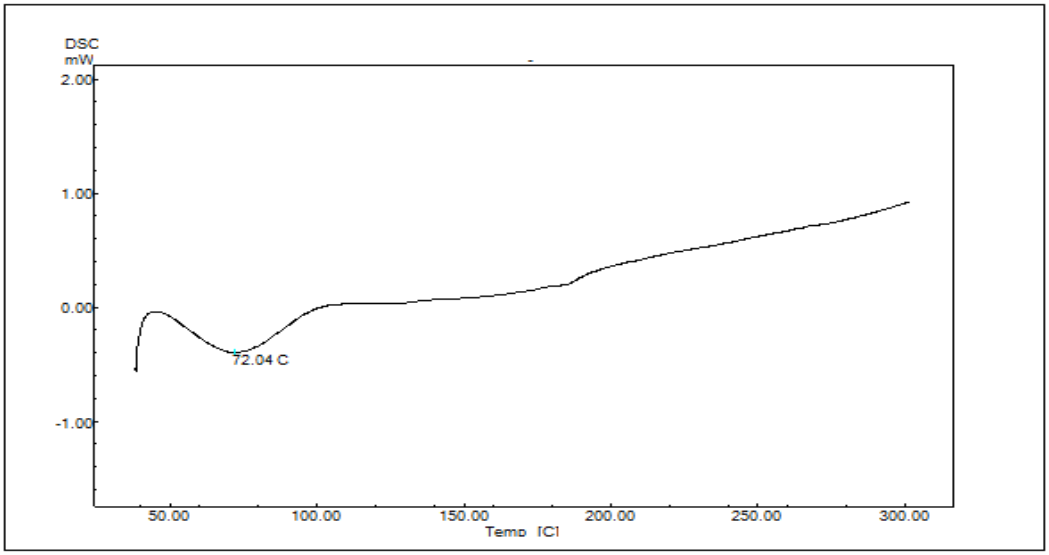

Figure 6: DSC spectra of HPMC K100LV

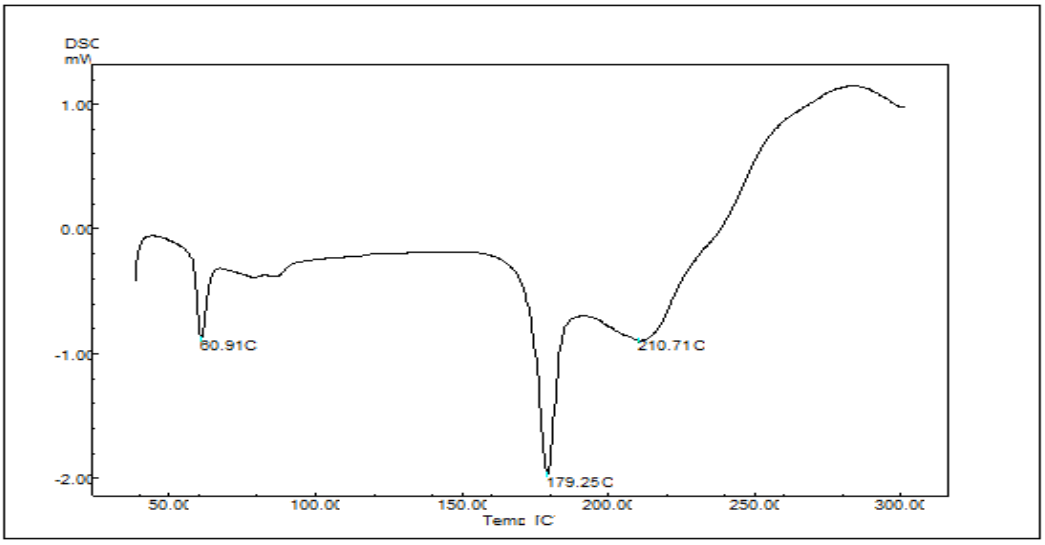

Figure 7: DSC spectra of Drug Blend

No any significant change was found in the characteristic peaks of Clopidogrel and excipients. Based on the results of DSC data obtained however, there was no chemical interaction between the pure drug and excipients.

Compatibility study with different Excipients

Table 3: Compatibility Data of Clopidogrel Bisulphate with Excipients

Sr. No.	Excipients	Temp. Condition	Initial	0.5 Week	1 Weeks	2 Weeks	3 Weeks	4 Weeks
			% Assay					
1	Avicel pH 112	25°C	99.10	99.29	99.56	99.33	98.78	98.55
		40°C	99.86	99.66	99.45	99.42	99.85	98.16
2	Lactose anhydrous	25°C	99.01	98.79	97.65	97.91	98.38	99.20
		40°C	98.26	97.16	98.36	99.20	97.95	97.79
3	HPMC K4M	25°C	99.3	99.22	98.48	98.23	97.47	98.24
		40°C	97.12	97.01	97.14	98.00	97.52	99.00

4	HPMC K100LV	**25˚C**	99.7	99.6	99.38	98.23	97.57	97.34
		40˚C	97.12	97.01	97.54	98.30	96.12	99.10
5	Sod. bi-carbonate	**25˚C**	97.21	97.32	97.15	98.34	97.23	99.33
		40˚C	96.89	97.23	98.13	99.21	98.23	98.00
6	Colloidal silicon dioxide	**25˚C**	99.01	98.79	97.65	97.41	96.38	97.20
		40˚C	98.46	97.76	96.96	96.70	96.51	98.09
7	PEG 6000	**25˚C**	99.65	99.43	99.38	98.33	97.67	97.14
		40˚C	97.32	97.11	97.01	96.80	96.52	96.43
8	Talc	**25˚C**	99.68	99.48	99.34	99.03	98.57	98.34
		40˚C	98.32	98.21	98.04	97.30	96.12	96.00
8	Magnesium stearate	**25˚C**	99.46	99.12	98.99	98.88	98.57	98.34
		40˚C	99.32	99.21	98.04	97.30	97.12	96.90
9	Hydrogenated castor oil	**25˚C**	99.80	99.41	99.34	99.20	98.30	98.23
		40˚C	96.89	97.23	99.13	98.21	98.23	99.00

Table 4: Compatibility Data of Clopidogrel Bisulphate with Excipients

Sr. No.	**Excipients**	**Temp. Condition**	**Initial**	**0.5 Week**	**1 Weeks**	**2 Weeks**	**3 Weeks**	**4 Weeks**
			% Related substance					
1	Avicel pH 112	25˚C	ND	ND	ND	ND	ND	ND
		40˚C	ND	ND	ND	ND	ND	ND
2	Lactose anhydrous	25˚C	ND	ND	ND	ND	ND	ND
		40˚C	ND	ND	ND	ND	ND	ND
3	HPMC K4M	25˚C	ND	ND	ND	ND	ND	ND
		40˚C	ND	ND	ND	ND	ND	ND
4	HPMC K100LV	25˚C	ND	ND	ND	ND	ND	ND
		40˚C	ND	ND	ND	ND	ND	ND
5		25˚C	ND	ND	ND	ND	ND	ND

	Sod. bi-carbonate	40˚C	ND	ND	ND	ND	ND	ND
6	Colloidal silicon dioxide	25˚C	ND	ND	ND	ND	ND	ND
		40˚C	ND	ND	ND	ND	ND	ND
7	Polyethylene glycols (PEG 6000)	25˚C	ND	ND	ND	ND	ND	ND
		40˚C	ND	ND	ND	ND	ND	ND
8	Talc	25˚C	ND	0.7	0.8	1.0	1.4	1.7
		40˚C	ND	0.5	0.7	0.9	1.2	1.9
8	Magnesium stearate	25˚C	ND	0.6	0.9	1.2	1.4	1.7
		40˚C	ND	0.8	0.9	1.1	1.3	1.6
9	Hydrogenated castor oil	25˚C	ND	ND	ND	ND	ND	ND
		40˚C	ND	ND	ND	ND	ND	ND

Table 5: Result of compatibility study with Excipients

Compatible Excipients	Incompatible Excipients
Avicel pH112	Talc
Lactose anhydrous	Magnesium stearate
HPMC K4M	--
HPMC K100LV	--
Sod. bi-carbonate	--
Colloidal silicon dioxide	--
Polyethylene glycols	--
Hydrogenated castor oil	--

The results shown in Table no. 5 indicate Clopidogrel Bisulphate was found to be compatible with Avicel pH112, lactose anhydrous, HPMC K4M, HPMC K100LV, Sod.bi-carbonate, Colloidal silicon dioxide, Polyethylene glycols (PEG 6000), and Hydrogenated castor oil. So, this permeation enhancer was used for further study.

Development of Calibration Curves of Clopidogrel Bisulphate

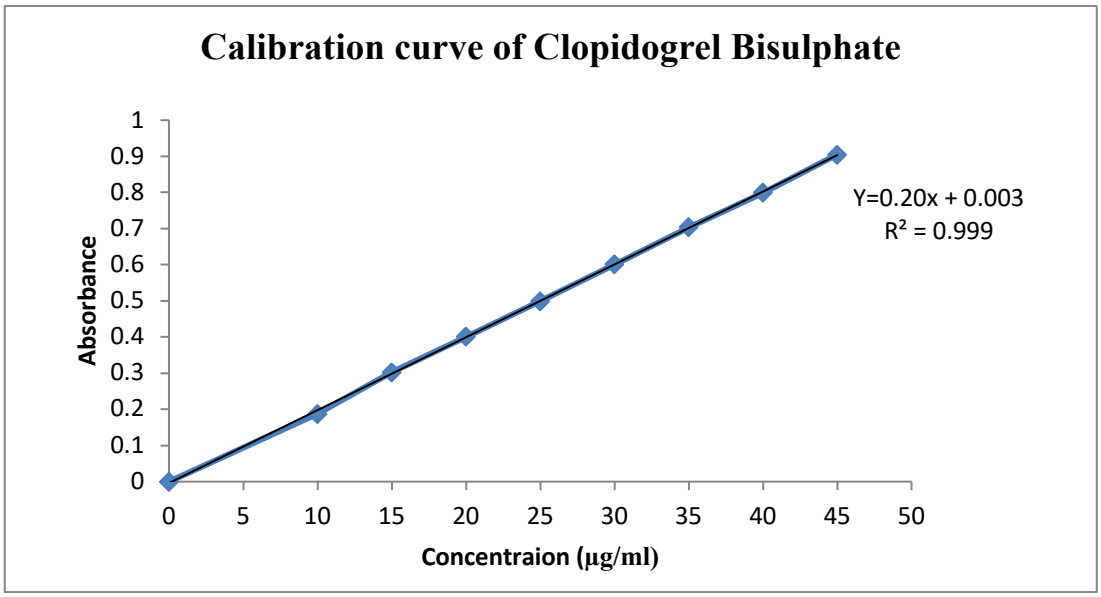

Figure 8: Calibration Curves of Clopidogrel Bisulphate distilled water pH 1

The correlation coefficient of calibration curves of Clopidogrel Bisulphate (Figure no. 8) in distilled water pH 1, 0.999 and was very close to 1. The linear graph obtained and the values of correlation coefficient showed that the Beer- Lambert's law was obeyed in the drug concentration range of 10-45µg/ml.

Characterization of Blend

The dried blend of different formulation was subjected for evaluation properties i.e. angle of repose, bulk density, tapped density and % compressibility.

Table 6: Micrometrical properties of blend. (Values are in Mean ± SD, n= 3)

Formulation	Angle of Repose(θ)±SD	Bulk Density (mg/ml) ±SD	Tapped Density (mg/ml) ±SD	Hausners Ratio ±SD	Compressibility Index (%) ±SD
F1	25.827±1.675	0.673±0.010	0.776±0.029	1.152±0.023	13.265±1.672
F2	26.565±0.973	0.603±0.008	0.660±0.013	1.150±0.011	13.636±2.018
F3	22.713±0.863	0.584±0.011	0.711±0.017	1.136±0.033	14.051±2.985
F4	26.565±0.973	0.603±0.008	0.660±0.013	1.150±0.011	13.636±2.018
F5	26.575±1.320	0.611±0.033	0.717±0.027	1.148±0.008	12.962±1.278
F6	25.706±0.929	0.627±0.034	0.714±0.029	1.112±0.031	12.220±1.916

The angle of repose, Bulk density, tapped density, Hausners Ratio, % Compressibility of all formulations (F1 to F6) was carried out. The range of Angle of repose between 22.713±0.863 to

26.565±0.973, Bulk density between 0.584±0.011 to 0.673±0.010, Tapped density between 0.660±0.013 to 0.776±0.029, Hausner Ratio between 1.112±0.031 to 1.152±0.023 and Compressibility index between 12.220±1.916 to 14.051±2.985. Hence, it indicated good flow property of blend.

Formulation & Development of Floating Tablet

Floating tablets of Clopidogrel Bisulphate were prepared by using combination of polymers by direct compression method.

Table 7: Formulation: 1

S. No.	Ingredients	F1(mg)	Percentage
1	Clopidogrel Bisulphate	98	35.0
2	Avicel pH112	50	17.9
3	Lactose anhydrous	39.24	14.0
4	HPMC K4M	40	14.3
5	HPMC K100LV	20	7.1
6	Sod. bi-carbonate	25.76	9.2
7	Colloidal silicon dioxide	1.4	0.5
8	Polyethylene glycols	2.8	1.0
9	Hydrogenated castor oil	2.8	1.0

Floating time achieve up to 6 hr., further improvement required to increase floating time.

Strategy: Increase the concentration of HPMC K4M along with same conc. of HPMC K100LV

Table 8: Formulation: 2

S. No.	Ingredients	F2(mg)	Percentage
1	Clopidogrel	98	35.0
2	Avicel pH 112	30	10.7
3	Lactose anhydrous	39.24	14.0
4	HPMC K4M	60	21.4
5	HPMC K100LV	20	7.1
6	Sod. bi-carbonate	25.76	9.2
7	Colloidal silicon dioxide	1.4	0.5
8	Polyethylene glycols (PEG 6000)	2.8	1.0
9	Hydrogenated castor oil	2.8	1.0

with increase conc. of HPMC K4MFloating time achieve up to 10 hr so further improvement required to increase floating time.

Strategy: Increase the concentration of Sodium bi carbonate with same conc. of HPMC K4M and HPMC K100 LV**.**

Table 9: Formulation: 3

S. No.	Ingredients	F3(mg)	Percentage
1	Clopidogrel Bisulphate	98	35.0
2	Avicel pH 112	16	5.7
3	Lactose anhydrous	39	13.9
4	HPMC K4M	60	21.4
5	HPMC K100LV	20	7.1
6	Sod. bi-carbonate	40	14.3
7	Colloidal silicon dioxide	1.4	0.5
8	Polyethylene glycols (PEG 6000)	2.8	1.0
9	Hydrogenated castor oil	2.8	1.0

with increase conc. of Sodium bicarbonate there is no improvement in Floating time.

Strategy: keep the conc. of sodium bi carbonate same as trial 2 with increase conc. of HPMC K4M.

Table 10: Formulation: 4

S. No.	Ingredients	F4(mg)	Percentage
1	Clopidogrel Bisulphate	98	35.0
2	Avicel pH112	10	3.6
3	Lactose anhydrous	39.24	14.0
4	HPMC K4M	80	28.6
5	HPMC K100LV	20	7.1
6	Sod. bi-carbonate	25.76	9.2
7	Colloidal silicon dioxide	1.4	0.5
8	Polyethylene glycols (PEG 6000)	2.8	1.0
9	Hydrogenated castor oil	2.8	1.0

Tablet floating time achieves up to 24 hr but it shows fast release at initial time point as well as low release at final time point (85%).

Strategy: Take a trial with decrease conc. of HPMC K4M to achieve desired release on last time point.

Table 11: Formulation: 5

S. No.	Ingredients	F5(mg)	Percentage
1	Clopidogrel	98	35.0
2	Avicel pH 112	20	7.1
3	Lactose anhydrous	39.24	14.0
4	HPMC K4M	70	25.0
5	HPMC K100LV	20	7.1
6	Sod. bi-carbonate	25.76	9.2
7	Colloidal silicon dioxide	1.4	0.5
8	Polyethylene glycols (PEG 6000)	2.8	1.0
9	Hydrogenated castor oil	2.8	1.0

Conc. of HPMC K4M optimized to achieve desirable release at last time point further improvement required for initial point.

Strategy: Take a trial with increase conc. of HPMC K100LV to achieve desired release on initial time point.

Table 12: Formulation: 6

Sr. No.	Ingredients	F6(mg)	Percentage
1	Clopidogrel Bisulphate	98	35.0
2	Avicel pH 112	20	7.1
3	Lactose anhydrous	24.24	8.7
4	HPMC K4M	70	25.0
5	HPMC K100LV	35	12.5
6	Sod. bi-carbonate	25.76	9.2
7	Colloidal silicon dioxide	1.4	0.5
8	Polyethylene glycols (PEG 6000)	2.8	1.0
9	Hydrogenated castor oil	2.8	1.0

Conc. of HPMC K4M & HPMC K100LV optimized to achieve desirable sustained release profile.

Evaluation of Prepared Tablets

Physical Parameter

The prepared floating tablets were subjected to physical parameters i.e thickness, weight variation, hardness, friability. All the floating tablet complies for all the physical parameter. The results are shown in table 13.

Table 13: Characteristics of floating tablet of Clopidogrel Bisulphate

Formulation Code	Thickness (mm)*	Weight variation (mg)*	Hardness (kg/cm^2) *	Friability (%)*	Drug content (%)
F1	4.133±0.0333	280.3 ± 1.764	4.413±0.1667	0.248	99.65±0.265
F2	4.237±0.0333	280.8 ± 2.404	4.457±0.1667	0.184	99.35±0.255
F3	4.056±0.0333	280.2 ± 2.603	4.446±0.1667	0.272	99.95±0.461
F4	4.167±0.0333	279.5±1.453	4.439±0.0673	0.207	98.95±0.273
F5	4.267±0.0333	280.5±2.309	4.843±0.0689	0.184	99.05±0.765
F6	4.147±0.0333	280.9±2.109	4.446±0.1667	0.140	99.55±0.651

*n = 20; Mean ±SD

The result of the all formulations was varied with drug: polymer ratio and thickness of all the formulations range from 4.056±0.0333 to 4.267±0.0333. The weight variation test was carried out as per official method and the average % deviation of all the formulations was found to be within the limited (as per pharmacopoeia standard the deviation should not more than 5% for tablet having weight 280mg). The tablet hardness of all the formulations was determined and it was found 4.413±0.1667 to 4.843±0.0689 kg/cm^2. The friability of compressed tablet was found to be within the limit that was less than 1%., The drug content within the limit 98.95±0.273 to 99.95±0.461. Hence, it is acceptable.

Floating Properties

Prepared floating tablet were evaluated for Floating lag time (FLT) and Total floating time (TFT) and results are given in figure 9 & 10 respectively.

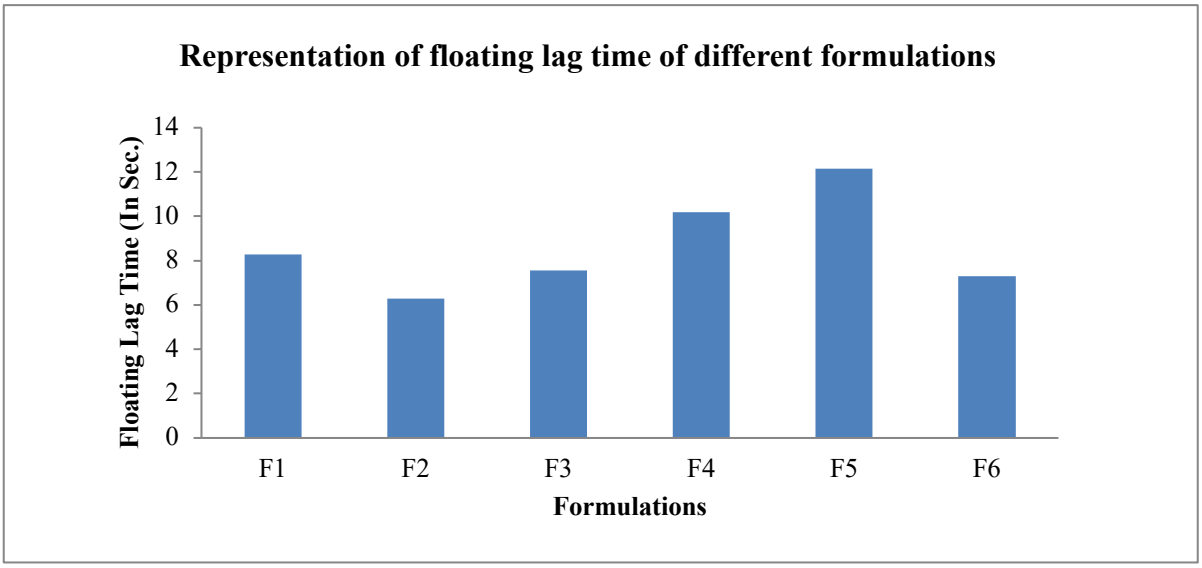

Figure 9: Representation of floating lag time of different formulations

From the above table floating log time (FLT) of all formulations (F1 to F6) was carried out and the minimum to maximum FLT between 6.283±0.072 to 12.15±0.086 second. the optimize formulation F6 showed desired FLT, it was satisfactory.

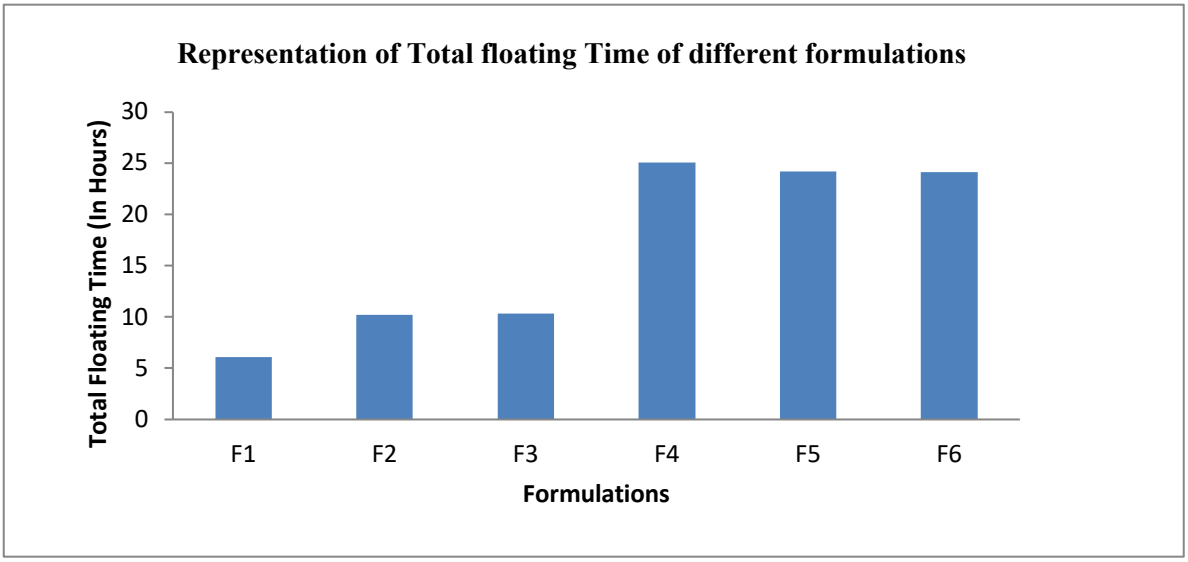

Figure 10: Representation of Total floating Time of different formulation

Figure showed Total floating time of all formulations F1 to F6 using different concentration of HPMC K4M and K100LV and other excipients. F5 & F6 have the highest TFT observed as compared to F1. It is acceptable for optimized formulation F6.

Table 14: Swelling Behaviour of Floating Tablet

Formulation Code	Increase in weight with time (Initial weight = 280mg)				
	1hr	2hr	3hr	4hr	5hr
F1	324	332	352	365	380
F2	330	342	355	366	378
F3	330	340	354	363	375
F4	327	342	351	361	369
F5	321	340	352	364	373
F6	324	339	350	363	376

Figure 11: Comparative Study of % swelling index

From the

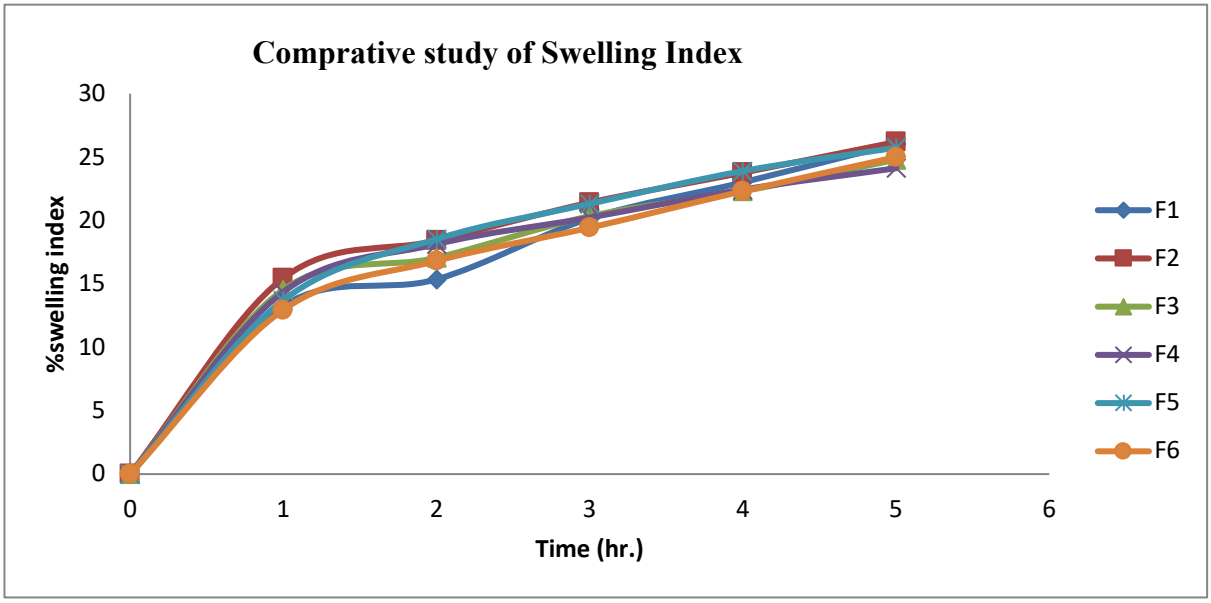

figure 11, it was observed that F1 to F6 has significant % swelling index due to using different concentration of HPMC K4M & K100LV. Swelling is vital factor to ensure buoyancy, drug dissolution and also influences drug release kinetics. % swelling index was calculated at 1,2,3,4 and 5h, it had been observed that the % of swelling index was also increased by increasing concentration of HPMC.

In-Vitro Dissolution Study

Figure 12: In-vitro drug release profile of different formulations

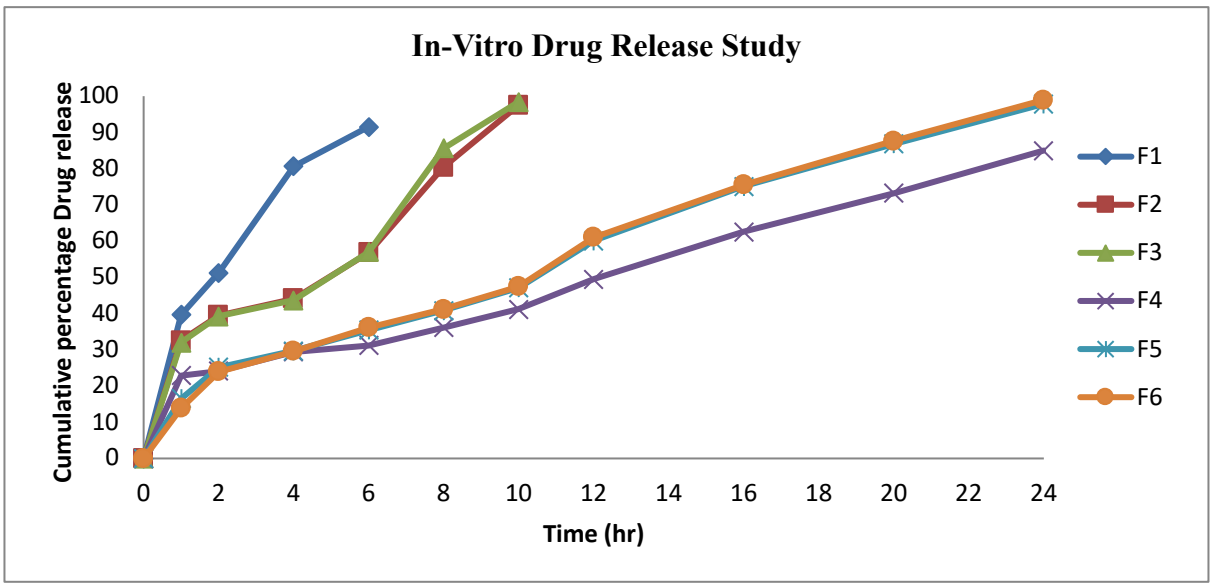

Table 15: In-Vitro Dissolution Profile of Formulation (F6) in 0.1 N HCl

Time in Hrs. T	T½	Log t	Cum. %Drug Released	Log Cum. %Drug Released	Cum. %Drug Remained	Log Cum. %Drug Remained
1	1.000	0.000	13.86	1.142	86.14	1.935
2	1.414	0.301	23.97	1.380	76.03	1.881
4	2.000	0.602	29.64	1.472	70.36	1.847
6	2.449	0.778	36.11	1.558	63.89	1.805
8	2.828	0.903	41.18	1.615	58.82	1.770
10	3.162	1.000	47.43	1.676	52.57	1.721
12	3.464	1.079	61.09	1.786	38.91	1.590
16	4.000	1.204	75.52	1.878	24.48	1.389
20	4.472	1.301	87.64	1.943	12.36	1.092
24	4.899	1.380	98.97	1.996	1.03	0.013

Formulation F6 showed optimization drug release as compared to other formulations. The Various Kinetics models were applied for optimized formulation F6 and the results are showed in table 15 The result indicated that the optimized formulation F6 followed the korsmeyer - peppas model with n value of 0.499 i.e. Drug release was observed by Non-Fickian diffusion.

Tablet Stability Study Data

Table 16: Stability Study Data

Stability Study Data
Product: Clopidogrel Bisulphate tablet
Stability Condition: 40˚C/75% RH
Batch no. F6

Test Detail	Initial		1 Month	2 Month	Remarks
Physical Appearance	Off White color, Biconvex round shape		Off White color, Biconvex round shape	Off White color, Biconvex round shape	**No change**
% Assay Mean (90-110% of label claim)	99.5		99.2	99.3	-
% Drug Release USP Apparatus: 2 (Paddle) Medium: 1.2 N HCl **RPM**: 50	**24hr**	98.97%	99.02	98.59	-

After 2 months, the optimized batch F6 was subjected for evaluation of physical parameters. When matrix tablets were stored at 40°C/ 75% RH, no change was appeared; the optimized formulation shows satisfactory results from stability studies.

Discussion

The present study aimed to develop a gastroretentive floating drug delivery system (GRFDDS) for Clopidogrel Bisulphate to enhance its oral bioavailability by prolonging gastric residence time and achieving sustained drug release. Clopidogrel, a prodrug with a narrow absorption window and pH-dependent solubility, particularly benefits from gastric retention due to its enhanced solubility in acidic media.

Among the six formulations (F1–F6) prepared using varying concentrations of hydrophilic polymers (HPMC K4M and HPMC K100LV) and effervescent agents, Formulation F6 demonstrated the most desirable characteristics. It exhibited a rapid floating lag time (7.29 ± 0.055 seconds), prolonged total floating duration (>24 hours), and excellent physical integrity, including acceptable weight variation, hardness, friability, and drug content uniformity. These attributes are crucial for ensuring tablet buoyancy, mechanical robustness, and consistent drug delivery in vivo (Namrata Rajkumar Singh*, 2020).

The sustained release profile observed in F6, with 98.97% drug release over 24 hours, indicates effective modulation of drug diffusion by the polymeric matrix. The presence of both high-viscosity (HPMC K4M) and low-viscosity (HPMC K100LV) cellulose derivatives allowed fine-tuning of the

swelling behavior and gel strength, which are key factors in controlling drug release(Jain et al., 2014). The increase in swelling index with increasing HPMC concentration further supports the role of polymer hydration in maintaining matrix integrity and buoyancy(Berardi et al., 2019). Release kinetics analysis revealed that the drug release from F6 followed the Korsmeyer-Peppas model ($R^2 = 0.977$; n = 0.499), indicating a non-Fickian (anomalous) diffusion mechanism, which combines diffusion and erosion processes. This is consistent with the behavior expected from hydrophilic matrix systems where both water penetration and polymer relaxation contribute to drug release.

Compatibility studies using FTIR and DSC confirmed the absence of significant interactions between Clopidogrel and the selected excipients, supporting the chemical stability of the formulation. Additionally, accelerated stability testing over a two-month period under ICH guidelines demonstrated that F6 retained its physical appearance, drug content, and dissolution profile, highlighting its formulation stability.

Conclusion

This study effectively established the development and evaluation of a gastric retentive floating drug delivery system (GRFDDS) for Clopidogrel Bisulphate, with the primary objective of enhancing its oral bioavailability and therapeutic efficacy. Floating tablet formulations were systematically prepared employing hydrophilic matrix-forming polymers—Hydroxypropyl Methylcellulose (HPMC K4M and HPMC K100LV)—in combination with an effervescent agent (sodium bicarbonate) and other pharmaceutically acceptable excipients. Among the six formulations developed, Formulation F6 demonstrated optimal performance, characterized by satisfactory physical attributes, a short floating lag time (7.29 ± 0.055 seconds), prolonged total floating duration (exceeding 24 hours), and sustained drug release (98.97% over 24 hours). The drug release kinetics of the optimized formulation conformed to the Korsmeyer-Peppas model ($R^2 = 0.977$; n = 0.499), indicative of a non-Fickian diffusion mechanism.

Both pre-compression and post-compression evaluations confirmed favorable micromeritic properties and robust mechanical integrity of the tablets. Drug-excipient compatibility studies, performed using DSC and FTIR analyses, revealed no significant chemical interactions. Additionally, stability studies conducted under ICH-recommended conditions verified the physical and chemical stability of the optimized formulation over a two-month period.

In conclusion, the formulated GRFDDS effectively addressed the inherent limitations of conventional Clopidogrel delivery by providing prolonged gastric retention, sustained drug release, and the potential for improved bioavailability. This formulation strategy holds promise for application to other therapeutic agents with similar biopharmaceutical limitations.

Author Contribution

PC – Data curation, Data analysis, Experimental work, Original Manuscript draft writing, and editing; **KKC -** Supervision, Manuscript writing and editing.

Conflict of Interest

Both the authors approved the submission of the manuscript and have no conflict of interest.

Ethic statement

There were no human/animal samples used in this study.

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Generative AI statement

The authors utilized generative AI tools for paraphrasing and language editing of the manuscript; however, all AI-generated content was thoroughly reviewed, critically evaluated, and appropriately modified before incorporation into the final version of the manuscript.

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