RESEARCH PAPER

Formulation and Evaluation of Clopidogrel Bisulfate Sustained Release Matrix Tablets by Melt Granulation Technique

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ABSTRACT

The present research work focuses on the formulation and evaluation of sustained release matrix tablets of Clopidogrel bisulfate using the melt granulation technique. The main objective of the study was to prolong drug release, enhance patient compliance, and maintain constant therapeutic levels. Clopidogrel, an antiplatelet agent with a short biological half-life, requires frequent dosing; hence, a sustained release formulation was designed to overcome this limitation. In this study, a total of Sixteen different formulations were prepared by the melt granulation technique using varying concentrations of hydrophilic polymers such as (PEG 4000) and Poloxamer 188, and hydrophobic polymers such as Stearic Acid and Beeswax, in ratios of 1:0.25, 1:0.5, 1:1, and 1:1.5. These polymers served as matrix-forming agents, along with other excipients including MCC, Talc, and Magnesium Stearate. The prepared granules were evaluated for pre-compression parameters including bulk density, tapped density, angle of repose, carr's index, hausner's ratio and compressibility index found to be within limits to ensure uniform flow properties. The compressed tablets were subjected to post-compression evaluations such as weight variation, hardness, friability, thickness, drug content uniformity and In vitro dissolution studies were carried out using a USP Type II dissolution apparatus in 0.1N HCl buffer for 12 hours to determine the drug release profile. All the formulations exhibited satisfactory compliance with Pharmacopeial standards in terms of in-vitro drug release over a 12-hour period. Among the hydrophilic polymer formulations, F7 containing drug and Poloxamer 188 in a 1:1 ratio demonstrated superior drug release (97.7%) after 12 hours compared to F3. Similarly, within the hydrophobic polymer group, formulation F9 consisting of drug and stearic acid in a 1:0.25 ratio showed a better dissolution profile than F13. Based on these results, F7 was identified as the optimized formulation containing optimized ratio of Poloxamer exhibited a controlled and sustained drug release pattern followed zero-order kinetics, as indicated by the higher regression coefficient (R^2 = 0.9906), suggesting that the release mechanism was governed by diffusion processes. The optimized formulation remained stable for up to 3 months. The results demonstrated that the melt granulation technique is an effective and reproducible method for formulating sustained release matrix tablets of Clopidogrel.

Keywords: Clopidogrel Bisulfate, matrix sustained release tablets, melt granulation, poloxamer 188, stearic acid, PEG-4000, Bees wax.

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INTRODUCTION

Conventional immediate-release (IR) oral dosage forms require frequent administration to maintain therapeutically effective plasma concentrations. Such frequent dosing often results in poor patient compliance, particularly in chronic conditions. IR formulations produce rapid drug absorption followed by a decline in plasma concentration due to distribution and elimination, leading to significant peak-to-trough fluctuations. These variations may cause sub-therapeutic effects or toxicity, especially in drugs with a narrow therapeutic index or short biological half-life.[1,2]

To overcome these limitations, modified-release drug delivery systems have been developed to control the rate and duration of drug release. Modified-release dosage forms are designed to alter the release characteristics of drugs to achieve therapeutic advantages[3,4]. Terms such as sustained-release, extended-release, prolonged-release, and controlled-release are commonly used. Controlled-release systems aim to provide drug release at a constant rate, ideally following zero-order kinetics, whereas sustained-release systems prolong drug release without necessarily achieving constant kinetics. Delayed-release systems, such as enteric-coated tablets, release the drug after a predetermined lag time.

Among various modified-release technologies, matrix tablets are one of the most widely used

approaches due to their simplicity, cost-effectiveness, and reproducibility. In matrix systems, the drug is uniformly dispersed within a polymeric matrix that controls drug release through diffusion, erosion, or a combination of both mechanisms[5,6]. Hydrophilic polymers such as hydroxypropyl methylcellulose (HPMC), hydroxypropyl cellulose (HPC), hydroxyethyl cellulose (HEC), polyethylene glycol (PEG), xanthan gum, sodium alginate, poloxamers, and poly(ethylene oxide) are frequently employed because of their gel-forming properties, which ensure controlled and predictable drug release.[6,7]

Oral drug delivery remains the most preferred route of administration due to its convenience, safety, and patient acceptability. However, conventional IR formulations often fail to maintain consistent therapeutic plasma levels. Sustained-release systems help maintain drug concentrations within the therapeutic window for extended periods, thereby reducing dosing frequency, minimizing plasma fluctuations, decreasing adverse effects, and improving patient adherence.[8,9]

Cardiovascular diseases (CVD) continue to be a major cause of morbidity and mortality worldwide. Platelet aggregation plays a crucial role in the pathogenesis of atherothrombosis, necessitating the use of antiplatelet agents. Clopidogrel, a thienopyridine derivative, irreversibly inhibits the P2Y12 adenosine diphosphate (ADP) receptor on platelets, thereby preventing platelet aggregation. The development of a sustained-release matrix tablet of Clopidogrel may provide stable plasma drug levels, reduce dosing frequency, and enhance patient compliance in long-term cardiovascular therapy.[9]

Overall, sustained-release matrix systems represent an important advancement in oral drug delivery, offering improved therapeutic efficacy, reduced side effects, and enhanced patient adherence.

Melt Granulation / Melt Agglomeration Technique

Melt granulation, also known as melt agglomeration, is a solvent-free granulation process widely applied in the pharmaceutical field to improve the flowability, compressibility, and homogeneity of powder formulations. In this technique, a low-melting-point binder acts as the granulating agent, binding fine solid particles together under the influence of heat and mechanical agitation. Upon heating, the binder melts and forms liquid bridges between particles, which on cooling, solidify to produce stable granules or agglomerates with enhanced physical characteristics.[10,11]

Unlike conventional wet granulation, melt granulation eliminates the need for water or organic solvents and therefore does not require drying. This makes it particularly suitable for moisture-sensitive or solvent-incompatible drugs and aligns with environmentally sustainable manufacturing practices. The process also offers opportunities for modulating drug release profiles through the selection of appropriate binders and process parameters, making it a valuable approach for controlled or sustained-release formulations.[11,12]

Hydrophillic Meltable Binders

S.No	Hydrophillic Meltable Binders	Typical Melting range (°C)
1.	Gelucire 50/13	44-50
2.	Poloxomer 188	50.9
3.	Polyethylene glycol2000	42-53
4.	Polyethylene glycol 4000	57-63
5.	Polyethylene glycol 6000	49-63
6.	Polyethylene glycol 8000	54-63
7.	Polyethylene glycol 10000	57-64
8.	Polyethylene glycol 20000	53-66
9.	Stearate 6000WL 1644	46-58

Hydrophobic Meltable Binders

S.No	Hydrophobic Meltable Binders	Typical Melting range (°C)
1.	Bees wax	56-60

2.	Carnauba wax	75-83
3.	Cetyl palmitate	47-50
4.	Glycerin monostearate	47-63
5.	Paraffin wax	47-65
6.	Stearic acid	46-69
7.	Glyceryl behenate	67-75
8.	Glyceryl palmitostearte	48-57
9.	Glyceryl stearate	54-63
10	Hydrogenated castor oil	62-86
11.	Steryl alcohol	56-60

POTENTIAL ADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM

•Avoid patient's compliance problem due to reduced frequency of dosing.

•Blood level oscillation characteristics of multiple dosing of conventional dosage form are reduced because a more even blood level is maintained.[12]

•Employ a less total drug.

•Minimize or eliminate local or systemic side effects.

•Minimize drug accumulation with chronic dosing.

•Obtained less potential of reduction in drug activity with chronic use.

Improved efficiency in treatment.

Cure or control condition more promptly.

Improved control of condition i.e. reduced fluctuation in drug level.

Improved bioavailability of some drugs.

Make a use of special effects, e.g. sustained release aspect for relief of arthritis by dosing before bedtime.

Overall, administrations of sustained release form enable increased reliability of therapy.

DISADVANTAGES OF SUSTAINED RELEASE DOSAGE FORM

•If there requires immediate change during the therapy or if any significant adverse effect is noted and prompt termination of therapy is needed, sustained release does notpermit immediate termination of therapy.[13]

•More costly process and equipment are needed in manufacturing of SRDDS.

•Physician has less flexibility in adjusting dosage regimen as this is fixed by design of dosage form. Risk of dose dumping, usually SRDDS contain drug amount that is 3-4 times more than conventional formulations.Sometimes this large quantity of drug may get rapidly released leading to toxicity.[14,15]

•Reduced drug absorption may delay onset of action. The effect of food on drug absorption.

•Kinetics may differ markedly from one SR formulations to another.

•Drug absorbed at specific time in GIT cannot be formulated in SRDDS.

•Increased potential for first pass clearance.

•In case of accidental failure of the product effective antidote may be difficult to employ.

MATERIALS AND METHODOLOGY

List of materials: All the materials used in the investigation were analytical grade listed in the table

List of all chemicals used

S.No	Name of the chemical	Role of formulation
1.	Clopidogrel bisulphate	API
2.	PEG-4000	Polymer
3.	Poloxomer 188	Polymer
4.	Stearic acid	Polymer
5.	Bees wax	Polymer
6.	MCC	Diluent
7.	Magnesium stearate	Lubricant
8.	Talc	Glidant
9.	Methanol	Solvent
10.	Ethanol	Solvent

PREFORMULATION STUDIES:

ORAGANOLEPTIC CHARACTERS:

The pre formulation studies such as the colour, odour, taste can be done by visually.

SOLUBILITY STUDIES:

The solubility studies are done by using various solvents such as the ethanol, methanol, acetone, and other organic solvents.

DRUG AND EXCIPIENT COMPATABILITY STUDIES:

The drug and excipient compatability studies are done by FTIR Studies by using Kbr pellet method. First the 1 gm of the drug powder is taken kept under for the FTIR studies. The 1gm of drug and polymer take and kept under FTIR studies the peaks which are came for drug product the nearer to the drug the polymer peaks will come. If they are not came the drug and excipients are in compatable with each other.[15,16]

DEVELOPMENT OF CALIBRATION CURVE

A standard stock solution of Clopidogrel (1000 µg/mL) was prepared by dissolving 10 mg of drug in 10 mL of 0.1 N HCl. A sub-stock solution (100 µg/mL) was then prepared by transferring 1 mL of the stock solution into a 10 mL volumetric flask and diluting to volume with 0.1 N HCl. Aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 mL of the sub-stock solution were further diluted to 10 mL with 0.1 N HCl to obtain concentrations of 5, 10, 15, 20, 25, and 30 µg/mL, respectively. The absorbance of each solution was measured at 236 nm using a UV–Visible spectrophotometer against 0.1 N HCl as the blank. A calibration curve was constructed by plotting absorbance versus concentration, and the linearity of the method was evaluated over the concentration range of 5–30 µg/mL

PRECOMPRESSION PARAMETERS:

The powder blend was evaluated for precompression properties to determine its flowability and suitability for tablet compression. Bulk density was determined by measuring the volume occupied by a known quantity of powder before tapping. Tapped density was measured after subjecting the powder to mechanical tapping until a constant volume was obtained.

The angle of repose was determined using the fixed funnel method to assess the flow characteristics of the powder blend. A lower angle of repose indicated better flow properties. Carr's compressibility index was evaluated to determine the compressibility and flow behavior of the powder. Lower compressibility index values indicated good flowability, while higher values suggested poor flow characteristics. Hausner's ratio was also determined as an indicator of interparticle friction and powder flow. Lower Hausner's ratio values indicated excellent flow properties, whereas higher values were associated with poor flowability. The results obtained from these parameters were used to evaluate the suitability of the powder blend for further processing and tablet formulation.

FORMULATION OF CLOPIDOGREL BISULFATE SR TABLETS BY MELT GRANULATION METHOD

Ingredients	**F1 (1:0.25)**	**F2 (1:0.5)**	**F3 (1:1)**	**F4 (1:1.5)**	**F5 1:0.25)**	**F6 (1:0.5)**	**F7 (1:1)**	**F8 (1:1.5)**	**F9 (1:0.25)**	**F10 (1:0.5)**	**F11 (1:1)**	**F12 (1:1.5)**	**F13 1:0.25)**	**F14 (1:0.5)**	**F15 (1:1)**	**F16 (1:1.5)**
Clopidogrel Bisulfate (mg)	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75	75
Polyethyleneglycol (PEG-4000)(mg)	18.75	37.5	75	112.5	-	-	-	-	-	-	-	-	-	-	-	-
Poloxamer188(mg)	-	-	-	-	18.75	37.5	75	112.5	-	-	-	-	-	-	-	-
Stearic acid (mg)	-	-	-	-	-	-	-	-	18.75	37.5	75	112.5	-	-	-	-
Bees wax (mg)	-	-	-	-	-	-	-	-	-	-	-	-	18.75	37.5	75	112.5
MCC(mg)	102.25	83.5	46	8.5	102.25	83.5	46	8.5	102.25	83.5	46	8.5	102.25	83.5	46	8.5
Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2

(mg)																
Talc (mg)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Total Weight (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

Matrix tablets: Different formulations of each containing75mg of Clopidogrel were prepared by melt granulation technique.

.5 Preparation and Evaluation of Clopidogrel Bisulfate Sustained-Release Tablets

Clopidogrel Bisulfate sustained-release matrix tablets containing 75 mg of drug were prepared by the melt granulation technique using different drug-to-polymer ratios (1:0.25, 1:0.5, 1:1, and 1:1.5). Accurately weighed quantities of drug, polymers, and excipients were blended uniformly and incorporated into the molten polymer maintained slightly above its melting point. The resulting mass was mixed thoroughly to obtain uniform granules, which were cooled, passed through a suitable sieve, lubricated, and compressed into tablets using a rotary tablet press fitted with a 6 mm punch. The prepared powder blends were evaluated for precompression properties, including bulk density, tapped density, angle of repose, Carr's compressibility index, and Hausner's ratio to assess flow characteristics and compressibility.

The compressed tablets were evaluated for post-compression parameters such as weight variation, thickness, hardness, friability, swelling index, and drug content. In vitro dissolution studies were carried out using USP Type II (paddle) apparatus containing 900 mL of 0.1 N HCl maintained at 37 ± 0.5°C and operated at 75 rpm for 12 h. Samples were withdrawn at predetermined intervals, analyzed spectrophotometrically at 236 nm, and the cumulative drug release was calculated. Drug–excipient compatibility was investigated by Fourier Transform Infrared (FTIR) spectroscopy in the range of 4000–400 cm^{-1}. The optimized formulation was subjected to accelerated stability studies according to ICH guidelines at 45°C and 75 ± 5% RH for three months and evaluated periodically for physical appearance, hardness, drug content, and dissolution characteristics.

3. RESULTS AND DISCUSSION

3.1 ORGANOLEPTIC PROPERTIES

. Table showing Organoleptic Properties

Properties	Observation	Reported standards
Appearance	Crystalline powder	Crystalline powder
Colour	White to off white colour	White to off white colour

3.2 CALIBRATION CURVE OF CLOPIDOGREL BISULFATE IN 0.1NHCL

Standard plot of Clopidogrel in pH 0.1N Hcl buffer

S.NO	Concentration (ug\ml)	Absorbance at 236nm
1.	5	0.204±0.313
2.	10	0.306±0.211
3.	15	0.424±0.093
4.	20	0.548±0.031

5.	25	0.745±0.228
6.	30	0.875±0.358

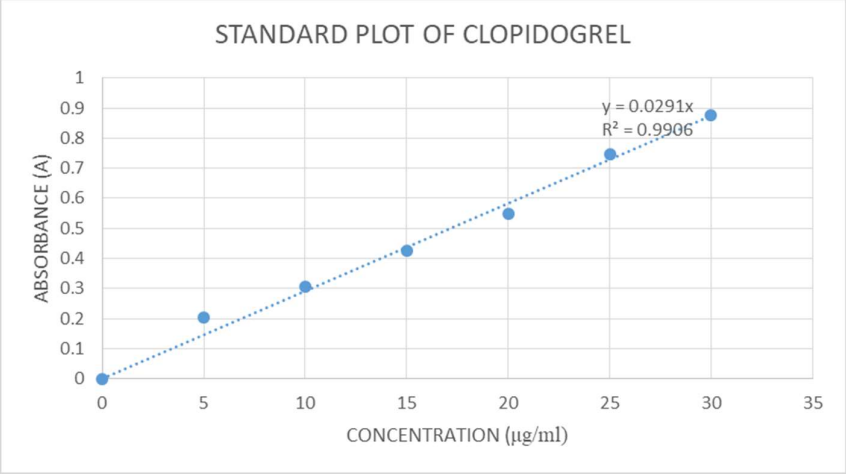


Fig.1 : Standard plot of Clopidogrel

3.3 SOLUBILITY STUDIES:

Solubility of pure drug

S.No	SOLVENT	SOLUBILITY (mg/ml)
1.	Distilled water	6.01
2.	Methanol	2.60
3.	Ethanol	3.89
4.	DMSO	7.03
5.	CCl4	0.83
6.	pH-4.5 acetate buffer	2.95
7.	pH-6.8 phosphate buffer	7.17
8.	PH-7.4 phosphate buffer	5.21
9.	0.1N HCl buffer	9.16

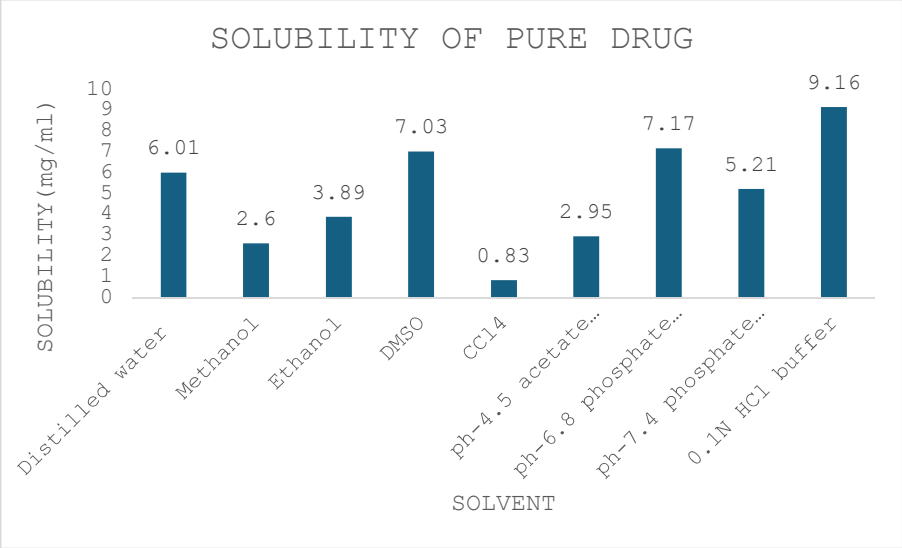


Fig.2: Solubility of pure drug

3.4 PRECOMPRESSION PARAMETERS

Pre-Compression parameters of powder blend of Clopidogrel bisulfate

Formulation code	Angle of repose(°)±SD	Bulk density (g/ml) ±SD	Tapped density (g/ml)±SD	Carr's index (%)±SD	Hausners ratio ±SD
F1	33.69±2.33	0.527±0.012	0.556±0.048	5.21±5.31	1.05±0.06
F2	28.39±2.97	0.609±0.07	0.672±0.068	9.37±1.15	1.11±0
F3	29.74±1.62	0.626±0.022	0.722±0.118	13.29±2.77	1.15±0.04
F4	34.90±3.54	0.505±0.034	0.594±0.01	14.98±4.46	1.17±0.06
F5	33.07±1.71	0.53±0.009	0.605±0.001	12.39±1.87	1.14±0.03
F6	30.96±0.4	0.564±0.025	0.637±0.033	11.45±0.93	1.12±0.01
F7	26.56±4.8	0.543±0.004	0.572±0.032	5.06±5.46	1.05±0.06
F8	33.02±1.66	0.527±0.012	0.607±0.003	13.17±2.65	1.15±0.04
F9	30.01±1.35	0.541±0.002	0.611±0.007	11.45±0.93	1.12±0.01
F10	30.01±1.35	0.537±0.002	0.585±0.019	8.20±2.32	1.08±0.03
F11	33.69±2.33	0.517±0.002	0.59±0.014	12.37±1.85	1.14±0.03
F12	28.07±3.29	0.508±0.031	0.581±0.023	12.56±2.04	1.14±0.03
F13	34.28±2.92	0.517±0.022	0.559±0.045	7.51±3.01	1.08±0.03

F14	33.69±2.33	0.515±0.024	0.557±0.047	7.54±2.98	1.08±0.03
F15	33.02±1.66	0.524±0.015	0.584±0.02	10.27±0.25	1.11±0
F16	28.81±2.55	0.549±0.01	0.635±0.031	13.54±3.02	1.15±0.04

Discussion: The all the F1-F16 formulations pre compression parameters such as the angle of repose,bulk density,tap density,husners ratio,compressability index all comes under the within range of limits. All the formulations fallow the good flow.

3.5 POST COMPRESSION PARAMETERS

Formulation code	%Weight variation	Hardness Kg/cm²	Friability %	Thickness (mm)	Swelling index %	Drug content
F1	196±3	5.6±0.24	0.75±0.19	5.6±0.17	26.19±0.62	84.8±0.41
F2	195±4	5.3±0.06	0.83±0.27	5.5±0.07	31.81±5	95.46±10.2
F3	186±13	5.5±0.14	0.58±0.02	5.5±0.07	37.07±10.26	94.4±9.19
F4	199±0	4.6±0.76	0.25±0.31	5.5±0.07	42±15.19	80.3±4.91
F5	201±2	5.4±0.04	0.66±0.1	5.7±0.27	28.07±1.26	89.0±3.79
F6	199±0	5.2±0.16	0.33±0.23	5.7±0.27	34.02±7.21	78.4±6.81
F7	200±1	5.5±0.14	0.75±0.19	5.6±0.17	38.05±11.24	97.6±12.39
F8	197±2	5.8±0.44	0.92±0.36	5.5±0.01	50.75±23.94	81.4±3.81
F9	198±1	5.6±0.24	0.25±0.31	5.1±0.33	11.39±15.42	86.9±1.69
F10	199±0	4.9±0.46	0.33±0.23	5±0.43	18.22±8.59	78.4±6.81
F11	200±1	5.8±0.44	0.66±0.1	5.1±0.33	26.21±0.6	87.46±2.45
F12	201±2	4.8±0.56	0.08±0.48	5.4±0.03	29.29±2.48	89.06±3.85
F13	201±2	5.5±0.14	0.50±0.06	5.1±0.33	9.83±16.98	76.2±9.01
F14	207±8	5.7±0.34	0.83±0.27	5.4±0.03	13.06±13.75	78.1±7.11
F15	201±2	5.4±0.04	0.41±0.91	5.7±0.27	15.34±11.47	84.8±0.41
F16	205±6	5.3±0.06	0.83±0.27	5.5±0.01	17.78±9.03	81.0±4.21

INVITRO DRUG RELEASE PROFILE OF CLOPIDOGREL BISULFATE

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8
0.5	9.3±.0.12	10.0±0.01	12.5±0.03	9.8±0.07	13.1±0.06	10.1±0.08	8.2±0.03	10.6±0
1	12.5±0.13	16.0±0.05	18.9±2.02	13.0±0.01	16.1±0.03	18.9±2.09	19.3±0.02	20.1±0
2	17.2±0.23	24.7±0.07	28.4±0.40	19.7±0.45	26.7±1.27	28.4±0.02	27.0±1.23	26.7±1
3	23.8±0.91	27.6±0.01	34.6±1.39	28.3±0.04	32.0±0.12	34.6±6.21	33.9±0.92	32.0±0
4	34.9±1.72	35.4±0.02	45.3±1.07	35.0±0.02	46.1±0.21	45.3±0.92	42.6±1.93	46.1±0
5	47.3±0.03	43.2±1.12	51.9±12.1	46.1±0.06	60.2±0.65	51.9±2.76	56.2±4.09	60.2±0
6	53.0±0.04	49.0±0.08	57.3±0.12	52.3±0.34	65.1±0.21	56.9±1.01	67.1±1.02	65.1±0
7	60.5±0.01	57.3±0.12	60.6±0.93	57.3±2.65	70.5±0.09	61.4±5.84	75.1±2.98	70.5±0
8	67.8±0.5	61.8±0.98	64.7±3.8	62.6±1.02	75.0±0.92	64.3±2.87	79.7±4.02	75.0±0
9	75.9±3.15	68.8±0.07	69.6±3.0	69.6±0.91	81.6±1.92	70.5±0.65	85.8±0.08	81.6±1
10	83.5±1.02	70.9±1.02	75.3±0.42	73.3±0.05	86.1±0.96	76.2±0.34	89.8±0.03	86.1±0
11	89.0±1.32	81.6±0.06	83.4±2.01	77.4±0.12	88.2±0.17	82.8±1.96	92.7±2.03	88.2±0

12	85.7±0.09	83.2±0.89	89.3±0.16	93.1±1.90	86.7±1.92	89.1±0.56	97.7±0.06	94.7±1

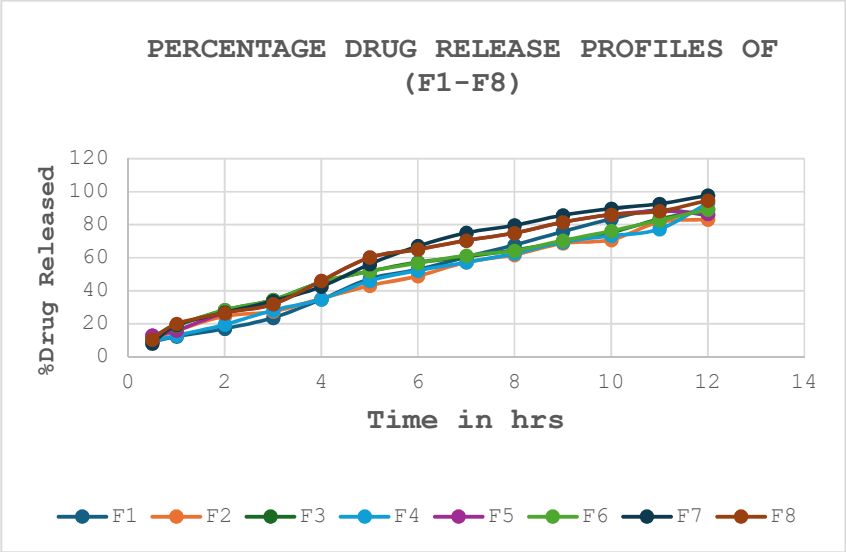


Fig.3: Percentage Drug Release Profile of Formulation F1-F8

INVITRO DRUG RELEASE PROFILE OF CLOPIDOGREL BISULFATE

Time (hrs)	F9	F10	F11					
0.5	14.2±0.06	12.3±0.01	9.2±0.09					
1	18.9±2.02	11.4±9.02	14.8±0.03					
2	28.4±0.40	19.3±0.02	23.0±0.19					
3	34.6±1.39	27.2±0.93	28.4±0.81					
4	45.3±1.07	34.2±0.92	36.6±0.21					
5	51.9±12.1	46.1±0.02	45.3±.004	43.2±9.6				45.3±1
6	57.3±0.12	51.5±0.21	50.4±0.10	49.4±0.02				51.9±1
7	60.6±0.93	57.3±1.90	52.4±0.14	50.7±2.03				56.3±0
8	64.7±3.8	60.6±0.01	58.1±6.21	57.3±0.01	62.4±0.93	58.1±6.21	57.3±0.26	56.0±1
9	69.6±3.0	64.7±0.81	61.4±0.32	64.3±0.05	67.7±3.8	61.4±0.32	64.3±0.03	61.4±2
10	75.3±0.42	69.6±0.10	69.9±2.01	66.3±0.04	72.6±3.0	69.9±2.01	68.3±0.01	64.3±9
11	83.4±2.01	75.4±0.91	71.7±1.02	70.9±0.32	75.3±0.42	71.7±1.02	71.7±0.01	69.6±1
12	85.3±0.16	83.7±7.21	78.3±0.32	75.8±1.02	82.4±2.01	78.3±0.32	75.4±0.21	72.5±0

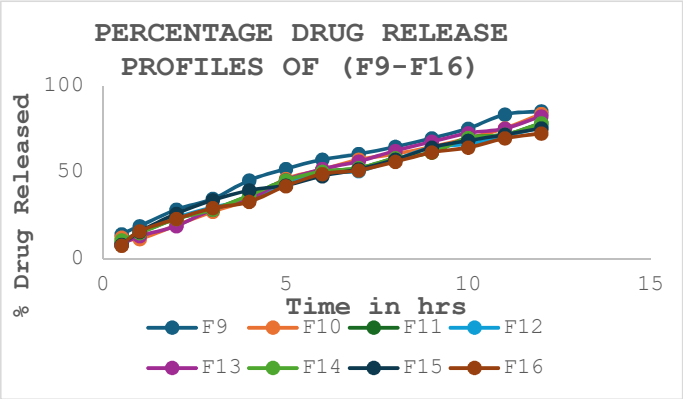


Fig.4: Percentage Drug Release Profile of Formulation F9-F16

3.6 COMPARASION OF INVITRO RELEASE PROFILES OF MARKETED FORMULATION OF CLOPIDOGREL BISULFATE WITH PREPARED TABLET(F7)

Comparision of Invitro Release Profiles of Optimized Formulation (F7) of Clopidogrel Bisulfate with Marketed Formulation

Time in hrs	% Drug Release (Formulated F7 – SR)	Time in mins	Drug Release (Plavix – Marketed IR)
0.5	14.2±0.06	10	36.2
1	19.3±0.02	20	64.4
2	27.0±1.23	30	88.1
3	33.9±0.92	40	90.7
4	42.6±1.93	50	94.3
5	56.2±4.09	60	99.4
6	67.1±1.02		
7	75.1±2.98		
8	79.7±4.02		
9	85.8±0.08		
10	89.8±0.03		
11	92.7±2.03		
12	97.7±0.061		

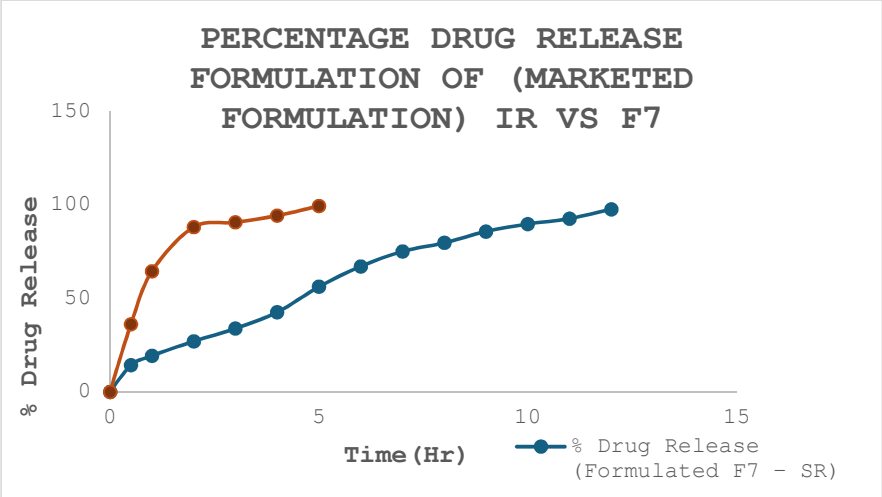


Fig.5: Percentage Drug Release Profile of Marketed formulation vs F7

3.7 Drug Release Kinetics and Mechanism

The drug release kinetics and mechanism of the optimized formulation (F7) were evaluated using various mathematical models. The correlation coefficient (R^2) values indicated that the formulation followed zero-order kinetics ($R^2 = 0.9732$), suggesting a concentration-independent release pattern. The Peppas model ($R^2 = 0.9814$) with an 'n' value of 0.6546 further confirmed a non-Fickian (anomalous) diffusion mechanism, indicating that the drug release occurred through a combination of diffusion and erosion processes.

Kinetics modelling of Optimized formulation

Formulation code	Zero order(R^2)	First order(R^2)	Higuchi(R^2)	Peppas(R^2)	n value
F7	0.9732	0.9188	0.9735	0.9814	0.6546

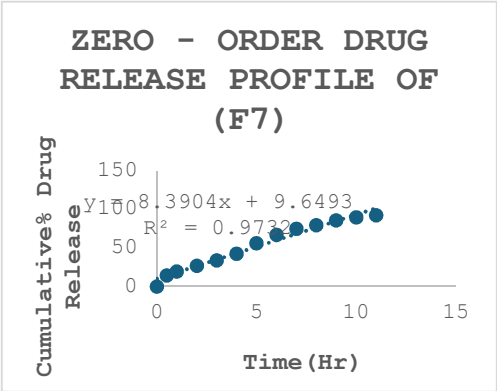


Fig.6: Zero Order profile of F7

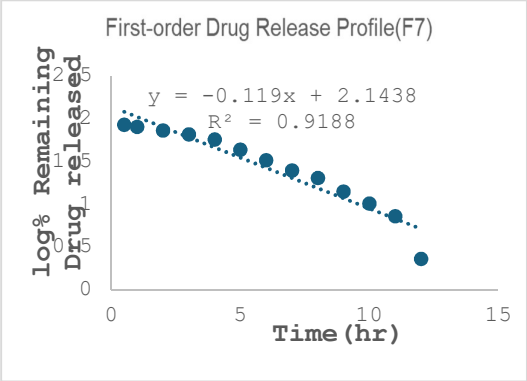
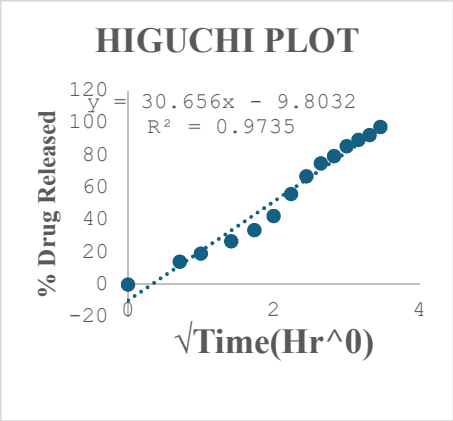


Fig.7: First Order profile of F7



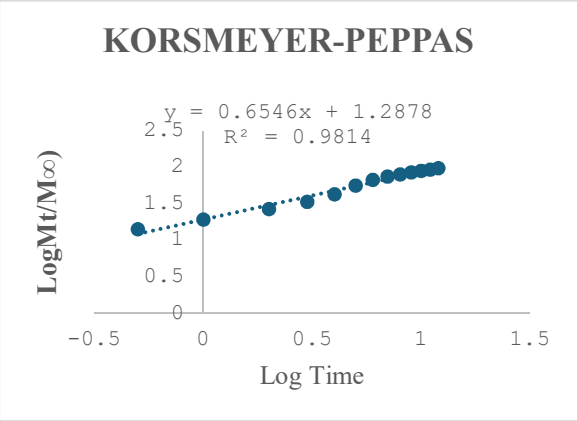


Fig.8: Higuchi plot of F7.

Fig.9: Peppas plot of F7

3.8 FTIR Analysis of Clopidogrel Bisulfate Tablets for Identification of Functional Groups and Drug-Excipient Interaction

For CLOPIDOGREL BISULPHATE
FTIR ANALYSIS OF CLOPIDOGREL

FUNCTIONAL GROUP	FTIR RANGE
C=O stretching	1749 cm-¹
C-H stretching (aromatic)	3106 cm-¹
C-H stretching (aliphatic)	2983 cm-¹
O-H stretching	3012 cm-¹
C-O stretching	1156 cm-¹
N-H stretching	3425 cm-¹

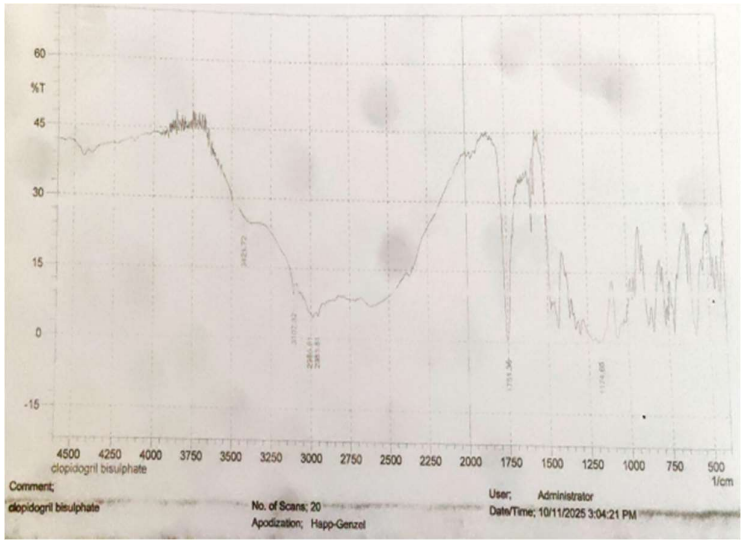


Fig.10: FTIR analysis of Clopidogrel bisulfate

FOR POLOXAMER 188
FTIR ANALYSIS OF POLOXAMER 188

FUNCTIONAL GROUP	FTIR RANGE
C-H stretching(aliphatic)	2800 cm^{-1}
C-O stretching	1100 cm^{-1}
O-H stretching	3260 cm^{-1}
C-O-C stretching	1000-1590 cm^{-1}

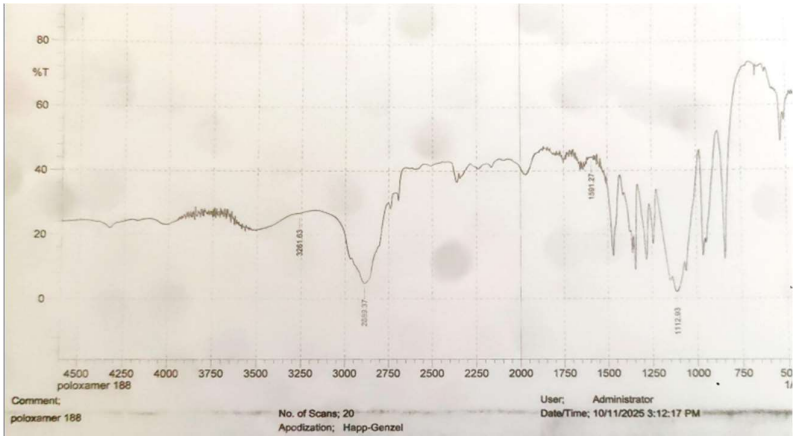
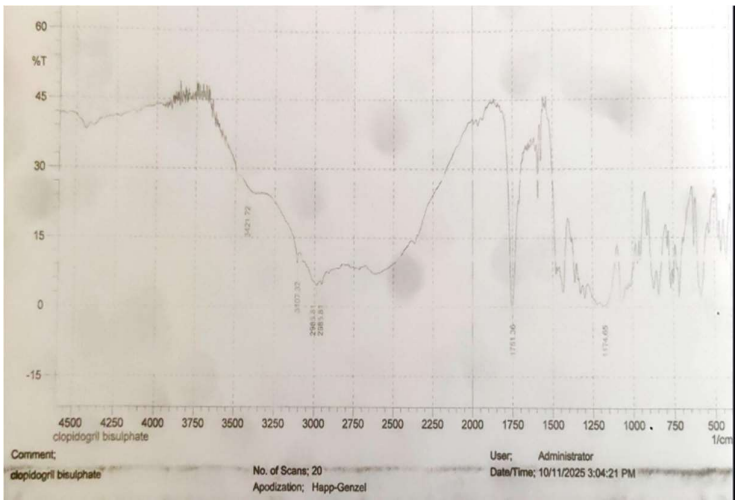


Fig.11: FTIR analysis of Poloxamer188

FOR CLOPIDOGREL BISULPHATE + POLOXAMER 188



Time(days)	Changes in physical appearance	Weight variation ±SD(%)	Friability	Hardness Kg/cm²	Drug content	Drug release
30	No change observed	200.0±0.2	0.75±0.99	5.5±0.1	97.5±1.1	96.2±0.6
60	No change observed	200.2±0	0.74±1	5.6±0	95.6±0.8	94.9±0.7
90	No change observed	200.4±0.2	0.76±0.98	5.7±0.2	96.2±2.2	95.9±0.3

Fig.12: FTIR Analysis of Clopidogrel bisulfate + poloxamer188

3.9 STABILITY STUDIES

Stability studies were performed for optimized formulation F7. The drug content and invitro drug release values indicate that the formulation was highly stable after 3 months time.

Stability studies

Sustained-release matrix tablets of Clopidogrel Bisulphate were successfully prepared using the melt granulation technique. FTIR studies confirmed no drug–excipient interactions. Pre- and post-compression parameters indicated good flow, compressibility, and acceptable tablet quality. Drug release was strongly influenced by polymer type and concentration, with hydrophilic polymers showing faster release compared to hydrophobic ones. Formulation F7 (Poloxamer 188, 1:1 ratio) showed the best sustained-release profile with 97.7% release at 12 hours. Higher polymer levels decreased release due to increased viscosity and thicker gel barrier formation. Kinetic modelling showed zero-order release with non-Fickian diffusion, confirming a diffusion-controlled mechanism. Stability studies indicated that the optimized formulation remained stable throughout the study period. Overall, Poloxamer-based matrices proved effective for achieving sustained drug release.

4. CONCLUSION

Sustained-release matrix tablets of Clopidogrel Bisulphate were successfully developed using the melt granulation method with both hydrophilic and hydrophobic polymers. FTIR and physical evaluation confirmed no drug–excipient incompatibility, while pre- and post-compression studies showed all formulations met pharmacopeial quality standards. Dissolution studies revealed that polymer concentration significantly affected drug release, with formulation F7 (Poloxamer 188, 1:1 ratio) showing the best sustained-release profile, achieving 97.7% release over 12 hours. The extended release was due to the formation of a viscous gel barrier that slowed drug diffusion. Kinetic analysis indicated zero-order release

with non-Fickian diffusion, and stability studies confirmed the formulation remained stable for 90 days. Overall, F7 can be considered a promising sustained-release dosage form offering prolonged therapeutic action and improved patient compliance.

REFERENCES

Passerini N, Calogerà G, Albertini B, Rodriguez L. Comparison of in-situ melt granulation of ibuprofen and ketoprofen using high-shear and fluidised-bed granulators. Int J Pharm. 2010;396(1-2):59–67.

Modi DJ, Shelat PK, Shastri DH. Fluidized hot melt granulation technique: An approach to improve micromeritic properties and dissolution rate of Efavirenz. J Drug Deliv Sci Technol. 2020;56:101540.

Mendez R, De Matas M, York P. Melt granulation for improving flow and compressibility of poorly flowing powders. Eur J Pharm Sci. 2003;19(5):345–352.

Nystrom C, Holm P. Solidification of melts for oral sustained release formulation. Drug Dev Ind Pharm. 1993;19(16):2143–2156.

Paradkar A, Pawar A, Chordiya J, Patil V, Ketkar A. Spherical crystallization of ibuprofen by solvent change method. J Pharm Pharmacol. 2002;54(2):203–210.

Paradkar A, Pawar A, Chordiya J. Melt granulation as an alternative technique for granulation of moisture-sensitive drugs. Pharm Technol Eur. 2004;16(4):42–49.

Schaefer T, Wørts O. Melt granulation of pharmaceutical powders: Influence of binder properties. Drug Dev Ind Pharm. 2002;28(5):569–583.

Rahman M, Siddiqui A, Khan M. Influence of waxy binders in melt granulation for sustained release formulations. AAPS PharmSciTech. 2005;6(4):E586–E594.

Maity S, Sa B. Effect of hydrophobic meltable binders on granulation and drug release. Int J Pharm. 2008;356(1-2):108–115.

Adebisi A, Conway B. Melt granulation for solid dosage forms: Mechanisms and process considerations. Int J Pharm. 2015;493(1-2):89–107.

Shukla A, Gupta R, Kumar R. Formulation and evaluation of Clopidogrel Bisulphate ODTs by melt granulation. Indian J Pharm Sci. 2009;71(3):312–318.

Mehta S, Patel N. Taste-masked Clopidogrel Bisulphate ODTs using ion exchange resins. Int J Pharm Pharm Sci. 2010;2(4):143–149.

Kulkarni P, Deshmukh A. Mouth dissolving tablets of Clopidogrel Bisulphate prepared by effervescent method. Int J Drug Dev Res. 2005;2(3):205–210.

Deshmukh P, Patil S. Solid dispersion-based Clopidogrel Bisulphate ODTs using β-cyclodextrin. Asian J Pharm Clin Res. 2007;1(2):34–39.

Usman S, Akram M, Usman A, Fatima S, Islam Q. Development of fixed-dose Clopidogrel and Aspirin tablets via compression strategy. J Pharm Sci Res. 2024;16(5):527–535.

Ajay Singh, Verma R, Yadav K. Controlled-release Clopidogrel Bisulphate microspheres prepared by ionotropic gelation. J Pharm Investig. 2024;54(2):121–131.

Patel K, Shah J. Fast-dissolving Clopidogrel Bisulphate tablets by direct compression. Res J Pharm Technol. 2012;5(8):1000–1007.

Arunkumar V, Rajalakshmi R. Fast-disintegrating Clopidogrel Bisulphate tablets by sublimation method. J Pharm Res. 2008;1(2):101–106.

Vora M, Patel K. Formulation of Clopidogrel sustained release matrix tablets using HPMC and EC. Int J Pharm Sci Rev Res. 2013;20(1):35–42.

Kesharwani S, Jain N. Clopidogrel sustained release pellets using melt granulation. J Pharm Investig. 2017;47(3):255–263.

Nokhodchi A, Ford JL, Rubinstein MH. The effect of moisture on mechanical strength of tablets prepared by wet and dry granulation. Int J Pharm. 1995;118(2):191–197.

Bhardwaj V, Jain N, Jat RC. Optimization of wet granulation process for sustained release tablets of propranolol. J Pharm Sci Res. 2007;9(4):221–228.

Patel V, Shah D. Comparative evaluation of wet and dry granulation techniques for carbamazepine tablets. Indian J Pharm Sci. 2010;72(3):375–381.

Rahman Z, Zidan A, Khan M. Formulation of sustained-release matrix tablets by wet granulation. AAPS PharmSciTech. 2008;9(4):1130–1137.

Kiran T, Rao D, Reddy S. Wet granulation process optimization for metformin sustained release tablets. Asian J Pharm Clin Res. 2012;5(3):62–68.