RESEARCH PAPER

Development and Characterization of a Dual Release Bilayer Delivery System of Ticagrelor for Optimized Therapeutic Efficacy

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ABSTRACT
Ticagrelor, a reversibly binding $P2Y_{12}$ receptor antagonist, plays a pivotal role in the prevention of thrombotic events in acute coronary syndrome; however, its clinical utility is constrained by poor aqueous solubility and suboptimal pharmacokinetic properties requiring frequent dosing. In this study, we report the rational design and development of a solid dispersion-enabled bilayer tablet system to achieve synchronized immediate and sustained drug release, thereby addressing these limitations. Solid dispersions of ticagrelor were engineered using hydrophilic carriers via solvent evaporation, with polyvinylpyrrolidone K30 emerging as the optimal carrier at a drug-to-polymer ratio of 1:0.5, significantly enhancing apparent solubility and dissolution behavior.
The optimized dispersion was subsequently integrated into a bilayer tablet architecture comprising an immediate-release layer for rapid pharmacological onset and a matrix-based extended-release layer to maintain prolonged drug exposure. Comprehensive physicochemical characterization confirmed acceptable pre and post-compression attributes, ensuring robust manufacturability and mechanical integrity. In vitro dissolution profiling revealed a well-defined biphasic release pattern, characterized by an initial burst release followed by sustained drug liberation over 24 hours, consistent with the intended therapeutic design. Release kinetics suggested diffusion-controlled mechanisms governing the extended-release phase.
Furthermore, accelerated stability studies conducted under ICH-recommended conditions demonstrated the formulation's resilience, with no significant alterations in drug content or release kinetics over time. Collectively, these findings highlight the potential of solid dispersion-based bilayer systems as a versatile platform for optimizing the delivery of poorly soluble drugs. The proposed formulation strategy offers a promising avenue to enhance the therapeutic performance of ticagrelor by improving bioavailability and reducing dosing frequency, thereby potentially augmenting patient adherence and clinical outcomes.

Keywords: Ticagrelor, Bilayer tablet, Solid dispersion, Immediate release, Extended release, Drug delivery system
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INTRODUCTION:

Ticagrelor is an oral antiplatelet agent belonging to the class of cyclopentyltriazolopyrimidines, used primarily for the prevention of thrombotic events in patients suffering from acute coronary syndrome (ACS) [1]. Ticagrelor acts as a reversible antagonist of the $P2Y_{12}$ receptor, inhibiting platelet aggregation and reducing the risk of myocardial infarction and stroke which is show in Fig. 1[1,2]. However, ticagrelor shows limitations such as variable bioavailability and a relatively short half-life (approximately 7–12 hours), necessitating frequent dosing schedules, which can reduce patient compliance[3].

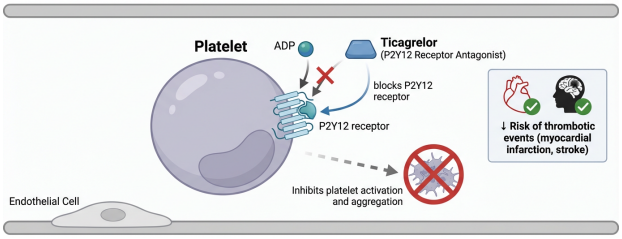

Figure 1: Mechanism of action of Ticagrelor in platelet inhibition.

Bilayer tablets are a novel oral dosage form designed to deliver two different release profiles from a single unit shown in Fig 2[4,5]. A bilayer tablet containing a fast release layer provides immediate therapeutic action, while the extended release layer ensures prolonged plasma concentration and reduces dosing frequency. This dosage form is especially beneficial for drugs used in chronic cardiovascular diseases where continuous therapeutic levels are required [4,6].

The present research focuses on the formulation development of a bilayer tablet of ticagrelor, containing an immediate release layer and a sustained release matrix layer. The prepared tablets were evaluated for physicochemical properties and in-vitro drug release behavior.

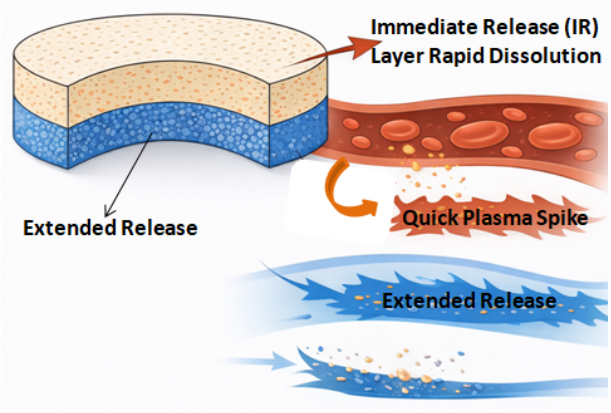

Figure 2: Design and mechanistic illustration of a solid dispersion-based bilayer tablet system for ticagrelor delivery

Materials and Methods

Materials

Ticagrelorwas obtained from LEE Pharma India (Gifted). HPMC K100M, ethyl cellulose, crospovidone, croscarmellose sodium, microcrystalline cellulose (MCC), lactose, magnesium stearate, and talc were purchased from recognized suppliers (Sigma-Aldrich and/or HiMedia India).

Pre-formulation Studies

Melting point

A small quantity of powder was placed into a fusion tube. That tube was placed in the melting point determining apparatus (microprocessor melting/ boiling point apparatus). The temperature of the apparatus was gradual increased automatically and read the temperature at which powder started to melt and the temperature when all the powder gets melted [7].

Solubility

Solubility of the drug was determined by taking some quantity of drug (about 10 mg) in the test tube separately and added the 5 ml of the solvent (water, 0.1N HCL, 6.8pH phosphate buffer, 4.5pH Acetate buffer) Shake vigorously and kept for some time. Note the solubility of the drug in various solvents (at room temperature) [8].

Differential scanning calorimetry (DSC)

DSC analysis of the ticagrelor was conducted on a DSC Polyma 214 that is equipped with cooling system and operating with universal analysis 214 software version NETZSCH. Dry nitrogen was used to purge the sample cell at a flow rate of 80mL/min. The DSC instrument was calibrated heat flow and for temperature using indium standard of high purity. Accurately weighed samples (1-3mg) were scanned at a heating rate of 10 C/min [9].

Formulation of Immediate and Extended Release Bilayer Tablets of Ticagrelor Incorporating Solid Dispersions

Bilayer tablets of ticagrelor were prepared by a sequential compression technique to obtain a dual-release system comprising an immediate release (IR) layer and an extended release (ER) layer to achieve rapid onset followed by sustained therapeutic action [10]. Prior to compression, solid dispersions (SDs) of ticagrelor were developed using the solvent evaporation method to enhance its aqueous solubility and dissolution characteristics. Twelve formulations were prepared to optimize the drug-polymer ratio and solvent suitability using polymers with varied physicochemical properties, including polyvinylpyrrolidone K30 (PVP K-30), Soluplus, polyethylene glycol 6000 (PEG 6000), and poloxamer 188, with methanol and methylene chloride as organic solvents. Accurately weighed polymers were dissolved separately in 50 mL of each solvent under continuous magnetic stirring, followed by gradual addition of ticagrelor to obtain homogeneous solutions, which were stirred for an additional 15 min. The solutions were cast into glass Petri dishes for solvent evaporation at room temperature for 4 h and subsequently vacuum-dried at 50°C for 24 h to ensure complete removal of residual solvents. The dried masses were pulverized, passed through a #30 sieve, and stored in a desiccator until further use. For the IR layer, the optimized solid dispersion equivalent to the required drug dose was blended with suitable diluents and superdisintegrants, followed by lubrication with magnesium stearate and talc. The ER layer was prepared by mixing ticagrelor with release retarding polymers and excipients, with or without wet granulation, followed by drying and lubrication. During compression, the ER blend was first introduced into the die cavity and lightly pre-compressed, after which the IR blend was added and

subjected to final compression using a bilayer tablet press to obtain tablets with adequate mechanical strength and interlayer integrity [11].

Evaluation Parameters of Bilayer Tablet

Weight variation

The uniformity of weight was assessed as per the specifications of the Indian Pharmacopoeia (IP). Ten tablets from the batch were randomly selected and individually weighed using a calibrated analytical balance. The average weight was calculated, and the percentage deviation of each tablet from the mean was determined. The tablets were considered compliant if not more than two tablets deviated from the permissible limits and none deviated by more than twice the specified percentage. According to IP, the allowed percentage deviation is ±10% for tablets weighing less than 85 mg, ±7.5% for tablets weighing between 85 mg and 250 mg, and ±5% for tablets weighing 250 mg or more [12].

Hardness

Tablet hardness was determined using a Monsanto hardness tester to evaluate mechanical strength. Ten tablets were randomly selected and individually placed between the plungers of the tester, and the force required to break each tablet was recorded in kg/cm². The mean hardness and standard deviation were calculated. Adequate hardness ensures sufficient mechanical integrity during handling, packaging, and transportation without adversely affecting disintegration and dissolution characteristics [13].

Thickness

Tablet thickness was measured using a calibrated digital vernier caliper. Ten tablets were selected randomly, and their thickness was measured in millimeters (mm). The average thickness and standard deviation were calculated to ensure uniform die fill, consistent compression, and dimensional stability of the formulation.

Drug content

Drug content uniformity was determined according to the procedures described in the Indian Pharmacopoeia. Ten tablets were randomly selected, individually powdered, and an accurately weighed portion equivalent to the labeled amount of ticagrelor was extracted using a suitable solvent. The solution was filtered, appropriately diluted, and analyzed using a validated analytical method such as UV-Visible spectrophotometry. The tablets complied with IP requirements if the individual drug content was within ±15% of the labeled claim. The mean drug content and relative standard deviation were calculated to assess batch uniformity.

Disintegration test

The disintegration test was performed only for the immediate release (IR) layer of the bilayer tablet. The test was conducted using an Electrolab disintegration test apparatus as per IP guidelines. Six tablets were placed in distilled water maintained at 37 ± 2°C, and the time required for complete disintegration of the IR layer was recorded. For uncoated tablets, the pharmacopeial limit specifies that disintegration should occur within 15 minutes.

Dissolution studies

In vitro dissolution studies were carried out using USP Apparatus II (paddle method) in an Electrolab dissolution test apparatus to evaluate the drug release profile of both immediate release (IR) and extended release (ER) layers. The dissolution medium consisted of 900 mL phosphate buffer (pH 4.5) containing 0.2% Tween 80, maintained at 37 ± 0.5°C with a paddle rotation speed of 50 rpm. Samples were withdrawn at predetermined time intervals, filtered, and analyzed for drug content using a validated analytical method. An equal volume of fresh dissolution medium was replaced after each sampling to maintain constant volume and sink conditions. The IR layer was designed to provide a loading dose with rapid drug release within 1 hour, while the ER layer was evaluated for sustained drug release up to 24 hours. The release profile was developed based on the pharmacokinetic characteristics of ticagrelor to maintain therapeutic plasma concentrations over an extended period. For comparison, dissolution studies were also performed under identical conditions using the marketed formulation Brilinta 90 mg. The release data were further fitted to various kinetic models, including zero-order, first-order, Higuchi, and Korsmeyer-Peppas models, to elucidate the mechanism of drug release [14].

Stability studies

Accelerated stability studies of the optimized ticagrelor solid dispersion bilayer tablets were conducted in accordance with ICH guidelines. The tablets were packed in 40 cc HDPE containers and stored in a stability chamber (Thermo Lab, India) at 40 ± 2°C and 75 ± 5% relative humidity. Samples were withdrawn at 0, 1, 2, and 3 months and evaluated for physical appearance, percentage drug content, and in vitro drug release profile. Any significant changes in drug content and dissolution behavior were statistically analyzed to assess the stability and integrity of the formulation under accelerated storage conditions.

Results and Discussion

Melting point

The melting point of Ticagrelor was determined by the capillary method and was found to be in the range of 137-139**°C** which is in close agreement with the reported melting point range of **136-139 °C** for Ticagrelor. The observed melting range was sharp and narrow, indicating uniform crystalline characteristics of the sample.

Solubility

The equilibrium solubility of Ticagrelor was determined in various physiological media at 25 ± 0.5 °C to evaluate its pH-dependent solubility profile. The results are summarized in Table 1.

Table 1. Solubility of Ticagrelor in Different Media at 25 °C

Media	Solubility (mg/mL)
pH 1.2 (0.1 N HCl)	0.01
pH 4.5 acetate buffer	0.01
pH 6.8 phosphate buffer	0.00
Water	0.01
0.1 N HCl + 0.2% Tween 80	0.47
pH 4.5 acetate buffer + 0.2% Tween 80	0.47
pH 6.8 phosphate buffer + 0.2% Tween 80	0.48
Water + 0.2% Tween 80	0.48

DSC

The thermal behavior of the pure drug sample was evaluated by Differential Scanning Calorimetry (DSC) to confirm its identity and assess its purity. The DSC thermogram exhibited a sharp, well-defined endothermic peak corresponding to the melting point of the drug in the temperature range of 139 °C shown in Fig 3.The presence of a single, narrow endothermic transition indicates the crystalline nature of the sample and confirms its thermal stability within the studied temperature range. The observed melting endotherm was in close agreement with the reported melting point of Ticagrelor, thereby confirming the identity of the drug.Furthermore, the absence of additional endothermic or exothermic events in the thermogram suggests that the sample was free from detectable impurities, polymorphic transitions, or degradation products. These findings confirm the purity and crystalline integrity of the obtained drug sample.

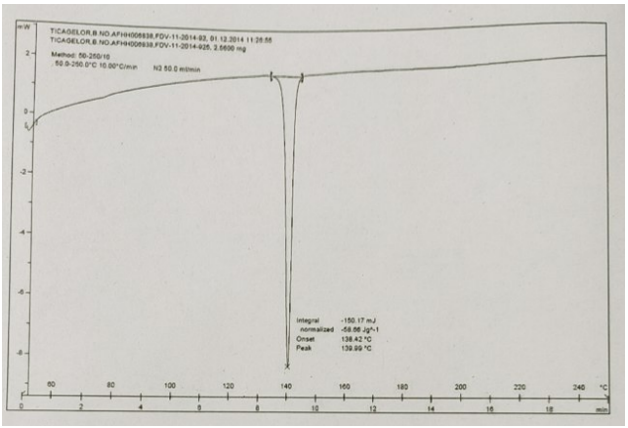

Figure 3: Differential scanning calorimetry (DSC) thermogram of ticagrelor.

Solid Dispersion Optimization

Solid dispersions of Ticagrelor (BCS Class IV) were prepared in a 1:1 drug-to-polymer ratio using hydrophilic carriers, namely polyvinylpyrrolidone K30 (PVP K30), polyethylene glycol 6000 (PEG 6000), poloxamer 188, Soluplus, Gelucire 50/13, and Stelliesters, employing methanol and methylene chloride as solvents. Methylene chloride failed to yield uniform dispersions, whereas methanol produced homogeneous solid masses with PVP K30, PEG 6000, poloxamer 188, and Stelliesters; Soluplus and Gelucire 50/13 exhibited unsatisfactory dispersion characteristics. UV spectrophotometric analysis demonstrated good linearity in the concentration range of 8-18 µg/mL. Comparative absorbance analysis (pure drug = 100%) revealed maximum enhancement with PVP K30 (114.66%), followed by Stelliesters (109.91%) and poloxamer 188 (109.48%), while PEG 6000 showed reduced apparent solubility (90.09%) present in table 2. Further optimization of PVP K30 ratios (1:0.5–1:2) indicated the highest enhancement at 1:0.5 (120.69%) based on table 3, whereas increasing polymer concentration slightly decreased absorbance, possibly due to increased matrix viscosity and diffusion limitations.

Overall, the ticagrelor-PVP K-30 solid dispersion at a 1:0.5 ratio demonstrated superior solubility enhancement and was selected for further development

Table 2: **Comparative Analysis of Absorbance and Percentage Drug Content of Ticagrelor Solid Dispersions with Different Carriers**

S. No.	Solid dispersion mass	Absorbance	Results in %
1	Ticagrelor	0.232	100.00
2	Ticagrelor + Stelliesters	0.255	109.91
3	Ticagrelor + PEG-6000	0.209	90.09
4	Ticagrelor + PVPk-30	0.266	114.66
5	Ticagrelor + Polaxamer 188	0.254	109.48

Table 3: Effect of Drug-to-Polymer Ratio on Absorbance and Percentage Drug Content of Ticagrelor PVP K-30 Solid Dispersions

S. No.	Solid dispersion mass	Absorbance	Results in %
1	Ticagrelor	0.232	100.00
2	Ticagrelor +PVPk-30 (1:0.5)	0.280	120.69
3	Ticagrelor +PVPk-30 (1:1)	0.266	114.66
4	Ticagrelor +PVPk-30(1:1.5)	0.260	112.07
5	Ticagrelor +PVPk-30 (1:2.0)	0.255	109.91

Pre-compression Evaluation

The pre-compression evaluation parameters of the powder blend, as presented in Table 4, indicate its flow and compressibility characteristics prior to tablet formulation.

Table 4: Pre-compression evaluation parameters of powder blend for final formulation

Parameter	Final formulation
Bulk density (gm/ml)	0.316
Tapped density (gm/ml)	0.509
Hausner ratio	1.61

Post-compression Evaluation

The post-compression evaluation parameters, as presented in Table 3, demonstrate the physical quality attributes of the prepared tablets. The average weight of 10 tablets was found to be within acceptable limits, indicating uniform die filling and consistency of the formulation process.The thickness of the tablets was found to be consistent, suggesting uniform compression during tablet punching. Additionally, the hardness values indicate that the tablets possess adequate mechanical strength to withstand handling, packaging, and transportation without breaking.Overall, these results confirm that the formulated tablets exhibit satisfactory physical characteristics, complying with standard pharmacopeia requirements

Table 5: Post-compression evaluation parameters of tablets for Batch No. FINAL FORMULATION with acceptance criteria and observed values

Parameters	Acceptance criteria	Observed value
Average weight(10 Tablets)	400 mg ± 5%	399.20 mg
Thickness	5.2 ± 0.4 mm	5.18 (5.11-5.22) mm
Hardness	15 ± 4kg/cm²	15.4 (14.1-16.8) kg/cm².

In Vitro Dissolution Study and Release Profile of Extended-Release Formulations

The in vitro dissolution study of all six extended-release formulations was carried out for 24 hours in pH 4.5 acetate buffer containing 0.2% Tween 80, and the results are presented in Table 4. All formulations exhibited a sustained drug release pattern over 24 hours, indicating the effectiveness of the extended-release matrix system. Among the batches, formulation 180/03 showed the highest drug release (88.88%) at 24 hours, with a relatively faster release profile as evident from significant drug release at early time points (35.48% at 6 hours and 61.54% at 12 hours). In contrast, formulation 180/05 exhibited the slowest release, with only 41.89% drug release at 24 hours, suggesting a stronger retardation effect of the matrix.

Table 6: In Vitro Dissolution Profile of Extended-Release Formulations

pH 4.5 Acetate Buffer with 0.2% tween 80, 900 ml, 50 RPM						
B.No.	Time in min	1hr	2hr	6hr	12hr	24hr
180/01	% DR	0.77	1.33	12.18	37.74	69.58

180/02	% DR	0.54	1.58	8.81	27.99	56.99
180/03	% DR	2.92	7.26	35.48	61.54	88.88
180/04	% DR	1.21	2.89	15.07	45.4	80.81
180/05	% DR	4.23	6.64	14.14	22.67	41.89
180/06	% DR	0.74	1.93	8.4	22.69	66.19

In vitro Dissolution Characterization of Biphasic (IR+ER) Drug Delivery System

The in vitro drug release profile of the developed IR+ER formulations was evaluated using pH 4.5 acetate buffer containing 0.2% Tween 80 (900 mL) at 50 rpm. The dissolution results are summarized in Table 5.

All formulations exhibited a biphasic release pattern, indicating the successful incorporation of both immediate-release (IR) and extended-release (ER) components. At the initial time point (1 h), most batches showed drug release within or near the target range (20 ± 10%), except IR+ER 5 and IR+ER 6, which exhibited relatively higher release (34.50% and 25.50%, respectively), suggesting a faster initial burst effect.

Table 7: Drug Release Profile of Immediate and Extended Release (IR+ER) Formulations Under Specified Dissolution Conditions

Time (hr)	**Batch No./ Expected % drug release with time**	IR+ER 1	IR+ER 2	IR+ER 3	IR+ER 4	IR+ER 5	IR+ER 6
1	**20± 10**	15.50	14.50	16.40	16.10	34.50	25.50
4	**30± 10**	38.37	36.20	42.50	40.40	50.60	40.70
12	**60± 10**	75.40	74.20	80.30	74.60	75.80	68.50
20	**NLT 80**	88.50	88.30	88.10	83.20	96.20	99.60
24	**100**	91.30	90.10	89.10	89.80	100.10	99.70

Stability Studies

Accelerated stability studies of the optimized ticagrelor solid dispersion bilayer tablets were carried out under ICH-recommended conditions (40 ± 2°C/75 ± 5% RH) for a period of three months. The tablets remained physically intact throughout the study, with no observable changes in color, texture, or structural integrity, indicating good physical stability of the formulation.

The percentage drug content at 0, 1, 2, and 3 months showed no significant variation, remaining within acceptable pharmacopeia limits. This suggests that the active pharmaceutical ingredient was chemically stable and did not undergo degradation under accelerated conditions.

Similarly, the in vitro drug release profiles at different time intervals exhibited negligible differences when compared to the initial release pattern. Statistical analysis revealed no significant change ($p > 0.05$) in dissolution behavior, confirming that the release characteristics of the bilayer tablet were maintained during the storage period.

Overall, the results demonstrate that the optimized formulation possesses excellent stability under accelerated conditions, indicating its robustness and suitability for long-term storage. The absence of significant changes in drug content and dissolution profile confirms that the formulation retains its efficacy and performance over time.

Conclusion

The present study successfully developed and evaluated a solid dispersion-based bilayer tablet of Ticagrelor designed to achieve both immediate and extended drug release. The formulation strategy effectively addressed the poor aqueous solubility of Ticagrelor by employing solid dispersion technology, where PVP K30 (1:0.5 ratio) demonstrated superior solubility enhancement. The

bilayer tablet system provided a rapid onset of action through the immediate release layer, followed by sustained drug release up to 24 hours from the extended-release matrix.

All pre-compression and post-compression parameters were found to be within acceptable pharmacopeial limits, indicating good flow properties and satisfactory mechanical strength of the tablets. In vitro dissolution studies confirmed that the optimized formulation achieved the desired biphasic release profile, closely matching the targeted drug release pattern. Furthermore, accelerated stability studies demonstrated that the formulation remained physically and chemically stable, with no significant changes in drug content or dissolution behavior over the study period.

Overall, the developed bilayer tablet system represents a promising approach for improving the therapeutic efficacy and patient compliance of Ticagrelor by reducing dosing frequency and maintaining sustained plasma drug levels. This formulation strategy can be further explored for other poorly soluble drugs requiring controlled and immediate drug release profiles.

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