



Bioavailability Enhancement and Polymorphic Stabilization of One BCS Class IV Metastable Drug Through Novel Formulation Approach

✉ Ramakant PANDA*, Srinivas LANKALAPALLI

GITAM School of Pharmacy, GITAM Deemed University, Andhra Pradesh, India

ABSTRACT

Objectives: This study aims to enhance the bioavailability and polymorphic stability of Ticagrelor, a metastable, low-soluble and low-permeable Biopharmaceutics Classification System Class IV drug, by exploring different formulation approaches.

Materials and Methods: Ticagrelor was taken as a model drug for the enhancement of bioavailability and polymorphic stability. Initially, various techniques, such as micronization, amorphous solid dispersion (ASD), and Self-Microemulsifying Drug Delivery System, were evaluated for dissolution enhancement. Based on the improvement in dissolution rate, polymorphic stability, and process viability, an ASD technique was selected for dissolution enhancement of Ticagrelor. Co-povidone VA 64 and vitamin E TPGS were used as carriers for the preparation of Ticagrelor solid dispersion (SD) by the solvent evaporation technique. The formulation was optimized and further evaluated for dissolution performance in biorelevant media fasted state simulated gastric fluid and fasted state simulated intestinal fluid. The bioavailability of the Ticagrelor SD tablet formulation was compared with a conventional immediate release tablet formulation prepared by wet granulation process in line with reference product Brilinta® (AstraZeneca LP). *In vivo* pharmacokinetic (PK) studies were carried out in Wistar rats with due approval from ethics committees such as CPCSEA and IAEC (CPCSEA/DIPS/02/23/61). Patients are not involved in this study, hence informed consent not applicable.

Results: The relative bioavailability and peak plasma concentration (C_{max}) of Ticagrelor SD formulation compared to conventional immediate release tablet formulation in line with Brilinta® (AstraZeneca LP) were found to be $141.61 \pm 2.29\%$ and $137.0 \pm 0.59\%$, respectively. Further, based on a dose-adjusted PKs study of Ticagrelor SD, a 70 mg Ticagrelor tablet formulated with the SD technique was found to be equivalent to a 90 mg dose of Ticagrelor conventional immediate release tablet formulation with a comparable C_{max} , area under the curve (AUC)_{0-24h} and AUC_{0-∞}. Visual observation of the dissected gastric organ through a stereomicroscope revealed no redness or bleeding post-administration of Ticagrelor SD formulations.

Conclusion: The SD technique with carrier co-povidone VA 64 and vitamin E TPGS prepared by the solvent evaporation process could yield a Ticagrelor formulation with improved bioavailability and polymorphic stability.

Keywords: Bioavailability, pharmacokinetics, polymorphic stability, gastrointestinal bleeding study, Ticagrelor, amorphous solid dispersion

INTRODUCTION

Drug dissolution and permeability play a critical role in achieving the desired bioavailability and pharmacological response, which in turn affects the clinical safety and efficacy of a drug significantly. In addition to drug dissolution and permeability, polymorphic transformation of metastable drugs during manufacturing, storage, and gastrointestinal (GI) transit

adds to the challenges in achieving the intended clinical safety and efficacy.

One such Biopharmaceutics Classification System (BCS) Class IV, cardiovascular medication is Ticagrelor (not ionized in the physiological pH range), which has a moderate intrinsic permeability and very poor solubility (less than 10 µg/mL). Brilinta®, AstraZeneca LP (Ticagrelor), has a median t_{max} of 1.50

*Correspondence: 121965201519@gitam.in, ORCID-ID: orcid.org/0009-0002-3938-3283

Received: 18.11.2023 , Accepted: 18.10.2025 Publication Date: 18.11.2025

Cite this article as: PANDA R, LANKALAPALLI S. Bioavailability enhancement and polymorphic stabilization of one BCS class IV metastable drug through novel formulation approach. Turk J Pharm Sci. 2025;22(5):333-348



Copyright© 2025 The Author. Published by Galenos Publishing House on behalf of Turkish Pharmacists' Association.
This is an open access article under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License.

hours and an absolute bioavailability of roughly 36%. According to reports, the active metabolite of Ticagrelor has a median half-life of 2.5 hours. Ticagrelor demonstrates polymorphism. There have been reports of Forms I, II, III, and IV (non-solvated) and numerous solvated (metastable) forms, suggesting that formulation and processing parameters can have a substantial impact on Ticagrelor's dissolution and clinical performance. Thus, it is imperative to improve Ticagrelor's bioavailability.^{1,2}

Currently, many techniques, such as micronization, solid dispersion (SD), polymeric amorphization, complexation, micro- and nano-emulsification [i.e., Self-Microemulsifying Drug Delivery System (SMEDDS) and Self-Nanoemulsifying Drug Delivery System], the co-crystal approach, the use of surfactants, and liposomal drug delivery, are being explored for enhancing the solubility and bioavailability of low-solubility drugs. Nonetheless, all these techniques have their own sets of advantages and disadvantages regarding drug loading, stability, and *in vivo* permeation. P-glycoprotein, an efflux transporter, plays an important role in drug transport. Surfactants like Vitamin TPGS and polysorbate are reported as permeation enhancers and are considered to play an important role in increasing intestinal permeability through the inhibition of the P-gp pump. Conventional mechanical micronization helps in enhancing intrinsic dissolution, but is limited to many drugs due to thermal and chemical degradation during the process. Novel techniques such as SD, micro-emulsifying drug delivery, co-crystal, and liposomal drug delivery are considered to improve both solubility and stability of drug formulations, significantly and hence could be the optimal alternatives to the conventional approaches of dissolution enhancement.³⁻⁷

Little research has been published to improve Ticagrelor's oral bioavailability; however, numerous crucial factors, including formulation stability, polymorphic transformation, and process technology viability, have not received enough attention. Amorphous SD (ASD) is one prominent technique explored to improve both the solubility and the permeability of BCS class IV drugs.⁸ The use of vitamin E TPGS as a carrier of solid dispersion has been reported to enhance drug dissolution.⁸⁻¹² Also, it is reported that Ticagrelor absorption is facilitated through the inhibition of P-glycoprotein. However, its sticky nature and low thermal stability lead to crystallization of drugs and may cause stability issues with the formulations.⁸⁻¹²

The current study intends to design an appropriate formulation technology that would not only enhance Ticagrelor's bioavailability but also improve polymorphic stability, ensuring consistent therapeutic antiplatelet effects, especially during the critical initial hours of treating an acute coronary event. The selection of an appropriate formulation technology was based on a preliminary screening study on three different formulation technologies, including SMEDDS, ASD, and micronization.

For the preparation of ASD of meta-stable Ticagrelor, various polymers Co-povidone VA 64, Soluplus®, and HPMCAS were explored initially based on their crystallization driving force (CDF), glass transition temperature (T_g) and hydrophobicity. The medium chain triglyceride, i.e., Labrafac lipophile WL 1349,

co-surfactant (Transcutol HP), surfactant (Polysorbate 80), and solubilizer diethylene glycol monoethyl ether were selected for the preparation of a self-microemulsifying drug delivery system for Ticagrelor.¹³⁻¹⁸

An appropriate analytical toolbox was explored to monitor the polymorphic transformation of Ticagrelor formulations during the preparation and storage period. A discriminatory dissolution method was developed for evaluating the *in vitro* dissolution performance of Ticagrelor formulations, considering pH 6.8 without surfactant as the dissolution medium with phosphate buffer. A biorelevant dissolution study was performed in FaSSGF and FeSSIF to simulate the GI environment.^{19,20}

One *in vivo* pharmacokinetic (PK) study was carried out in Wistar rats (CPCSEA/DIPS/02/23/61) and aimed to compare the bioavailability of the ASD of Ticagrelor with a conventional immediate-release tablet formulation in line with the reference product Brilinta® (AstraZeneca LP). In a dose-adjusted PKs study in Wistar rats, a 70 mg dose of Ticagrelor ASD was compared with a 90 mg dose of a conventional immediate-release tablet formulation of Ticagrelor. GI bleeding studies were carried out to evaluate any episode of bleeding in the stomachs of Wistar rats.

MATERIALS AND METHODS

Materials

Ticagrelor was acquired as a gift sample from Mankind Research Center (a division of Mankind Pharma Ltd., India). Kolidone VA 64 and Soluplus were provided as a gift sample from BASF (Ludwigshafen, Germany). HPMC Acetate Succinate was collected as a gift sample from Shin Etsu Co. Pearlitol SD 200 (Roquette) was supplied by the Signet Chemical Corporation (Mumbai, India). Anhydrous calcium hydrogen phosphate was supplied by Sudeep Pharma (India), sodium starch glycollate was supplied by Amit Hydrocolloid (India), and Polyplasdone XL was supplied by Ashaland (New Milford CT, USA). Labrafac Lipophile WL 1349 and Transcutol HP were provided by Gattefosse (Saint Priest, Cedex, France). A gift sample of vitamin E TPGS was taken from Seqens GmbH (Germany), Opadry YS-1-7040 white from Colorcon Asia Pvt Ltd. (India), and Polysorbate 80 purchased from Croda Singapore PTE Ltd. Acetonitrile and methanol (HPLC grade) were received from Merck Chemicals (Germany). Ammonium acetate, ammonium hydroxide and potassium dihydrogen orthophosphate (KH₂PO₄) were collected from Qualigen (Thermo Fisher Scientific, Mumbai, India). The analytical column, Chromosil, 250 × 4.6 mm, 5.0 μm, was purchased from Chrom Separations Inc (USA). FaSSIF, FeSSIF and FaSSGF 3F Powder were received from Biorelevant (UK).

HPLC analysis

Shimadzu LC-10 AT VP HPLC with PDA detector (Shimadzu Corporation, Japan) was used for quantification of Ticagrelor. Reverse-phase chromatography was adopted as described by Bueno et al.²¹ with some modifications. A C8 reverse-phase analytical column (Chromosil, 250 × 4.6 mm, 5.0 μm) and

a mobile phase of 50 mM acetonitrile: ammonium acetate (57:43 v/v with pH adjusted to 8.2) were used in the analysis. The column temperature was set to 25 °C, with an injection volume of 20 µL, and a flow rate of 0.7 mL/min was maintained. Ticagrelor absorbance was taken at 270 nm.

Ultraviolet (UV) analysis

A UV-Visible spectrophotometer (Shimadzu 1900 series with Lab Solution software) was used for the dissolution of Ticagrelor formulations. For standard preparation, phosphate buffer pH 6.8 and methanol were prepared in a 70:30 ratio. For the standard calibration curve, different concentrations of Ticagrelor standard solution were prepared from 2 µg/mL to 20 µg/mL, and absorbance was measured at 222 nm. Similarly, dissolution samples of Ticagrelor withdrawn at 5, 10, 15, 30, 45, 60, and 75 minutes were diluted with the dissolution medium, and their absorbance was taken at 222 nm.

Screening and optimization of formulation technology for Ticagrelor

In a preliminary screening study, different formulations of Ticagrelor were prepared using the techniques of conventional wet granulation, SD, and micro-emulsification (SMEDDS). Conventional wet granulation was adopted to prepare a film-coated tablet dosage form with a similar Qualitative (Q1) and Quantitative (Q2) composition to that of the reference product Brilinta® (AstraZeneca LP). Ticagrelor of differing particle size (D90) was used in the formulation of an immediate-release tablet using the wet granulation process. Solvent evaporation techniques were performed to prepare Ticagrelor SD. Co-povidone (Kolidone VA 64), Soluplus, HPMC acetate succinate, and permeation enhancer vitamin E TPGS were explored for the preparation of SD. The SD thus obtained was further blended with other excipients for tablet compression, followed by film coating. Ticagrelor (SMEDDS) was prepared with medium-chain triglyceride (Labrafac lipophile WL 1349, Gattefosse), co-surfactant Transcutol HP (Gattefosse), surfactant Polysorbate 80, and solvent ethanol. The SMEDDS thus obtained were filled into size X hard gelatin capsules. The above dosage forms of Ticagrelor prepared with different formulation technologies were evaluated to select a stabilized Ticagrelor dosage form with a superior dissolution profile.

Preparation of conventional immediate release tablets (TICA-IR)

A conventional immediate-release Ticagrelor film-coated tablet formulation was prepared by an aqueous wet granulation process. Two different particle size ranges of Ticagrelor, (A) D90: 26.96 microns, and (B) D90: 12.88 microns, were considered. The qualitative (Q1) and quantitative (Q2) composition, as well as the manufacturing process, were similar to the reference product Brilinta® (AstraZeneca LP). Ticagrelor and intragranular excipients were sifted and blended. The blended dry mix was then granulated with purified water and dried to achieve a loss on drying of 1.0-1.50% w/w. The dried granules are sifted and milled to obtain granules sized at mesh 30. The sifted granules were then blended with extra

granular ingredients and compressed into tablets, followed by film coating.

Preparation and optimization of immediate-release Ticagrelor tablets with SD technology (TICA-SD)

Polymers co-povidone VA 64, Soluplus, and HPMC Acetate succinate were screened for their drug loading efficiency and their capacity to form an ASD. Ticagrelor and polymer were dispersed in ethanol under continuous stirring using a magnetic stirrer at 300 rpm for 1 h. The drug-polymer dispersion in ethanol was then processed in a rotary evaporator at 50 °C to obtain an SD of Ticagrelor. The SDs thus obtained were extra-dried and sifted through a sieve of mesh # 30 and characterized by XRPD. The sized SD powder was blended with Pearlitol SD 200, calcium hydrogen phosphate dihydrate, sodium starch glycolate, and hydroxypropyl-cellulose in a blender for 10 minutes at 12 RPM. Magnesium stearate was added and blended further for 3 minutes at 12 RPM. The blended mass is then compressed into a tablet in a rotary compression machine. The compressed tablets were coated with Opadry YS-1-7040, with an inlet temperature of 65±5 °C, at 6 RPM. Placebo tablets without Ticagrelor were also prepared by the same method as that used for preparing TICA-SD tablets.

The formulations of Ticagrelor SD were optimized with different ratios of Ticagrelor (TICA), vitamin E TPGS, and carriers, i.e., co-povidone VA 64 (CP VA64), Soluplus, and hypromellose acetate succinate (HPMCAS). The solvent evaporation technique was explored for the preparation of ASD. For the preparation of Ticagrelor SD (TICA-SD) with carrier co-povidone VA 64, different combinations such as TICA: TPGS: CP VA 64-1: 0.4: 1, TICA: TPGS: CP VA 64-1: 0.4: 2, and TICA: TPGS: CP VA 64-1: 0.4: 4 were used. The same combinations were followed for the preparation of Ticagrelor SD (TICA-SD) with Soluplus and HPMCAS also.

Preparation of immediate-release Ticagrelor capsules with SMEDDS technology (TICA-SMEDDS)

TICA-SMEDDS were prepared and optimized with a composition of Ticagrelor (10% w/w), Labrafac Lipophile WL 1349 (45% w/w), Transcutol HP (35% w/w), Polysorbate 80 (10% w/w) and ethanol (5% w/w). The solvent ethanol is lost during the homogenization process. The microemulsion pre-concentrate thus obtained was filled in a size 00 hard gelatin capsule and evaluated for dissolution.

Characterization of Ticagrelor and its formulations

Polarized microscopy

The crystal properties and morphology of pure crystalline Ticagrelor and Ticagrelor SD were evaluated by polarized microscopy (Olympus BX 53) with IPV P Class software (Image Pro-Vision). The samples were evaluated by polarized microscopy with a magnification of 20X, 40X, and 100X, with and without a polarizer, to identify small traces of crystalline Ticagrelor in samples of ASD. Further, the particle size, shape, and the presence of any agglomerates were also evaluated with the help of IPV-P Class software.

PXRD

PXRD analysis was performed on the SD and its tablet formulations (initial and 6-month stability) to determine the Ticagrelor crystallinity. PXRD patterns were recorded using the Rigaku Miniflex 600 XRD System (Tokyo, Japan) with Ni-filtered Cu-K α radiation at 1.54 Å, power of 40 kV and 15 mA. The sample scanning was carried out from 2 θ of 5° to 120°, at 0.02° steps and with a 5°/minute increment.

Differential scanning calorimetry (DSC)

The DSC curve for the SD sample was obtained using a DSC 60 plus thermal analyzer (Shimadzu Asia Pacific Pte Ltd.). The required quantity of samples [TICA active pharmaceutical ingredient and (API) TICA-SD] was taken in the DSC pan, and the thermogram was recorded at a heating rate of 10 °C/min from 0 to 350 °C.

Dynamic vapor sorption (DVS)

To understand the moisture-induced glass transition event of Ticagrelor and its SD, water vapor sorption experiments were carried out on a DVS automated moisture sorption instrument (DVS Adventure/Resolution instruments, Surface Measurement Systems UK) at 25 °C. The sample of Ticagrelor API and SD (11-50mg) was dried for about 300 minutes under a continuous air flow to achieve the dry mass before being subjected to relative humidity (RH) of 0% to 95% at a ramping rate of 2% RH per hour. The partial pressure was then decreased in a similar manner. The camera accessory was used to take sample images during the experiment.

Assay by HPLC

To prepare a standard stock solution, the 10 mg Ticagrelor reference standard was transferred to a 10 mL volumetric flask. The sample was added to 5 mL of methanol and sonicated to dissolve. We made up the final volume to 10 mL with methanol, and mixed well. The standard solution was prepared by diluting 2 mL of a standard stock solution to 20 mL with the mobile phase. The test solution for Ticagrelor SD was prepared by dissolving a SD sample equivalent to 90 mg of Ticagrelor in 25 mL of methanol. The solution was sonicated to get a clear solution and filtered through a 0.45 micron syringe filter. The first few mL of filtered solution was discarded, and the Ticagrelor was quantified using HPLC at 270 nm. A test solution for Ticagrelor film-coated tablets was prepared by dissolving samples from 20 crushed tablets equivalent to 90 mg of Ticagrelor, and the further processing was conducted as per the Ticagrelor SD method. A test solution for the Ticagrelor capsule was prepared by dissolving the capsule content (from 20 capsules) equivalent to 90 mg of Ticagrelor, and the further process was followed as per the Ticagrelor SD.

In vitro dissolution study

Dissolution testing of Ticagrelor formulations was conducted using a USP II paddle apparatus with the aid of a dissolution tester (Electrolab TDT-08 L instrument). The dissolution method includes a phosphate buffer with pH 6.8, 900 mL, a paddle at 75 rpm, with a sampling time of 10, 20, 30, 45, and 75 minutes. A comparative dissolution profile of the dosage forms

prepared with conventional wet granulation, SD, and micro-emulsification (SMEDDS) techniques was carried out to select the best formulation technique suitable for the dissolution enhancement of Ticagrelor.

Researchers carried out Bio-relevant dissolution for the finalized formulation of SD with co-povidone VA 64 in FaSSIF and FaSSGF to assess the *in vivo* absorption of the Ticagrelor dosage form. The above media were prepared by taking a specified quantity of FaSSIF powder and making up the volume to 1 L with monobasic sodium phosphate monohydrate (NaH₂PO₄ · H₂O) buffer of pH 6.5. The absorbance of the Ticagrelor standard solution and sample solution was measured using a UV-Visible spectrophotometer (Shimadzu 1900 series with LabSolutions software) at 222 nm.

Dissolution samples were withdrawn at the 5, 15, 30, 60, and 75 min time points and filtered through a 0.45 µm syringe filter. The dilution of the filtrate was done with a mixture of methanol-phosphate buffer 6.8 (70:30), and absorbance was measured in a UV-Visible spectrophotometer (Shimadzu 1900 series with Lab solution software) at 222 nm to calculate the dissolution of Ticagrelor.

Stability study

Ticagrelor tablets prepared by SD were packed in an HDPE container with induction sealing and were subjected to the stability study at accelerated (40 °C/75% RH) and long-term storage (30 °C/75% RH) conditions as per ICH. Stability of the Ticagrelor tablet with SD technology was evaluated for assay, related substance, dissolution, and PXRD at both initial and 6-month time intervals.

In vivo experiments

PK study

An *in vivo* study was carried out in Wistar rats to evaluate the relative bioavailability between conventional Ticagrelor tablets 90 mg and Ticagrelor tablets 90 mg prepared with an SD approach. Further, a dose-adjusted comparative bioavailability study was carried out between the Ticagrelor conventional TABLET 90 mg and the Ticagrelor SD tablet 70 mg for the assessment of *in vivo* bioequivalence.

Wistar rats weighing 350-400 g were housed in individually ventilated cages and provided with an autoclaved pellet diet, bedding, and water ad libitum. The Wistar rats were maintained in a light and noise-controlled environment. The rats were put into four groups at random with n=2 per group, namely TICA-IR TABLET-90, TICA-IR TABLET-90M, TICA-SD TABLET-90, and TICA-SD TABLET-70. A test sample equivalent to 90 mg Ticagrelor was administered orally to the animal using normal saline as a vehicle. Blood was withdrawn at 1, 3, 5, 8, 12, and 24 hours by orbital puncture, and plasma was separated by centrifugation. Plasma samples were precipitated with methanol. Methanol samples were centrifuged to remove suspended debris. The supernatant methanol samples were analyzed by RP-HPLC on a BDS Hypersil C 8 Column, mobile phase methanol: Water (20:80, v/v), a flow velocity of 1.0 mL/min, and a UV detector with a wavelength of 254 nm were used.

The primary PK parameters, such as C_{max} , T_{max} , AUC_{0-t} , $AUC_{0-\infty}$, and $t_{1/2}$ were calculated using PKSolver® software (Version 2.0).

Construction of standard calibration curve: Blood samples were collected from Wistar rats and serum was separated through centrifugation. Different dilutions, i.e., 100 ng/mL, 500 ng/mL, and 2000 ng/mL, were prepared in the serum. The serum was precipitated using methanol and centrifuged with a Remi benchtop clinical centrifuge at 1000 RPM for 10 minutes. The supernatant methanol samples were analyzed by RP-HPLC on a BDS Hypersil C 8 Column with a mobile phase of methanol: water (20:80, v/v), a flow rate of 1.0 mL/min, and a UV detector at 254 nm. The standard calibration curve was constructed with the data obtained for 100 ng/mL, 500 ng/mL, and 2000 ng/mL.

Monitoring of GI bleeding

Test samples equivalent to 90 mg Ticagrelor were administered orally to Wistar rats with normal saline as a vehicle. Animals were observed for 12 hours for side symptoms and then sacrificed. The gastric organs were dissected and observed for bleeding and other related symptoms through a stereo microscope with 10X magnification.

RESULTS

Screening and optimization of formulation technology for Ticagrelor

An ASD formulation with co-povidone, based on the screening dissolution study of Ticagrelor dosage forms, yielded a superior dissolution rate compared to Ticagrelor SMEDDS capsules and conventional immediate release tablets with micronized API.

Hence, the SD formulation technology was selected for further investigations. The physical parameters for the dosage forms prepared with different formulation technologies are shown in Table 1. The images of the dosage forms prepared with different formulation technologies are depicted in Figure 1.

Characterization of Ticagrelor and its formulations

Ticagrelor formulations prepared with different dissolution enhancement techniques, such as micronization, SD, and micro-emulsifying drug delivery (SMEDDS) were evaluated for their dissolution profiles in a discriminatory dissolution method. Ticagrelor tablets prepared with SD technology were evaluated for dissolution profile, PXRD, and DSC. The dissolution profiles for all the formulations prepared with the above technology were compared with the conventional immediate-release tablet formulation that has a similar Q1/Q2 (composition) and process technology to the reference product Brilinta® (AstraZeneca LP).

Particle morphology of Ticagrelor by polarized microscopy

The particle morphology and crystal properties of two different lots of Ticagrelor were evaluated with a polarized microscope (Olympus-BX 53). Ticagrelor API, taken for this study, showed positive birefringence with a polarized microscope as shown in Figure 2, indicating the crystalline nature of the API.

Particle size distribution (PSD) of Ticagrelor

Ticagrelor with two different particle size ranges was considered in the formulation process. Ticagrelor API was analyzed with a polarized microscope (Olympus BX 53) equipped with image provision technology-polarizing (IPV-P) class software for PSD, shape and agglomerates. Using the IPV-P class software,

Table 1. Physical evaluation parameters for the Ticagrelor dosage form prepared with different formulation technology

Parameters	TICA-IR tablets	TICA-SD tablets	TICA-SMEDDS capsules (hard gelatin)
Size/shape/dimensions	9.5 mm, Round, Bi convex	19x8 mm, Oblong, Biconvex	Size 00, lock length -23 mm
Weight	309 mg±2% w/w	1340 mg±2% w/w	900 mg±2% w/w
DT	4-5 minutes	4-5 minutes	3-4 minutes

DT: Disintegration time, IR: Immediate release, SD: Solid dispersion, SMEDDS: Self-Microemulsifying Drug Delivery System, TICA: Ticagrelor

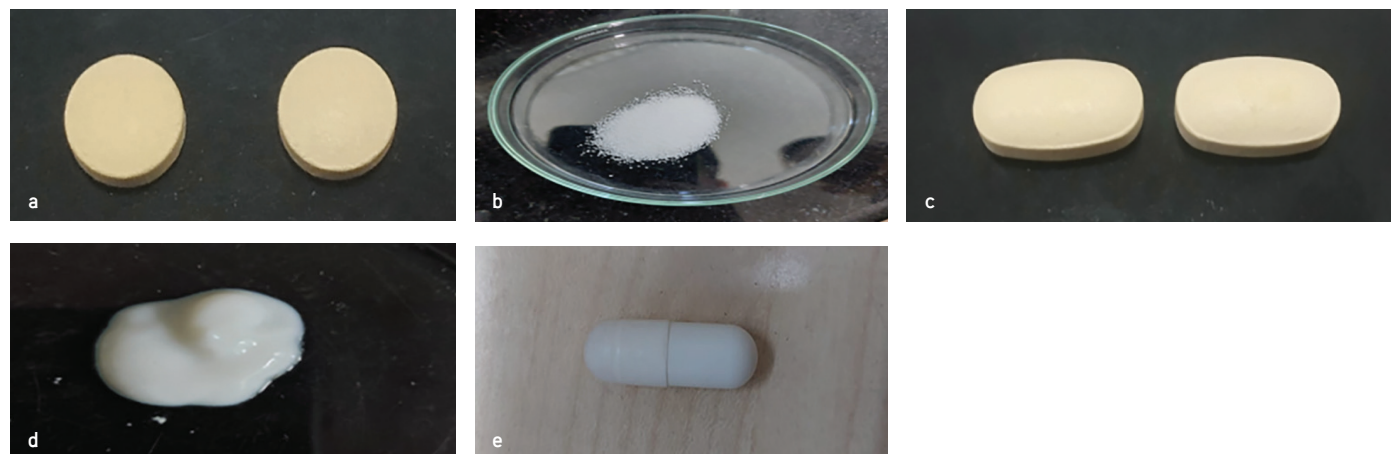


Figure 1. Ticagrelor formulations prepared with different dissolution enhancement techniques. (a) TICA-IR Tablets (In line with Brilinta® AstraZeneca LP); (b) TICA-SD; (c) TICA-SD tablets; (d) TICA-SMEDDS (e) TICA-SMEDDS Capsules (Hard gelatin)

TICA: Ticagrelor, IR: Immediate release, SD: Solid dispersion, SMEDDS: Self-Microemulsifying Drug Delivery System

PSD with D10, D50, and D90 were obtained and presented in Table 2. The optical microscopy images of the two different lots of API presented in Figure 2.

Optical microscopy for Ticagrelor SD

The Ticagrelor ASD sample was analyzed using an optical microscope (Olympus-BX 53) with and without the polarizer, at magnifications of 20X and 100X. Birefringence, an optical property of the crystalline solid, can be clearly observed with the help of a polarized optical microscope. Small traces of undesirable crystalline Ticagrelor in the sample of ASD could be identified when analyzed using the optical microscope equipped with a polarizer. No birefringence could be observed in the sample when analyzed by the optical microscope without a polarizer, as shown in Figure 2.

The impact of the traces of crystalline solids in the ASDs of Ticagrelor was further evaluated during the accelerated stability study to rule out any crystal growth and subsequent

crystallization that could lead to a polymorphic transformation.

The particle size, shape, and presence of agglomerates were also evaluated with the help of IPV-P Class software. The results are presented in Table 3 and Figure 3.

Powder X-ray diffraction (PXRD) of Ticagrelor

The Ticagrelor API used in the current study was analyzed with the Rigaku Miniflex 600 XRD System. The PXRD pattern of Ticagrelor is shown in Figure 4. Sharp diffraction peaks of 2θ at 10.50° , 13.36° , 14.74° , 18.18° , 19.06° , 21.12° , 22.52° , and 24.12° were observed against the reported 2θ values, Table 4, indicating that the Ticagrelor API used in the current study is a mixture of polymorphic forms II, III, and IV of Ticagrelor. Hence, it can be considered a metastable form of Ticagrelor.

Ticagrelor exhibits polymorphism. Four non-solvated polymorphs (Polymorph I, II, III and IV) and many solvated crystalline polymorphs are reported, which can be clearly distinguished by X-ray powder diffraction. Apart from the

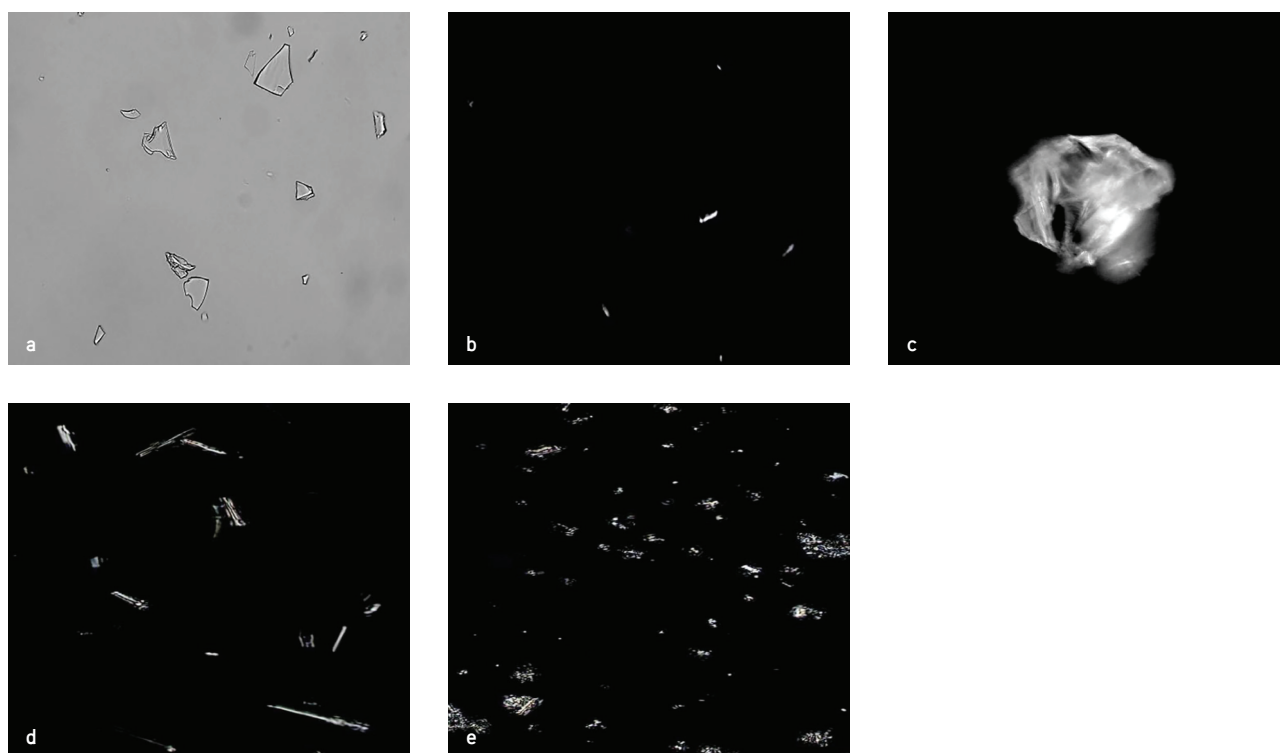


Figure 2. Optical microscopic images of Ticagrelor SD. (a) TICA-SD co-povidone VA 64, 20X without polarizer; (b) TICA-SD co-povidone VA 64, 20X with polarizer; (c) TICA-SD co-povidone VA 64, 100X with polarizer; (d) TICA-API (D90: 26.969 μm), 20X with polarizer; (e) TICA-API (D90: 12.8805 μm), 20X with polarizer obtained from polarized microscope (Olympus -BX 53) with IPV-P class software

API: Active pharmaceutical ingredient, IPV-P: Image provision technology-polarizing, SD: Solid dispersion, TICA: Ticagrelor

Table 2. Particle size and shape for two different lots of Ticagrelor analyzed through a polarized microscope (at 20X) with IPV-P class software (image provision technology)

PSD (μm)	Sample A			Sample B		
	Particle	Agglomerate	Total	Particle	Agglomerate	Total
D ₁₀	3.946	3.946	3.946	3.355	9.3666	3.3550
D ₅₀	10.011	10.011	10.011	6.344	14.9524	6.5353
D ₉₀	26.969	26.969	26.969	11.839	26.5635	12.8805

IPV-P: Image provision technology-polarizing, PSD: Particle size distribution

above four polymorphic forms, Form α is also reported as an anhydrous form, which has no sharp peak in the PXRD. It is reported that form II is a metastable form, whereas form I is a thermodynamically stable form. The interconversion of form II to form I and vice versa takes place reversibly through a temperature-induced phase transition upon heating/cooling.^{22,23} Different crystal habits of Ticagrelor (TICA) form II were studied and reported by Ren et al.²⁴ The impact of the anisotropic surface

chemistry of the crystal on the physicochemical properties of the crystal, such as solubility and tableting, was reported.

PXRD for Ticagrelor SD

The PXRD pattern of crystalline Ticagrelor and Ticagrelor SD prepared with co-povidone VA 64, Soluplus, and HPMCAS is shown in Figure 5. Sharp crystalline peaks with 2θ at 10.50° , 13.36° , 14.74° , 18.18° , 19.06° , 21.12° , 22.52° and 24.12° were observed for the API Ticagrelor, whereas all the crystalline peaks disappeared in the SD samples.

Crystalline Ticagrelor was completely converted to amorphous form for three formulations prepared with co-povidone VA 64, Soluplus and HPMCAS. However, the stability of the ASD depends on the hygroscopicity and CDF. Faster dissolution and satisfactory stability of the ASD prepared with carrier co-povidone VA 64 could be attributed to its low CDF.¹⁶

The PXRD pattern of Ticagrelor API, SD with co-povidone VA 64, tablets prepared with SD, and placebo is shown in Figure 6.

Table 3. PSD of SD of Ticagrelor prepared with co-povidone VA 64

PSD for TICA-SD

Parameters	Particle	Agglomerate	Total
D10	2.290	0.000	2.2896
D50	3.946	0.000	3.9463
D90	12.952	0.000	12.9522

PSD: Particle size distribution, SD: Solid dispersion, TICA: Ticagrelor

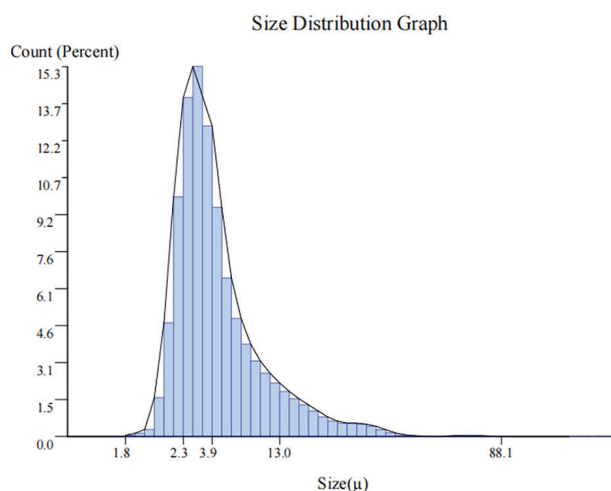


Figure 3. PSD of SD of Ticagrelor prepared with co-povidone VA 64

PSD: Particle size distribution, SD: Solid dispersion

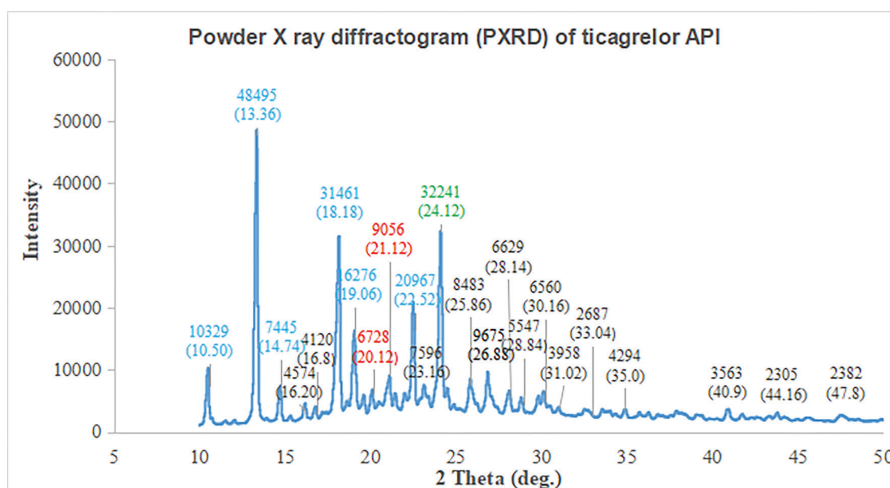


Figure 4. X-ray diffractogram of the Ticagrelor API used in the present study

API: Active pharmaceutical ingredient

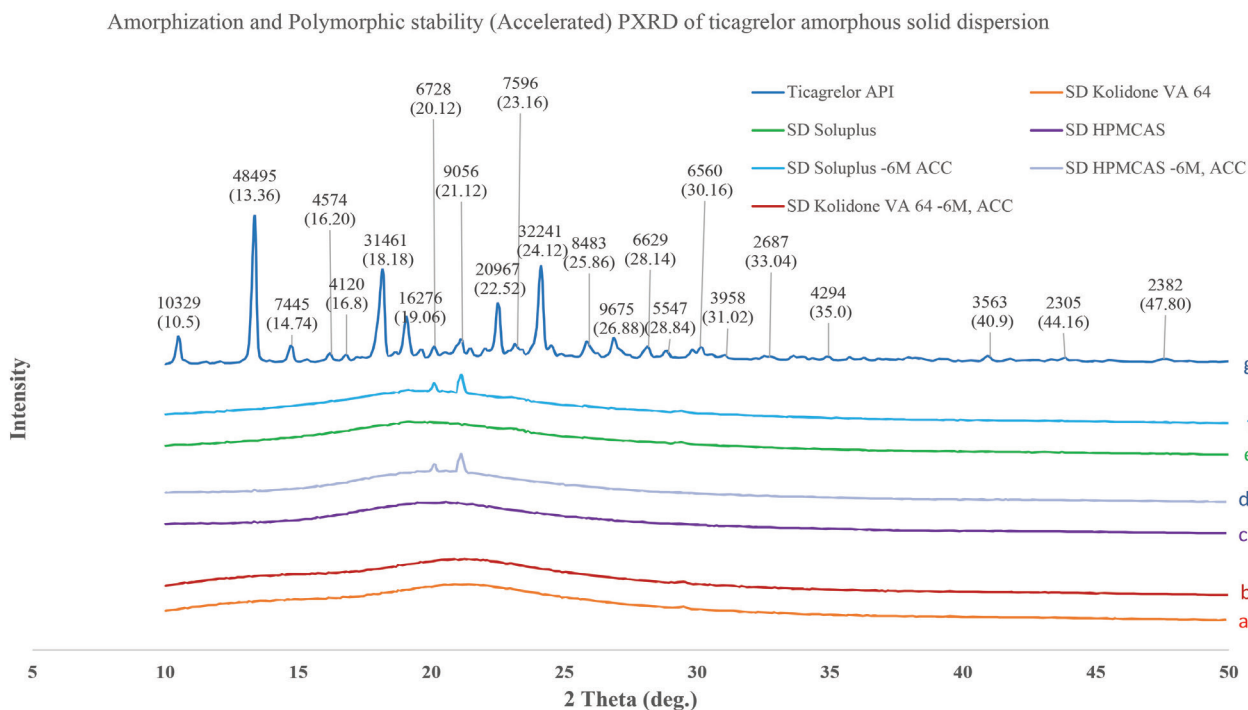


Figure 5. Amorphization and comparative polymorphic stability of Ticagrelor SD at accelerated storage condition. (a) PXRD of Ticagrelor SD to Kolidone VA 64; (b) PXRD of Ticagrelor SD with Kolidone VA 64 at 6M Accelerated condition; (c) PXRD of Ticagrelor SD HPMCAS; (d) PXRD of Ticagrelor SD HPMCAS at 6M Accelerated condition; (e) PXRD of Ticagrelor SD with Soluplus; (f) PXRD of Ticagrelor SD with Soluplus at 6M Accelerated condition; (g) PXRD of Ticagrelor API

API: Active pharmaceutical ingredient, D90: Diameter at which 90% of the particles are smaller (particle size distribution parameter), IPV-P: Image provision technology-polarizing (microscope imaging software, as stated), SD: Solid dispersion, TICA: Ticagrelor

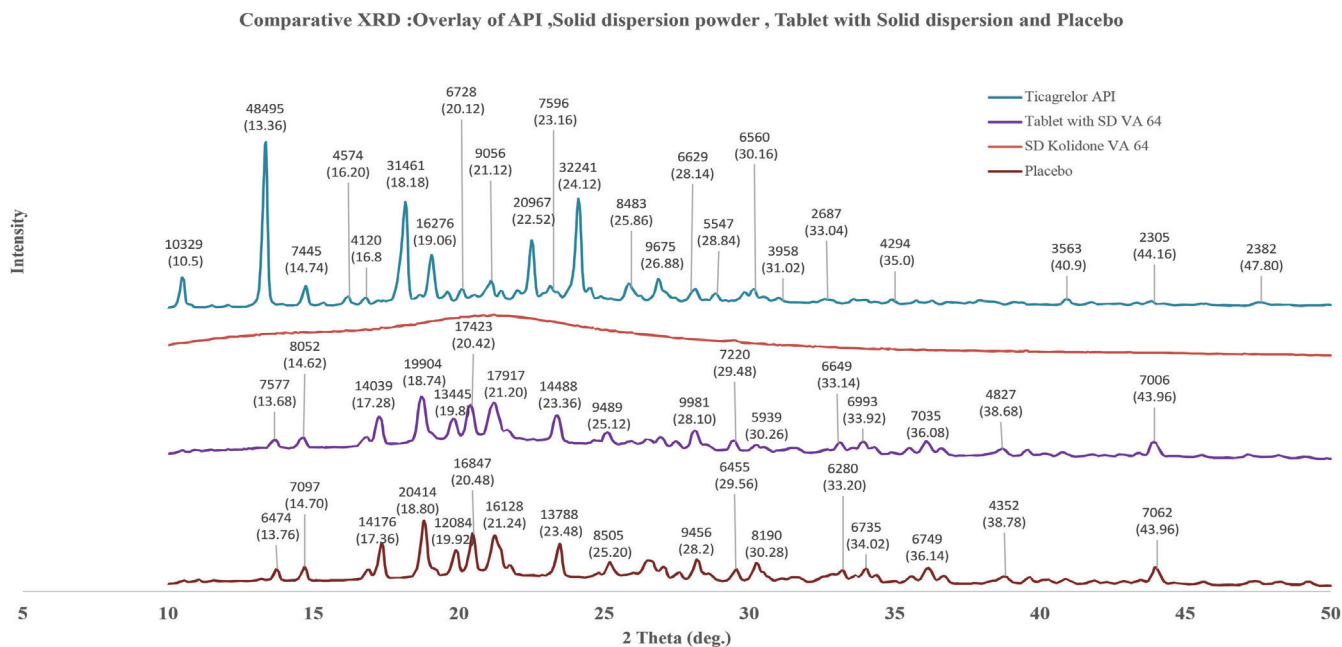


Figure 6. PXRD pattern of Ticagrelor API, placebo, optimized SD and its tablet formulation

API: Active pharmaceutical ingredient, PXRD: Powder X-ray diffraction, SD: Solid dispersion

The sharp characteristic peaks of the crystalline Ticagrelor API with 2θ at 10.50° , 13.36° , 14.74° , 18.18° , 19.06° , 21.12° , 22.52° and 24.12° were found to have disappeared in the SD formulation. However, in the PXRD of the SD tablets, only the placebo peaks appeared. Hence, it is concluded that no polymorphic change is observed in the Ticagrelor ASD during or after compression of the tablet.

Stability study of Ticagrelor SD

No significant change was observed in the assay, dissolution, and related substances for the optimized Ticagrelor tablets prepared with SD [TICA-SD Tablet with co-povidone (1:0.4:4)]. Further, in the PXRD of the stability sample, no crystalline peaks were observed up to 6 months.

In the PXRD of stability samples of Ticagrelor SD prepared with carrier Soluplus and HPMCAS, two crystalline-characteristic peaks 2θ at 20.12° and 21.12° corresponded to Ticagrelor polymorphic form I. However, no crystalline peaks were observed for the stability sample of Ticagrelor SD, prepared with carrier Co-povidone VA 64. The comparative polymorphic stability of Ticagrelor ASD with different carriers is depicted in Figure 5.

Differential scanning calorimetry (DSC)

The DSC thermogram of Ticagrelor used in the present study was generated at a $10^\circ\text{C}/\text{min}$ heating rate over a range of 0 to 350°C to understand transitions as a function of temperature and time. Also, specific information, i.e., glass Tg, melting point (Tm), and crystallization temperature (Tc) obtained from the endothermic and exothermic processes was studied. The

endothermic peak at 140°C and exothermic peak at 315°C in Figure 7 indicate the melting and crystallization temperatures, respectively. The reported onset melting temperature for different polymorphs of Ticagrelor is given in Table 4. It can be noted that the precise value of the melting point is influenced by the purity of the compound, the sample weight, the heating rate, and the particle size. Hence, the experimental values may slightly differ from the reported values.

DSC for Ticagrelor and its SD

The DSC thermogram of pure Ticagrelor and Ticagrelor SD is presented in Figure 7. For the Ticagrelor API, the endothermic and exothermic peaks at 140°C and 315°C indicate the melting and crystallization temperature, respectively, whereas the endothermic peak of Ticagrelor SD at 52.72°C indicates the glass transition temperature (Tg).

Stabilized amorphous Ticagrelor reported by Davis et al.²⁵ EP 2 813 216 A1. Amorphous Ticagrelor has a relatively low glass transition temperature (Tg), about 46°C . It is, therefore, essential to prevent re-crystallization by increasing the glass transition temperature (Tg) to stabilize the ASD of Ticagrelor.

From the DSC thermogram, it is evident that the glass transition temperature (Tg) of Ticagrelor SD is increased to 52.72°C due to the presence of Co-povidone VA 64 as a carrier. Co-povidone VA 64 is an excellent crystallization inhibitor and a matrix-forming agent with a glass transition temperature (Tg) of 101°C . The absence of any exothermic peak in the DSC thermogram indicates the absence of crystallization in the sample of SD prepared with co-povidone VA 64.

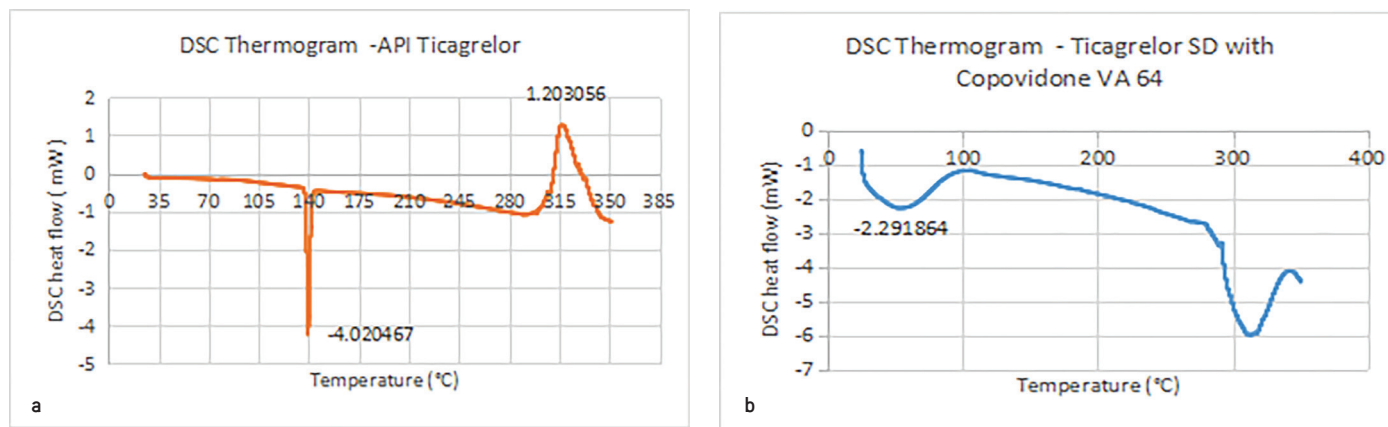


Figure 7. DSC thermogram of (a) pure Ticagrelor API and (b) Ticagrelor SD

API: Active pharmaceutical ingredient, DSC: Differential scanning calorimetry, SD: Solid dispersion

Table 4. Reported 2 Theta (2θ) value and onset melting temperature for different polymers of Ticagrelor²²

Polymorphic form	2 theta value (XRD)	Characteristic high intensity peaks	On set of melting (DSC)
Form I	5.3,8.0, 9.6, 13.9, 15.3, 20.1,20.7,21.0,21.3, 26.2, 27.5	5.3,20.1,20.7,21.0,21.3	151 °C (146 -152 °C)
Form II	5.5, 6.8, 10.6,13.5, 14.9, 18.3, 19.2,22.7,24.3, 27.1	5.5,13.5,18.3,22.7,24.3	137.5 °C (136-139 °C)
Form III	5.6, 12.5, 14.0,17.4,18.4, 21.4, 22.2, 22.9,24.1, 24.5	14.0,17.4,18.4,21.4, 24.1	132 °C (127-132 °C)
Form IV	4.9, 6.0,9.2,11.6, 12.8, 15.6,16.4, 17.2, 18.1	4.9,9.2,11.6,15.6,16.4	139 °C

DSC: Differential scanning calorimetry, XRD: X-ray diffraction

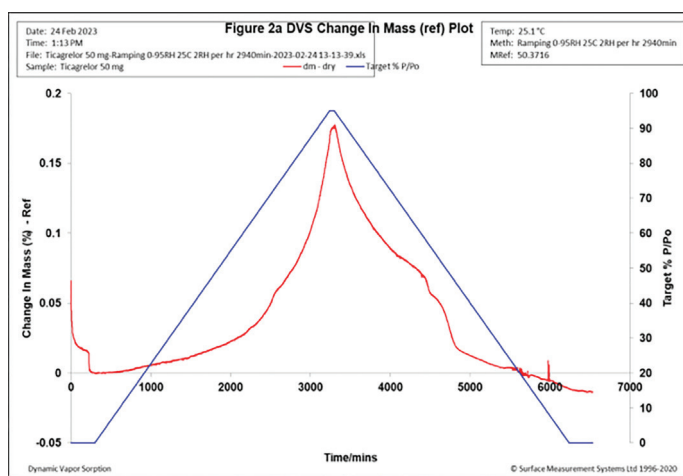
DVS

For the ramping experiment, the % change in mass versus time plots for the sample of Ticagrelor API and SD of Ticagrelor at 25 °C are shown in Figure 8, respectively.

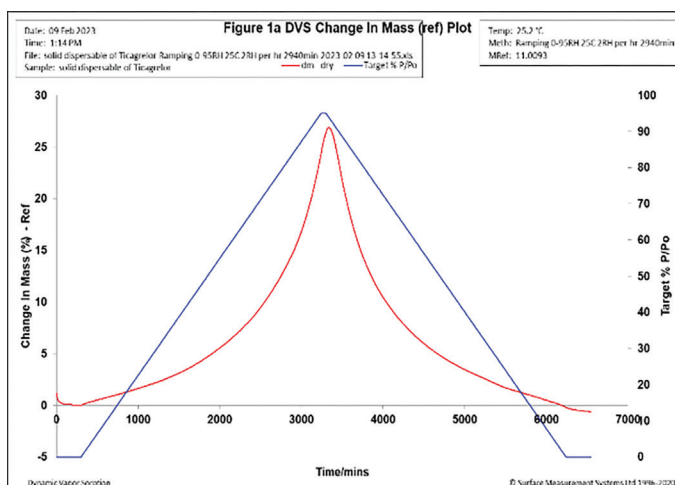
In Figure 8, the red line indicates the net percent change in mass with respect to time, while the blue line represents the sample RH. The profile of the Ticagrelor SD sample shows a relatively higher mass uptake than the Ticagrelor API. This suggests that there was a bulk sorption mechanism occurring in the sample of SD of Ticagrelor, whereas a surface sorption process occurred in the Ticagrelor API sample.

The video camera accessory captured images of the SD sample of Ticagrelor and its API. Figure 9 shows snapshots of the SD of Ticagrelor during the RH ramping experiment at 25.0 °C to visualize RH-induced transformation. For a sample of Ticagrelor SD, there were distinct changes in the visual appearance. However, this is not observed in the case of the Ticagrelor API samples.

The RH where transformation occurs from surface adsorption to bulk absorption represents the glass transition relative humidity (RH_g). The glass transition RH values for Ticagrelor API and Ticagrelor SD were found to be 59.9% and 64.4%, respectively.



a



b

Figure 8. RH ramping experiment for (a) Ticagrelor API; (b) SD of Ticagrelor representing glass transition RH at 25.0 °C
API: Active pharmaceutical ingredient, RH: Relative humidity, SD: Solid dispersion

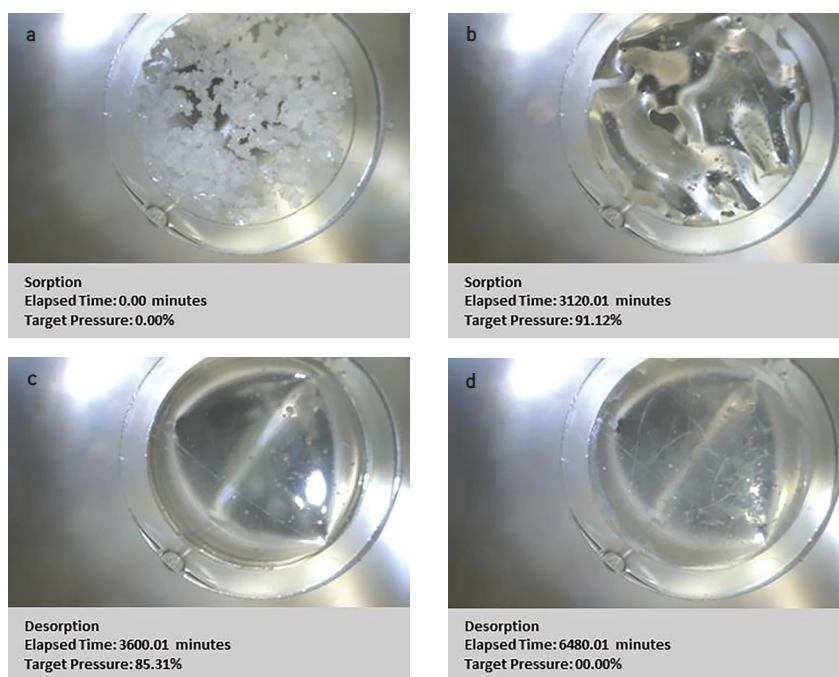


Figure 9. Real-time images of the Ticagrelor SD sample during the RH ramping experiment at 25.0 °C represent the RH-induced transformations and glass transitions. (a) sorption at 0 % pressure; (b) sorption at 91.12 % pressure; (c) desorption at 85.31 % pressure; (d) desorption at 0 % pressure

RH: Relative humidity, SD: Solid dispersion

In vitro dissolution study

To evaluate the dissolution performance of the Ticagrelor dosage form, a dissolution study was performed with the USP II paddle apparatus at 75 RPM and 900 mL of phosphate buffer pH 6.8; both with and without a surfactant. With its good discriminatory power, phosphate buffer pH 6.8 without surfactant was selected for the formulation trials. The sample analysis was performed with a UV-Visible spectrophotometer (Shimadzu 1900 series with LabSolutions software) at 222 nm.

The dissolution profiles for all the formulations of Ticagrelor were generated in phosphate buffer pH 6.8, as presented in Figure 10. As per the result, the dissolution after 75 minutes was found to be 10% (% RSD-1.1), 15% (% RSD-3.0), 24% (% RSD-0.5), 107% (% RSD-0.6), 30% (% RSD-2.8) and 27% (% RSD-0.3) for TICA-IR TABLET 90 (D₉₀:26.96 μ), TICA-IR TABLET 90 (D₉₀:12.88 μ), TICA-SD TABLET 90 with co-povidone VA 64 (1:0.4:1), TICA-SD TABLET 90 with co-povidone (1:0.4:4), TICA-SD TABLET 90 with soluplus (1:0.4:4), TICA-SD TABLET 90 with HPMCAS (1:0.4:4) and TICA-SMEDDS CAPSULE 90 respectively. The dissolution profile obtained for

the conventional immediate release tablet formulation [TICA-IR TABLET 90 (D₉₀:26.96 μ)] was found to be similar to the reported dissolution profile of reference product BRILINTA® (AstraZeneca LP).¹⁸

Bio-relevant dissolution

Based on the comparative dissolution profile of formulations prepared with different technologies, the SD technique with co-povidone VA 64 was superior and yielded faster dissolution compared to other techniques such as micronization and microemulsifying drug delivery. Hence, Ticagrelor tablets with SD technology, i.e., TICA-SD tablets with co-povidone (1:0.4:4), were further evaluated with biorelevant media (FaSSGF & FeSSIF) to simulate the *in vivo* realistic environment.

Based on the results of the TICA-SD Tablet with co-povidone (1:0.4:4), the dissolution rates at 75 minutes were found to be 107% (% RSD-0.6), 100% (% RSD-0.5) and 100% (% RSD-0.6) in phosphate buffer pH 6.8, FaSSGF, and FaSSIF, respectively (Figure 10).

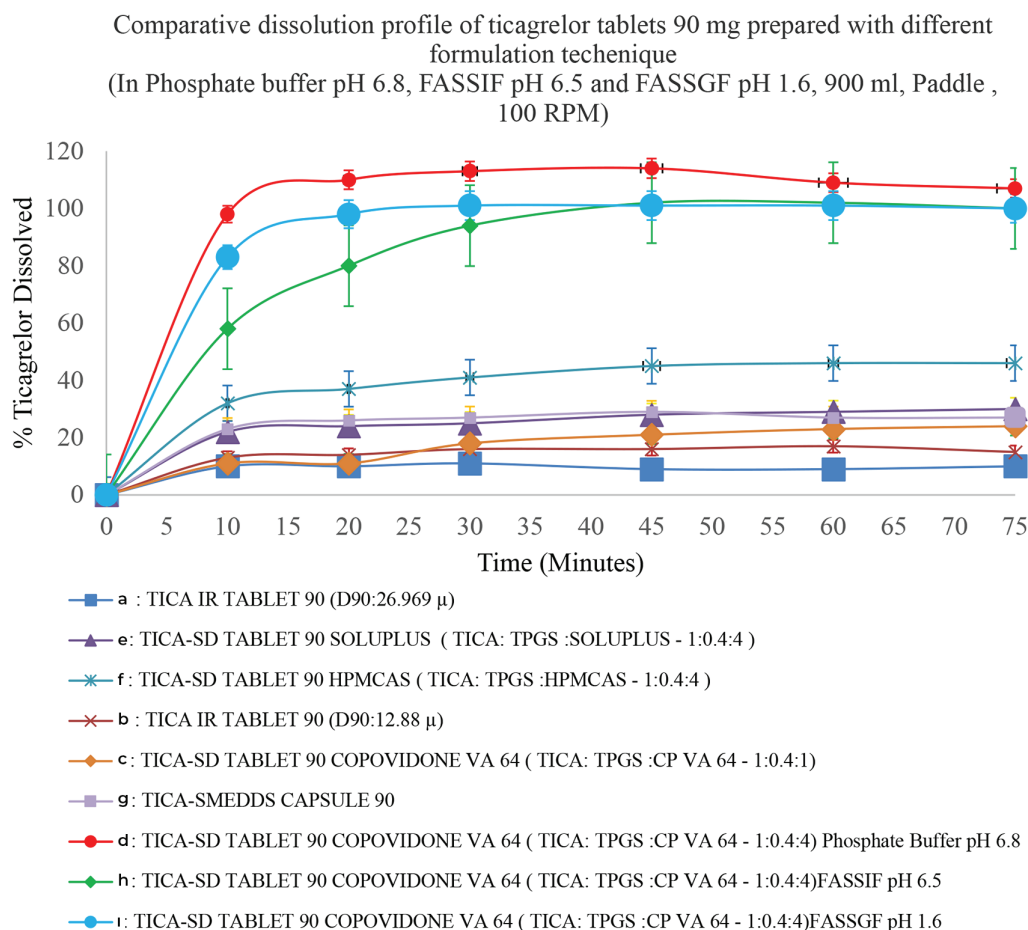


Figure 10. Comparative dissolution profile of Ticagrelor formulations, (a) conventional IR tablet (D₉₀:26.96 μ); (b) conventional IR tablet (D₉₀:12.88 μ); (c) TICA-SD tablet with copovidone (1:0.4:1); (d) TICA-SD TABLET 90 with copovidone VA 64 (1:0.4:4); (e) TICA-SD tablet with Soluplus (1:0.4:4); (f) TICA-SD tablets 90 with HPMCAS (1:0.4:4); (g) TICA-SMEDDS capsule 90; (h) TICA-SD TABLET 90 with copovidone VA 64 (1:0.4:4); in FASSIF pH 6.5; (i) TICA-SD TABLET 90 with copovidone VA 64(1:0.4:4) in FASSGF pH 1.6

IR: Immediate release, SD: Solid dispersion, SMEDDS: Self-microemulsifying drug delivery system, HPMCAS: Hydroxypropyl methylcellulose acetate succinate, FaSSIF: Fasted state simulated intestinal fluid, FaSSGF: Fasted state simulated gastric fluid

Dissolution data are presented as mean $\pm$ SD, where n is the number of observations (n=6).

In vivo results for Ticagrelor formulations

PK study

To evaluate comparative bioavailability, the Wistar rats were randomly divided into 4 groups (n=6), namely TICA-IR TABLET 90, TICA-IR TABLET 90M, TICA-SD TABLET 90, and TICA-SD TABLET 70, for dosing as outlined in Table 5 below. The samples equivalent to the required dose were administered orally to the Wistar rats using normal saline as a vehicle. The animal dose for the Wistar rat was calculated considering the human dose using the equation below.²⁶

$$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)} \times (\text{Animal km}) / (\text{Human km})$$

Where HED is the human equivalent dose

Km is the correction factor estimated by dividing the average body weight (kg) of a species by its body surface area (m²).

The relative bioavailability and peak plasma concentrations ($C_{\max}$) of Ticagrelor formulations are summarized in Table 6. The plasma concentration-time graph for the optimized Ticagrelor SD formulation is presented in Figure 11.

Monitoring of GI bleeding

Visual observation of the dissected gastric organ through a radical stereo microscope with 10X magnification (Figure 12) revealed no redness or bleeding post administration of the formulations of Ticagrelor.

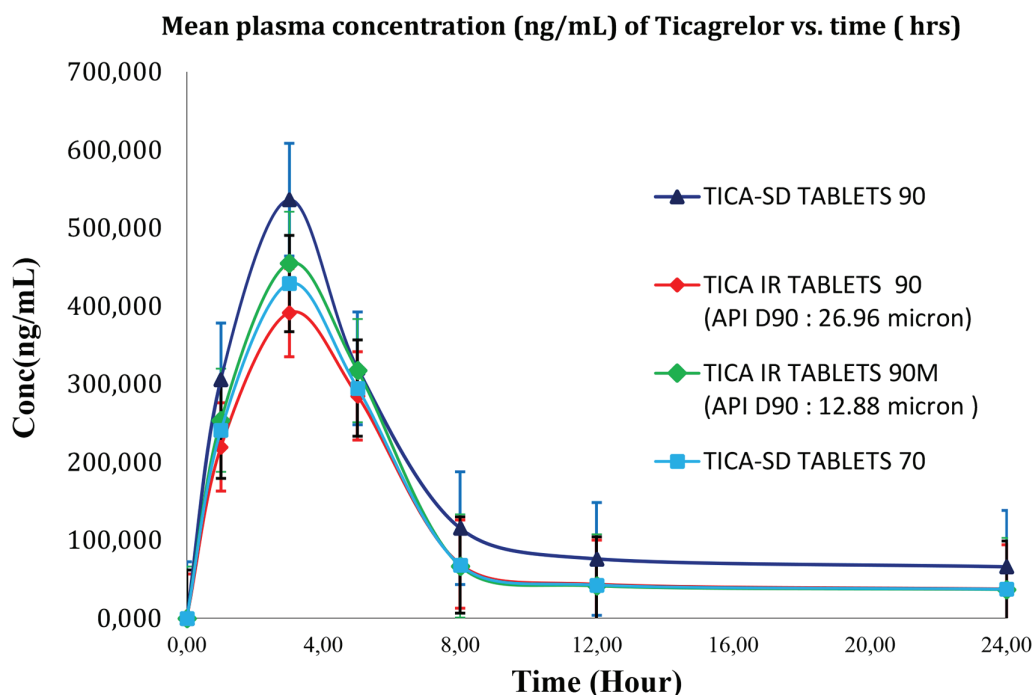


Figure 11. Comparative plasma concentration-time profiles of Ticagrelor in Wistar rats following oral administration of Ticagrelor conventional immediate release tablet formulations (TICA-IR TABLETS 90, TICA-IR TABLETS 90M, n=6) and Ticagrelor SD tablet formulations (TICA-SD TABLETS 90, TICA-SD TABLETS 70, n=6)

IR: Immediate release, n: Number of animals (sample size), SD: Solid dispersion, TICA: Ticagrelor

Table 5. Details of the formulation dosing group, along with the formulation code for PK study.

Group (n=6)	Formulation code	Formulation technology	Ticagrelor PSD (D_{90})	Dose
I	TICA-SD TABLET 90	SD	D_{90} : 26.96 μm	9 mg/kg
II	TICA-IR TABLET 90M	Conventional wet granulation (with micronized Ticagrelor)	D_{90} : 12.88 μm	9 mg/kg
III	TICA-SD TABLET 70	SD	D_{90} : 26.96 μm	7 mg/kg
IV	TICA- IR TABLET 90	(Conventional immediate release tablet formulation in line with Brilinta® AstraZeneca LP)	D_{90} : 26.96 μm	9 mg/kg

IR: Immediate release, PSD: Particle size distribution, SD: Solid dispersion, TICA: Ticagrelor

Table 6. Details of PK parameters for different Ticagrelor tablet formulations

PK parameters	TICA-SD TABLET 90	TICA-IR TABLET 90M	TICA-SD TABLET 70	TICA-IR TABLET 90
C_{max} (ng/mL)	536.25±7.8	454.75±11.2	428.77±5.4	391.45±7.4
AUC_{0-t} (h*ng/mL)	3736.90±71.00	2867.75±87.1	2757.28±59.9	2639.68±92.70
$AUC_{0-\infty}$ (h*ng/mL)	4462.23±154.27	3191.73±150.30	3096.55±135.40	2992.89±160.25
T_{max} (h)	3.0±0.00	3.0±0.00	3.0±0.00	3.0±0.00
$T_{1/2}$ (h)	7.63±0.30	6.094±0.40	6.46±0.20	6.50±0.40
Relative bioavailability (%)	141.61±2.29	108.65±0.52	104.48±1.40	-

IR: Immediate release, PK: Pharmacokinetic, PSD: Particle size distribution, SD: Solid dispersion, TICA: Ticagrelor

**Figure 12.** Gastric lumen of the Wistar rat after administration of (a) TICA-IR TABLET 90; (b) TICA-SD TABLET 90; (c) API 90 mg/kg, and (d) untreated

Parameters	TICA-IR TABLET 90	TICA-SD TABLET 90	API/90
Redness	*	*	*
Bleeding	*	*	*

*None; **Slight; ***Moderate; ****High; *****Severe. API: Active pharmaceutical ingredient, IR: Immediate release, SD: Solid dispersion, TICA: Ticagrelor

DISCUSSION

The analytical toolbox comprising optical microscopy (Olympus -BX 53), PXRD, DSC and DVS (surface management system), explored in this work, has proven to be very useful in characterizing, screening and monitoring the polymorphic stability of Ticagrelor formulations. The evaluation of the particle morphology and crystal properties of Ticagrelor using the polarized microscope (Olympus BX-53) reveals the crystalline nature of the API. It is clear from the PXRD report that the Ticagrelor API employed in this investigation is a mixture of various metastable polymorphs, necessitating careful attention while choosing the appropriate formulation and process technology. The DSC thermogram of Ticagrelor

provides specific information, i.e., glass transition temperature (T_g), melting point (T_m) and crystallization temperature (T_c), which are critical for ensuring polymorphic stability during formulation and processing.

The ASD technique formulated with co-povidone VA 64 and vitamin E TPGS was found to be the most promising method to enhance *in vitro* dissolution performance and polymorphic stability of metastable Ticagrelor. Optical microscopy (Olympus BX 53) has proven to be an important tool to evaluate the impact of small traces of crystalline solids on the ASDs of Ticagrelor, providing an early indication of crystallization leading to a polymorphic transformation. Amorphization of crystalline Ticagrelor could be possible with all three carriers, i.e., Co-

povidone VA 64, Soluplus, and HPMCAS. However, faster dissolution and satisfactory stability of the ASD prepared with carrier co-povidone VA 64 could be attributed to its low CDF. Co-povidone VA 64 was found as an excellent crystallization inhibitor and could elevate the glass transition temperature (T_g) of Ticagrelor SD to 52.72 °C, thereby ensuring improved polymorphic stability. The RHg for the ASD, determined with the help of DVS, could provide important insights into the RH-induced polymorphic transformation.

Formulation of ASD with polymer co-povidone VA 64 [i.e., TICA-SD tablet with co-povidone (1:0.4:4)] showed significantly faster dissolution by 10.7-fold compared to the Ticagrelor tablet formulation prepared in line (similar Q1/Q2) with reference product BRILINTA® (AstraZeneca LP).

Surprisingly, the dissolution rate of a Ticagrelor SD formulation with soluplus [TICA-SD tablet with soluplus (1:0.4:4)] and with HPMCAS was increased only by three- to four-fold compared to that of the conventional immediate release Ticagrelor tablet formulation.

Despite complete amorphization of Ticagrelor with co-povidone VA 64, Soluplus and HPMC Acetate Succinate (Figure 6), the kinetics of dissolution of solid dispersion with Soluplus and HPMC Acetate Succinate were found to be significantly slower compared to SD with co-povidone VA 64. The dissolution of the ASD depends on various factors, such as hygroscopicity, hydrophobicity, glass transition temperature (T_g), and CDF. Although amorphization enhances solubility and bioavailability to a great extent, its CDF leads to a polymorphic transformation, thereby favoring one thermodynamically stable crystalline form during *in vitro* and *in vivo* dissolution. Also, increased molecular mobility leads to kinetic instability. Low molecular weight excipients are known to lower CDF and elevate the glass transition temperature (T_g). The lower dissolution rate of SD with Soluplus and HPMC Acetate succinate may be attributed to their higher CDF and hydrophobicity.^{14,27} The impact of micronization on the dissolution of Ticagrelor was not found to be significant. An increase in 1.5-fold dissolution was observed for the conventional IR formulation with micronized Ticagrelor (D90:12.88 μ).

Formulation prepared with SMEDDS technology could increase the dissolution of Ticagrelor by 2.7-fold only, which could be attributed to the drug precipitation or crystallization during *in vitro* dissolution. Higher percentages of oil, surfactant, and co-surfactant may help to improve the dissolution further. However, a further increase in the percentage of components of SMEDDS would significantly increase capsule fill weight. Hence, capsule formulation is not feasible.

Ticagrelor is absorbed with a median t_{max} of 1.5 h (range 1.0–4.0). The faster rate of dissolution in the biorelevant media, i.e., more than 90% dissolution at 30 minutes in both FaSSGF (pH 1.6) and FaSSIF (pH 6.5), gives a high degree of assurance that the drug Ticagrelor would be in a highly dissolved state to be absorbed in the absorption window. Further, the presence of vitamin E TPGS, one known PG Efflux inhibitor, in the formulation would enhance the permeability of Ticagrelor and thereby increase its bioavailability.

No crystalline peaks were observed for the stability sample of Ticagrelor SD prepared with carrier Co-povidone VA 64, whereas two crystalline characteristic peaks at 2 theta 20.12 and 21.12, corresponding to the Ticagrelor polymorph form I, were observed for the Ticagrelor SD with carriers Soluplus and HPMCAS, indicating that Ticagrelor SD prepared with carrier Co-povidone VA 64 could provide superior polymorphic stability compared to those prepared with Soluplus and HPMCAS.

The bioavailability and peak plasma concentration (C_{max}) of Ticagrelor SD (TICA-SD TABLET 90) formulation were found to be 141.61±2.29% and 137.0±0.59%, respectively, compared to the conventional immediate release tablet formulation in line with Brilinta® (AstraZeneca LP) (TICA-IR TABLET 90). The bioavailability of Ticagrelor with micronization could not be enhanced significantly. The relative bioavailability of the Ticagrelor tablet with micronized API (TICA-IR TABLET 90M) was found to be 108.65±0.52% compared to the conventional immediate-release tablet formulation (TICA-IR TABLET 90). Based on the results of a dose-adjusted PKs study of Ticagrelor SD, the AUC₀₋₂₄ and peak plasma concentration (C_{max}) of 70 mg dose of Ticagrelor SD (TICA-SD TABLET 70) formulation were found to be similar to these parameters of conventional immediate release tablet formulation of Ticagrelor tablets (TICA-IR TABLET 90), indicating that 70 mg dose of Ticagrelor tablet with SD technique would be equivalent to 90 mg dose of conventional immediate release tablet formulation, prepared in line with reference product Brilinta® (AstraZeneca LP) for the desired therapeutic action.

Numerous works on increasing the oral bioavailability of Ticagrelor have been reported. Kim et al.²⁸ reported the 219.78±36.33% relative bioavailability of an SD formulation compared to pure Ticagrelor in a PK study. Na et al.²⁹ reported a 2.2-fold increase in relative bioavailability of one TPGS/PVA-based nanosuspension compared to the reference product Brilinta® 90 mg, (AstraZeneca LP) in rats. In another study, the oral relative bioavailability of Ticagrelor SMEDDS in rats increased by 6.3 times compared to a raw Ticagrelor suspension, as reported by Na et al.³⁰ A 5-fold increase in oral bioavailability for Ticagrelor SMEDDS compared to pure Ticagrelor was reported by Aparna et al.³¹

Ticagrelor is a third-generation oral antiplatelet drug with a higher risk of GI bleeding compared to clopidogrel. As per the USFDA approval package for Ticagrelor (Brilinta®, AstraZeneca), the most common adverse reactions (>5%) are bleeding and dyspnea. This includes getting out of breath, nose bleeds, heavier periods, bleeding gums, and bruising. Based on the above facts on Ticagrelor adverse reactions, there will always be an increased risk of GI bleeding associated with the administration of Ticagrelor formulations with significantly higher bioavailability compared to the reference product Brilinta® 90 mg (AstraZeneca LP). Hence, it is highly recommended to evaluate the impact of improved dissolution and bioavailability in the proposed formulations, which may lead to the adverse reaction of GI bleeding.³²

The proposed SD formulation of Ticagrelor in the current study has a superior bioavailability compared to the conventional immediate release tablet formulation as offered by Brilinta® AstraZeneca LP. It is well-supported by a GI bleeding study in Wistar rats. The study reveals no GI redness or bleeding owing to the improved dissolution and bioavailability of the proposed formulation with SD technology.

In summary, the optimized Ticagrelor ASD formulation demonstrated enhanced bioavailability, minimal or low adverse reactions, and improved polymorphic stability. The adopted solvent evaporation manufacturing process would also enable a feasible and scalable process transition to spray drying and FBP technology.

CONCLUSION

TICA-SD, with co-povidone VA 64 and vitamin E TPGS, could be able to enhance the dissolution of Ticagrelor by 10.7 fold and have a relative bioavailability of 141.61±2.29% compared to a conventional immediate release tablet formulation prepared in line with Brilinta® (AstraZeneca LP). Based on a dose-adjusted PK study, the SD formulation of Ticagrelor allows a lower dose (70 mg) of Ticagrelor to achieve an equivalent therapeutic effect to that of the reference product Brilinta® 90 mg (AstraZeneca LP). No adverse reactions were noted in the GI bleeding study, which may be attributed to the enhanced dissolution and bioavailability of the SD formulation. The manufacturing process is feasible and is scalable to industrial-scale operation. PXRD and DSC data are in good agreement regarding the transformation of crystalline Ticagrelor to amorphous form. SD is found to be a superior technique in enhancing the bioavailability and stability of poorly soluble, metastable Ticagrelor and in enhancing the bioavailability and stability of poorly soluble, metastable, Ticagrelor, and could be extended to other BCS Class IV drugs.

The SD technique with carrier co-povidone VA 64, and vitamin E TPGS prepared by the solvent evaporation process could yield a Ticagrelor formulation with improved bioavailability and polymorphic stability.

Ethics

Ethics Committee Approval: Due approval obtained from ethics committees such as CPCSEA and IAEC (approval number: CPCSEA/DIPS/0223/61, dated: 21.02.2023).

Informed Consent: Study conducted in Wistar rats hence patient informed consent not applicable.

Footnotes

Authorship Contributions

Concept: R.P., S.L., Design: R.P., S.L., Data Collection or Processing: R.P., S.L., Analysis or Interpretation: R.P., S.L., Literature Search: R.P., S.L., Writing: R.P., S.L.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: The authors declared that this study received no financial support.

REFERENCES

- Food and Drug Administration. Drug Approval Package: Brilinta (ticagrelor) NDA #022433. Available online: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022433orig1s000toc.cfm. Accessed 11 October 2023.
- Panda R, Lankalapalli S. Bioavailability and polymorphic stability challenges affecting drug product's potential: a critical evaluation and pertinent solution. *Asian J Pharm Clin Res.* 2023;16:9-23.
- Guo Y, Luo J, Tan S, Otieno BO, Zhang Z. The applications of vitamin E TPGS in drug delivery. *Eur J Pharm Sci.* 2013;49:175-186.
- Constantinides PP, Wasan KM. Lipid formulation strategies for enhancing intestinal transport and absorption of P-glycoprotein (P-gp) substrate drugs: *in vitro/in vivo* case studies. *J Pharm Sci.* 2007;96:235-248.
- Kou L, Sun R, Bhutia YD, Yao Q, Chen R. Emerging advances in P-glycoprotein inhibitory nanomaterials for drug delivery. *Expert Opin Drug Deliv.* 2018;15:869-879.
- Guan Y, Wang LY, Wang B, Ding MH, Bao YL, Tan SW. Recent advances of D- α -tocopherol polyethylene glycol 1000 succinate based stimuli-responsive nanomedicine for cancer treatment. *Curr Med Sci.* 2020;40:218-231.
- Khadka P, Ro J, Kim H, Kim I, Kim JT, Kim H, Cho JM, Yun G, Lee J. Pharmaceutical particle technologies: an approach to improve drug solubility, dissolution and bioavailability. *Asian Journal of Pharmaceutical Sciences.* 2014;9:304-316.
- Liu X, Feng X, Williams III R, Zhang F. Characterization of amorphous solid dispersions. *J Pharm Investig.* 2018;48:19-41.
- Goddeeris C, Willems T, Houthoofd K, Martens JA, Van den Mooter G. Dissolution enhancement of the anti-HIV drug UC 781 by formulation in a ternary solid dispersion with TPGS 1000 and Eudragit E100. *Eur J Pharm Biopharm.* 2008;70:861-868.
- Chen W, Miao YQ, Fan DJ, Yang SS, Lin X, Meng LK, Tang X. Bioavailability study of berberine and the enhancing effects of TPGS on intestinal absorption in rats. *AAPS Pharm SciTech.* 2011;12:705-711.
- Dintaman JM, Silverman JA. Inhibition of P-glycoprotein by D- α -tocopheryl polyethylene glycol 1000 succinate (TPGS). *Pharm Res.* 1999;16:1550-1556.
- Shin SC, Kim J. Physicochemical characterization of solid dispersion of furosemide with TPGS. *Int J Pharm.* 2003;251:79-84.
- Veith H, Wiechert F, Luebbert C, Sadowski G. Combining crystalline and polymeric excipients in API solid dispersion—opportunity or risk? *Eur J Pharm Biopharm.* 2021;158:323-335.
- Hancock BC, Parks M. What is the true solubility advantage of amorphous pharmaceuticals? *Pharm Res.* 2000;17:397-404.
- Teja SB, Patil SP, Shete G, Patel S, Bansal AK. Drug-excipient behavior in polymeric amorphous solid dispersions. *J Excip Food Chem.* 2013;4:70-94.
- Strojewski D, Krupa A. Kollidon® VA 64 and Soluplus® as modern polymeric carriers for amorphous solid dispersal. *Polim Med.* 2022;52:19-29.
- Butreddy A. Hydroxypropyl methylcellulose acetate succinate as an exceptional polymer for amorphous solid dispersion formulations: a review from bench to clinic. *Eur J Pharm Biopharm.* 2022;177:289-307.
- Na YG, Byeon JJ, Wang M, Huh HW, Son GH, Jeon SH, Bang KH, Kim SJ, Lee HJ, Lee HK, Cho CW. Strategic approach to developing a self-

- microemulsifying drug delivery system to enhance antiplatelet activity and bioavailability of ticagrelor. *Int J Nanomedicine*. 2019;14:1193-1212.
19. U.S. Food and Drug Administration. Dissolution Methods Database. Available from: <https://www.fda.gov/drugs/drug-approvals-and-databases/dissolution-methods-database>. Accessed 21 October 2025.
 20. Biorelevant.com. Physico-chemical properties of FaSSiF, FeSSiF and FaSSGF. Available from: <https://biorelevant.com>. Accessed 21 October 2025.
 21. Bueno LM, Manoel JW, Giordani CF, Mendez AS, Volpato NM, Schapoval EE, Steppe M, Garcia CV. HPLC method for simultaneous analysis of ticagrelor and its organic impurities and identification of two major photodegradation products. *Eur J Pharm Sci*. 2017;97:22-29.
 22. Bohlin M, Cosgrove S, Lassen B, inventors; AstraZeneca AB, assignee. Crystalline and amorphous form of a triazolo(4,5-d)pyrimidine compound. United States patent US 7,265,124 B2. 2007 Sep 4.
 23. Mohamed S, Hejtmankova L, Ridvan L, Tkadlecova M, Dammer O. Novel pharmaceutical solid forms of (1S,2S,3R,5S)-3-[7-[(1R,2S)-2-(3,4-difluorophenyl)cyclopropylamino]-5-(propylthio)-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-5-(2-hydroxyethoxy)cyclopentane-1,2-diol: cocrystal and solvate. WO2014000719 A1. 2014 Jan 03.
 24. Ren Y, Shen J, Yu K, Phan CU, Chen G, Liu J, Hu X, Feng J. Impact of crystal habit on solubility of ticagrelor. *Crystals*. 2019;9:556.
 25. Davis D, Sedmak G, inventors; Zentiva AS, assignee. Stabilized amorphous ticagrelor. European patent EP 2 813 216 A1. 2014 Dec 17.
 26. Nair AB, Jacob S. A simple practice guide for dose conversion between animals and humans. *J Basic Clin Pharm*. 2016;7:27-31.
 27. Löbmann K, Grohgan H, Laitinen R, Strachan C, Rades T. Amino acids as co-amorphous stabilizers for poorly water-soluble drugs. Part 1: preparation, stability and dissolution enhancement. *Eur J Pharm Biopharm*. 2013;85(3PtB):873-881.
 28. Kim SJ, Lee HK, Na YG, Bang KH, Lee HJ, Wang M, Huh HW, Cho CW. A novel composition of ticagrelor by solid dispersion technique for increasing solubility and intestinal permeability. *Int J Pharm*. 2019;555:11-18.
 29. Na YG, Pham TMA, Byeon JJ, Kim MK, Han MG, Baek JS, Lee HK, Cho CW. Development and evaluation of TPGS/PVA-based nanosuspension for enhancing dissolution and oral bioavailability of ticagrelor. *Int J Pharm*. 2020;581:119287.
 30. Na YG, Byeon JJ, Wang M, Huh HW, Son GH, Jeon SH, Bang KH, Kim SJ, Lee HJ, Lee HK, Cho CW. Strategic approach to developing a self-microemulsifying drug delivery system to enhance antiplatelet activity and bioavailability of ticagrelor. *Int J Nanomedicine*. 2019;14:1193-1212.
 31. Aparna A, Kumar YS, Bhikshapathi DVRN. Formulation and *in vivo* evaluation of ticagrelor self-nanoemulsifying drug delivery systems. *Pharm Nanotechnol*. 2021;9:61-69.
 32. Guo CG, Chen L, Chan EW, Chui CS, Wong AY, Wong ICK. Systematic review with meta-analysis: the risk of gastrointestinal bleeding in patients taking third-generation P2Y12 inhibitors compared with clopidogrel. *Aliment Pharmacol Ther*. 2019;49:7-19.