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Advancing Ticagrelor Bioavailability: A Comprehensive Review of Solubility Enhancement Techniques

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ABSTRACT: Ticagrelor (TICA) inhibits platelet activity by reversibly binding to the $P2Y_{12}$ receptor, it is classified as a BCS class IV drug with low solubility and permeability. BCS Class IV drugs have a major challenge due to their reduced rate of dissolution, which leads to poor bioavailability. The absolute bioavailability of TICA after oral administration is ~36%. Various techniques, including particle size reduction, solid dispersion, lipid-based formulation, co-crystals, and polymeric micelles can increase solubility. This article discusses the methodology used to increase the solubility of ticagrelor, thereby emphasizing the research that has been conducted and documented. The increased bioavailability of ticagrelor is apparent when formulated as a solid dispersion (SD), self- microemulsifying drug delivery system (SMEDDS), self-nanoemulsifying drug delivery system (SNEDDS), nanostructured lipid carriers (NLC), suspensions, and co-crystals. Among these approaches, co-crystals and solid dispersions are highly recommended for improving the solubility of ticagrelor. This review provides insights into formulation strategies for improving ticagrelor solubility, guiding future research on its bioavailability and efficacy.

Keywords: **ticagrelor; solubility enhancement; bioavailability; formulation strategies.**

Introduction

Coronary artery disease (CAD) is a significant contributor to global morbidity and mortality, primarily due to its potential to develop into acute coronary syndrome (ACS). In 2008, a total of 405,309 individuals in the United States died from coronary heart disease, with an estimated 785,000 new coronary events and 470,000 recurrent cases annually. Heart failure, hypertension, stroke, and other arterial disorders contribute to the proportion of cardiovascular-related deaths, with acute coronary syndrome (ACS) accounting for approximately half of these cases [1].

Ticagrelor (TICA) is an inhibitor of the platelet $P2Y_{12}$ receptor that is taken orally. It binds reversibly to the $P2Y_{12}$ receptor to inhibit platelet aggregation and block ADP-mediated platelet activation. Ticagrelor represents the inaugural agent in the novel antiplatelet drug class known as cyclopentyl triazolo pyrimidines. Compared to clopidogrel, it demonstrates higher potency, a faster onset of pharmacological effect, and reduced interpatient variability in response. Therefore, when used in conjunction with aspirin as dual antiplatelet treatment (DAPT), TICA has pharmacodynamic advantages over clopidogrel as a $P2Y_{12}$ inhibitor [2]. TICA demonstrated faster and more potent antiplatelet activity compared to clopidogrel, as well as a shorter duration of action than prasugrel. After 2 hours of drug administration, TICA exhibited over 90% antiplatelet activation [3]. Ticagrelor operates as a reversible and orally active P2Y12 receptor blocker that does not rely on metabolic transformation for activation. The metabolite AR-C124910XX accounts for nearly 30-40% of the drug's platelet inhibition capacity. As a result, ticagrelor inhibits platelets more quickly and effectively than clopidogrel [4]. TICA was developed by AstraZeneca, TICA received FDA approval in 2011. The commercial formulation of TICA, Brilinta 90 mg tablets, contains excipients such as mannitol, sodium starch glycolate, dibasic calcium phosphate, and hydroxypropyl cellulose, as listed on RxList [5,6].

TICA has a low solubility of around 10 µg/mL at all pH ranges and low permeability. According to the study, TICA absolute bioavailability after oral administration is approximately 36% [7]. Drugs in this class tend

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to exhibit significant inter- and intra-subject variability due to poor solubility and permeability. As a result, these drugs are generally not considered good oral candidates unless the dosage is very low. However, estimates suggest that approximately 5% of widely known oral drugs worldwide fall under BCS Class IV. This is closely related to the absorption window, which plays a crucial role in determining the success or failure of the drug [8].

A variety of innovative approaches have been introduced to enhance bioavailability and therapeutic outcomes, including techniques such as particle size reduction, solid dispersion, lipid-based delivery systems, micro- and nanoparticle technologies, and micellar formulations [9]. Additionally, research has investigated modifications in solid-state forms, including salts, polymorphs, and co-crystals [10]. Recently, substantial efforts have focused on improving the solubility of Ticagrelor (TICA), employing diverse strategies such as solid dispersion methods, crystallization techniques, nanostructured lipid carriers (NLC), self-micro emulsifying drug delivery systems (SMEDDS), and nano-suspensions within the framework of TICA formulation development [5].

Despite ticagrelor's significant therapeutic potential in treating acute coronary syndrome (ACS), its clinical effectiveness is often limited by poor water solubility and low oral absorption. Therefore, this review is urgently needed to comprehensively explore and summarize recent advancements in strategies aimed at improving ticagrelor's bioavailability, particularly through enhancing its aqueous solubility, to support the development of more effective formulations and improve patient outcomes. The article discusses various formulation technologies, such as particle size reduction, solid dispersions, lipid-based systems, co-crystallization, and nanosuspension techniques, alongside their impact on therapeutic effectiveness. This literature review provides a foundational insight into various formulation strategies explored to enhance the solubility of ticagrelor, serving as a reference for future research and innovation in optimizing its bioavailability and therapeutic effectiveness.

Methods

This review collected relevant literature by searching electronic databases such as PubMed, Scopus, Web of Science, ScienceDirect, ResearchGate, and Google Scholar. Only English-language articles published between 2015 and 2025 were included. The search terms used were "ticagrelor" in the title or abstract, and "enhancement," "solubility," and "bioavailability" in the abstract and full text.

This review compiles original research that explores how various formulation approaches impact the solubility and bioavailability of Ticagrelor. It encompasses studies utilizing in vitro, ex vivo, and in vivo models, including methods like dissolution testing, permeability evaluation, and pharmacokinetic studies. A range of solubility enhancement techniques are systematically discussed, such as reducing particle size, forming solid dispersions, using lipid-based systems, developing cocrystals, nanosuspensions, and micellar formulations.

The scope of this review is limited to studies specifically focusing on formulation strategies, thus excluding studies related to pharmacodynamics, clinical efficacy, or combination therapy of Ticagrelor. Emphasis was placed on studies reporting physicochemical characterization, enhanced dissolution, and improved bioavailability, along with detailed information regarding excipients and formulation methodology.

Result and Discussion

Solubility

Solubility refers to the capacity of a substance to dissolve within a solvent to form a uniform mixture. It is quantitatively described as the highest concentration of a substance that can be dissolved in a solvent under defined conditions of pH, temperature, and pressure. [11]. According to the United States Pharmacopeia, solubility is defined as the volume of solvent, measured in milliliters, required to dissolve one gram of solute [12]. Improving solubility can be accomplished through multiple approaches, such as salt formation, complexation, particle size reduction (micronization), solid dispersion, pH adjustment, use of co-solvents, co-crystal formation, and incorporation into polymeric micelles. One notably effective method involves converting crystalline drug substances into their amorphous form. [13]. Amorphous drugs exhibit superior solubility compared to their crystalline forms, attributable to their structural characteristics, increased surface area, and improved wettability. The amorphous form exhibits superior solubility due to its higher entropy, enthalpy, volume, and free energy compared to the crystalline structure [14].

Ticagrelor

Ticagrelor (TICA), $C_{23}H_{28}F_2N_6O_4S$, is a white solid crystalline powder with a solubility of 10 µg/mL in water throughout the pH range. It has a molecular mass of about

522.6 g/mol [15]. According to patents, TICA exhibits four polymorphic forms (I, II, III, and IV) and several pseudo polymorphs, including the monohydrate and DMSO solvate. Different crystal forms exhibit variations in properties such as stability, solubility, and fluidity [16]. Among these, TICA form II stands out for its superior stability, making it widely utilized in clinical applications and highly valuable commercially [17]. Compared to clopidogrel, Ticagrelor (TICA) provides stronger and more reliable platelet aggregation inhibition, along with a favorable tendency to lower the risk of myocardial infarction, without a corresponding rise in major bleeding events. TICA is quickly absorbed in the gastrointestinal tract and exhibits a rapid onset of action, with an average oral bioavailability of around 36%, limited by hepatic first-pass metabolism. TICA and its active metabolites exhibit a very high plasma protein binding rate (>99.7%) [18]. The maximum plasma concentration (Cmax) of TICA is typically reached within 1.5 hours, while its active metabolite reaches Cmax in approximately 2.5 hours. Both TICA and its active metabolite are primarily eliminated via the liver, with only about 1% excreted in the urine. The plasma half-life of TICA is around 7 hours, while the active metabolite has a half-life of approximately 8.5 hours. Ticagrelor (TICA) is metabolized by the CYP3A4 enzyme and serves as a substrate for P-glycoprotein (P-gp). Additionally, it acts as a mild inhibitor of P-gp, potentially enhancing the systemic exposure of co-administered drugs that are also P-gp substrates. [19]. Ticagrelor (TICA) administration is not recommended for patients with a history of hyperuricemia or uric acid nephropathy [20].

The stability of ticagrelor was examined by subjecting it to hydrolytic (both acidic and alkaline), oxidative, photolytic, and thermal stress conditions, following the guidelines set by the International Conference on Harmonization (ICH). The stability of Ticagrelor (TICA) varies according to the specific stress conditions applied. Hydrolytic stability was assessed across a pH range of 4.0 to 9.0 using ammonium acetate buffers, where TICA remained stable. Nevertheless, under other stress conditions, its degradation followed zero-order kinetics. At a temperature of 80°C, TICA exhibits a half-life of 1.125 hours and a degradation rate constant of 0.00013 µmol/L·hour. [21]. Thermal analysis (Figure 1) using thermogravimetry (TGA/DTG) The melting point of Ticagrelor (TICA) was determined to be 142.5 °C using differential scanning calorimetry (DSC) [15].

TICA is unstable to light [22], Using the Q-SUN Xe-1 xenon test chamber in window mode, photolytic degradation of Ticagrelor was assessed under light wavelengths between 300 and 800 nm, with an intensity of 1.50 W/m². After 4 hours, Ticagrelor's concentration decreased by 77%, corresponding to a half-life of 1.92 hours and a degradation rate constant of 0.065 µmol/L·h. The compound also exhibited oxidative sensitivity, with a half-life of 7.45 hours and a degradation rate constant of 0.019 µmol/L·h [21].

Approaches for Improving Water Solubility and Bioavailability

Approximately 90% of drug candidates and 40% of approved medications are poorly water-soluble drugs (PWSDs). Drugs with low solubility dissolve more slowly and don't reach sufficient blood concentrations [23]. Consequently, solubility enhancement studies are frequently required to achieve adequate solubilization. Various strategies, including particle size reduction [24], solid dispersion (SD) [25], self-micro and nano-emulsifying drug delivery systems (SMEDDS and SNEDDS, respectively) [26,27], complexation [18], salt or co-crystal

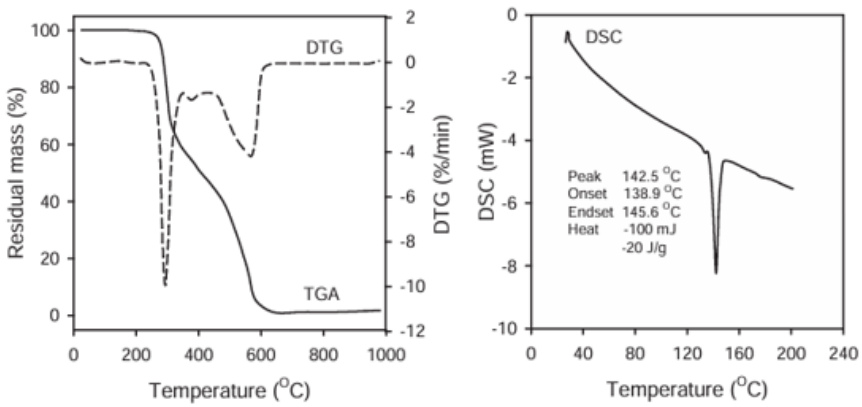

Figure 1. Ticagrelor differential scanning calorimetry (DSC) curve, thermogravimetry, and derivative thermogravimetry (TGA/DTG) [15].

formation [28], micelles [29], and nanocrystals [30], have been employed to improve drug solubility. The solubility of a pharmaceutical compound in aqueous solutions is an important property that influences several factors, including its oral absorption, suitability for parenteral administration, and ease of handling and testing in both laboratory and industries. Table 1 presents the underlying concepts, benefits, and limitations of different approaches used to improve the solubility of drugs with poor water solubility.

Recent Advancements for Solubility Enhancement of Ticagrelor

Ticagrelor is more effective in treating acute coronary syndrome (ACS) than other P2Y12 inhibitors. TICA acts directly, noncompetitively P_2Y_{12} reversibly, and does not require metabolic activation [31]. The limited solubility of ticagrelor presents a significant challenge in its formulation. Hence, this article aims to present different approaches utilized to enhance the oral solubility and bioavailability of ticagrelor. Table 2. shows recent advancements in the solubility enhancement of ticagrelor.

One frequently utilized strategy to enhance the solubility of poorly water-soluble drugs is the solid dispersion method [32]. Based on carrier properties, SD is categorized into four generations: the first generation involves crystalline carriers, the second uses amorphous polymers, the third combines surfactant polymers, and the fourth includes release-modifying agents. Particularly, third-generation SD is distinguished by its rapid

Table 1. Strategies for enhancing the solubility of poorly water-soluble drugs: principles, advantages, disadvantages, and applications.

No	Strategy	Principle	Advantages	Disadvantages	Application	Ref.
1.	Particle Size Reduction	Decreasing particle size enhances surface area and accelerates dissolution rate.	Increase the ratio of surface area to volume.	Significant surface charge on small particles, individual particles increases the tendency for particle aggregation. This can lead to thermal stress, which may negatively affect heat-sensitive or unstable active ingredients.	coenzyme Q10 nanocrystals formulation for improving drug solubility.	[24]
2.	Solid Dispersions	Dispersing the drug within a hydrophilic carrier matrix improves solubility and dissolution rate.	Significantly increases solubility and dissolution; flexibility in formulation.	It is not typically used as a commercial product due to the transformation from the amorphous form of the drug to the less soluble crystalline form during long-term storage. This, in turn, can increase drug mobility, leading to phase separation and instability. Additionally, large-scale production is constrained by the high cost of preparation methods.	Itraconazole and Kollidon® VA64 amorphous solid dispersions	[61,62]
3.	Lipid Based Formulation	Dissolving the drug in lipids or lipid mixtures enhances solubility (e.g., self-micro and nano-emulsifying drug delivery systems, NLC, SLN etc.)	Improves solubility for lipophilic drugs; high bioavailability, protects unstable drugs	Stability may be a challenge; limited excipient use for lipid-based formulations.	Self-emulsifying systems for cepharanthine	[63]

No	Strategy	Principle	Advantages	Disadvantages	Application	Ref.
4	Complexation	Forming a complex between the drug and a ligand (e.g., cyclodextrins) to improve solubility.	Enhances solubility without altering the drug's structure; often used for stabilization; high API concentrations are achievable.	Higher production costs; and optimization of molarity are needed. Cyclodextrins demonstrate Renal toxicity occurs in many species, which limits their applicability in preclinical toxicology evaluations.	complexation of Rivaroxaban with β-Cyclodextrin	[64,65]
5	Salt Formation	Forming salts of ionic drug compounds to enhance solubility.	Simple process; improves solubility and crystal stability.	Ineffective for non-ionic drugs; potential side effects from the counterion.	The solubility and bioavailability of the BCS Class II drugs indomethacin and naproxen can be enhanced through salt formation with (1R,2R)-1,2-diphenylethylenediamine.	[66]
6	Co-Crystal Formation	Forming co-crystals with a coformer to enhance solubility.	Improves solubility without altering the API's molecular structure; compatible for oral formulations.	Requires time and resources to screen for suitable coformers.	Carbamazepine co crystallized with nicotinamide	[67]
7	Polymeric Micelles	Forming micelles using surfactants to enhance drug solubility in a hydrophobic core.	Suitable for lipophilic drugs; enables liquid and injectable formulations; specific drug control and release can be implemented.	Requires surfactants at specific concentrations (CMC); potential irritation from surfactants; Micelle disintegration occurs upon dilution after oral administration, resulting in in vivo instability below the critical micelle concentration. Additionally, micelles often suffer from low drug loading capacity.	Polymeric Micelle of Paclitaxel.	[68]

dissolution rate and its ability to inhibit precipitation under supersaturated conditions. [33]. A novel SD formulation was prepared using the solvent evaporation technique with d-α-tocopheryl polyethylene glycol-1000 succinate (TPGS) and Neusilin® US2. TPGS acts as a P-glycoprotein (P-gp) inhibitor, enhancing drug absorption, while Neusilin® US2 improves the powder's flowability and stability. The optimized SD significantly increased the release of TICA by 2.2-fold and 34-fold compared to the physical mixture and the commercial product (Brilinta®), respectively [34]. SD transforms TICA into an amorphous state, significantly altering its pharmacokinetics by improving solubility and absorption. Crystalline drugs require more energy to disrupt their crystal lattice, which limits solubility and bioavailability. By converting TICA into an amorphous state, the energy required for dissolution is reduced, leading to enhanced solubility and, consequently, improved drug absorption in the gastrointestinal tract [35].

Self-microemulsifying drug delivery systems (SMEDDS) are gaining attention for their effectiveness in the oral administration of poorly soluble drugs, attributed to their straightforward preparation and notable advantages in improving solubility and oral bioavailability [36,37]. SMEDDS is a single-phase, stabilized system consisting of oil, surfactant, and cosurfactant, devoid of a water phase. After entering the gastrointestinal tract, SMEDDS generates an oil-in-water microemulsion characterized by globule sizes between 20 and 200 nm, which improves drug dissolution and absorption through increased surface area. SMEDDS offers several advantages, including

improved transcellular and paracellular absorption, decreased metabolism by gastrointestinal enzymes (CYP/CYP450), and enhanced lymphatic transport, thereby safeguarding the drug from first-pass metabolism [7,38]. Na et al. (2019) [7] formulated a self-microemulsifying drug delivery system (SMEDDS) for Ticagrelor. The optimized mixture, containing 10.0% Capmul MCM, 53.8% Cremophor EL, and 36.2% Transcutol P, resulted in a 5.7-fold enhancement in oral bioavailability, with an AUC_{0}–∞ value of 2,525.29 ng·h/mL, compared to the unprocessed drug. In vitro studies demonstrated enhanced cellular uptake and permeability, while ex vivo experiments showed improved inhibition of platelet aggregation. The data suggest that the TICA SMEDDS formulation holds significant promise for enhancing ticagrelor's therapeutic efficacy in the treatment of acute coronary syndrome. The TICA SMEDDS formulation enhances ticagrelor's bioavailability through several key mechanisms. First, SMEDDS improves drug solubility. TICA's poor solubility limits its bioavailability. The use

Table 2. Recent advancement for solubility enhancement of ticagrelor.

No	Strategies	Material	Methodology	Result	Ref.
1	Solid Dispersion	Neusilin® US2, an inorganic, microporous adsorbent that inhibits drug re-crystallization and boosts bioavailability, and TPGS, a surfactant and P-gp inhibitor that improves drug solubility and permeability, are examples of excipients that promote solubility in solid dispersions. The high surface area and porosity of Neusilin® US2 aid in the efficient dispersion of medications, whereas TPGS improves solubility by amorphizing the drug and acting as a surfactant.	The solid dispersion was prepared using the solvent evaporation technique with ethanol as the solvent.In the preliminary study, TPGS and Neusilin® US2 were identified as appropriate excipients and incorporated into the formulation.	In distilled water over a 90-minute period, the optimized solid dispersion system demonstrated an enhancement in drug release by 2.2 times compared to the physical mixture (Ticagrelor: TPGS: Neusilin® US2 in a 1:2:2 weight ratio) and a 34-fold increase relative to the commercial formulation (Brilinta®). Furthermore, after oral administration in rats, this formulation significantly increased Ticagrelor's peak plasma concentration (Cmax) and relative bioavailability by 238.09 ± 25.96% and 219.78 ± 36.33%, respectively, compared to the pure drug.	[34]
		In solid dispersions, excipients such lipid carriers, hydrophilic polymers (e.g., PVP, HPMC, P188, P407, PEG6000, IR, K12, PVP/VA S-630, HS-15, TPGS), and surfactants (e.g., Cremophor EL, sodium oleate) are used to improve drug solubility.	The solid dispersion was formulated using the solvent evaporation technique, with ethyl alcohol serving as the solvent. Optimization was carried out to select the appropriate hydrophilic polymer (PEG6000, TPGS, P188 etc), pH conditions (4, 7, 10), and also weak base (Maglumine, MgO, sodium oleate, sodium hydroxide) for the SD formulation.	Within 60 minutes, the dissolution rate of ticagrelor from the optimized formulation [SD8 (ticagrelor: sodium oleate: D-α-tocopherol polyethylene glycol 1000 succinate at a ratio of 1:3.5:0.5)] was 17.7-fold higher than that of Brilinta in distilled water, and 1.13 times greater in a medium containing 0.2% w/v Tween 80.	[5]
		To increase ticagrelor's solubility, this journal employs PEG 4000 and Neusilin® US2 in solid dispersion formulations. PEG 4000 decreases drug crystallinity, increases wettability, and inhibits P-gp efflux, while Neusilin® US2 expands the contact surface with the dissolving medium by acting as an adsorbent. Ticagrelor's release and bioavailability are enhanced by this combination.	The solid dispersion of ticagrelor, PEG 4000, and Neusilin US2 was prepared using the melt adsorption technique. The process involved heating the mixture in a porcelain cup to the melting point (57–63°C) and subsequently cooling it to room temperature. The resulting TICA-SD was sieved using a 22# ASTM sieve to achieve a uniform powder size.	At the 30-minute evaluation point, the percentage of drug released from TICA-SD formulations was limited to 2.30% and 6.59%, respectively. In stark contrast, the TICA-SD formulation demonstrated a significantly enhanced release profile of 86.47%. Complementary Caco-2 cell assays confirmed a 3.83-fold increase in TICA permeability with the TICA-SD formulation. In rats, TICA-SD-based tablets showed a relative bioavailability of 748.53% and 153.43% compared to TICA-SD tablets, respectively.	[69]

No	Strategies	Material	Methodology	Result	Ref.
2	Self-micro-emulsifying drug delivery systems (SMEDDS)	Capmul MCM (oil), the main excipient that increases ticagrelor's solubility, with a solubility of 101.19 mg/mL. Other excipients utilized in the formulation, such as Cremophor EL (surfactant) and Transcutol P (cosurfactant), in addition to Capmul MCM, aid in the emulsification, stability, and dissolution of ticagrelor.	A formulation of SMEDDS incorporating TICA was developed and optimized utilizing a design of experiments methodology., specifically employing Scheffé's mixture design. The preliminary phase entails the careful selection of appropriate excipients—such as oils, surfactants, and cosurfactants—to achieve optimal solubility of TICA. Following this, evaluations of emulsification performance and phase separation were conducted. The emulsification efficiency of the self-microemulsifying drug delivery system (SMEDDS) was classified based on parameters including droplet size, transmittance, and the occurrence of phase separation. After determining the SMEDDS formulation, the maximum concentration of each constituent required to solubilize a single dose of TICA (90 mg) was established, aiming to minimize the overall formulation volume.	The in vitro drug release of the selected TICA-SNEDDS formulations, F4 and F6, in phosphate buffer pH 6.8 were approximately 98.45% and 97.86%, respectively, demonstrating significantly enhanced dissolution of TICA compared to the pure TICA suspension, which achieved only 28.05% after 12 hours. In 0.1 N HCl, the drug release from F4 and F6 were 62.03% and 73.57%, respectively, markedly higher than the 10.35% release observed for the pure TICA suspension. Furthermore, ex vivo permeability studies revealed that F4 exhibited an improved apparent permeability coefficient of 2.7×10^{-6} cm²/s, compared to 0.6708x	[7]
3	self-nano emulsifying drug delivery system (SNEDDS)	Solubility investigations and pseudo-ternary phase diagram analyses confirm that the components used to improve ticagrelor solubility within the self-emulsifying drug delivery system (SEDDS) include clove oil as the lipid phase, Tween-80 as the surfactant, and PEG-400 as the co-surfactant.	Using a UV spectrophotometer, maximum TICA solubility was identified and excipients were chosen accordingly. The TICA-SNEDDS formulation was developed using several ratios of oil, surfactant, and co-surfactant (1:1, 2:1, and 3:1), and the nanoemulsion area was described using a pseudo-phase diagram. The oil phase consisted of polyethylene glycol 400 (PEG-400) ranging from 20 to 45%, Tween-80 as the surfactant at 45 to 70%, and selected clove oil as an excipient at 10 to 20%. A total of six formulations were assessed for various parameters, including zeta potential, polydispersity index, cloud point, particle size, self-emulsification efficiency, thermodynamic behavior, entrapment efficiency, in vitro drug release, ex vivo drug permeability, among other evaluations.	After 12 hours, the pure Ticagrelor (TICA) suspension achieved a dissolution rate of only 28.05%, whereas the selected TICA-SNEDDS formulations, F4 and F6, demonstrated markedly enhanced in vitro drug release in phosphate buffer at pH 6.8, reaching approximately 98.45% and 97.86%, respectively. These results reflect a substantial improvement in the dissolution profile of TICA. In 0.1 N HCl, the drug release from F4 and F6 were 62.03% and 73.57%, respectively, markedly higher than the 10.35% release observed for the pure TICA suspension. Furthermore, ex vivo permeability studies revealed that F4 exhibited an improved apparent permeability coefficient of 2.7×10^{-6} cm²/s, compared to 0.6708×10^{-6} cm²/s for the pure drug suspension.	[70]

No	Strategies	Material	Methodology	Result	Ref.
4	Nanostructured Lipid Carriers (NLC)	This study utilized glycerol monostearate as the solid lipid owing to its significant solubility for ticagrelor (TICA). Capmul MCM functioned as the liquid lipid to improve medication solubility and loading capacity. Surfactants such as Tween 80 and poloxamer 188 were utilized to stabilize the nanostructured lipid carriers (NLC) and enhance the solubility and dispersion of TICA.	Firstly, the solubility of ticagrelor (TICA) to different solid lipids (glycerol monostearate, myristic acid, palmitic acid, etc), liquid lipids (capmul MCM, capryol PGMC, oleic acid, etc), and 1% w/v surfactant (tween 80, span 80, poloxamer 188, etc.) were evaluated by a semi-quantitative method to optimize efficiency encapsulation TICA in NLC. To create TICA-loaded nanostructured lipid carriers (TICA-NLCs), the ultrasonication method of hot melt emulsification was employed. In the optimization of TICA-NLCs, the Box-Behnken design incorporated three independent variables: total lipid content, the ratio of liquid lipid to total lipid, and surfactant concentration. Guided by preliminary studies, three response parameters were evaluated: encapsulation efficiency (%), polydispersity index, and particle size (nm). Subsequently, the optimized TICA-NLC formulation was subjected to further characterization.	Glycerol stearate was chosen as a solid lipid, Capmul MCM as a liquid lipid, and a 1:1 mixture of Poloxamer 199 and Based on solubility study findings, Tween 80 was selected as the surfactant for the formulation of TICA-loaded nanostructured lipid carriers (TICA-NLC). Utilizing the Box-Behnken design, the optimized TICA-NLC formulation exhibited a high encapsulation efficiency of 92.1% alongside a notably small particle size of 87.6 nm. Cellular uptake of TICA-NLC was recorded to be 1.56 times higher than that of crude TICA on Caco-2 cells. In the pharmacokinetic study, TICA-NLC showed higher oral bioavailability of 254.99% compared to crude TICA.	[42]
5	Nanosuspension formulation	The study employed polyvinyl alcohol (PVA) and D-α-tocopherol polyethylene glycol 1000 succinate (TPGS) as stabilizing agents to formulate a ticagrelor nanosuspension via the antisolvent precipitation technique. Through the formation of amorphous nanostructures, these materials enhanced the physicochemical properties of ticagrelor—particularly its solubility, wettability, and permeability—resulting in a marked increase in oral bioavailability over the commercial alternative.	Various polymers and surfactants were evaluated as stabilizing agents based on the solubility equilibrium properties of Ticagrelor (TICA). A nanosuspension of Ticagrelor (TICA-NSP) was prepared utilizing the antisolvent precipitation technique. Following optimization through the Box-Behnken design, the formulation underwent comprehensive evaluation, including pharmacokinetic profiling, permeability assays, dissolution testing, and additional relevant analyses	Utilizing 18.8 mg of D-α-Tocopherol, 150 mg of PVA, and 15 mL of an aqueous solution, the developed TICA-NSP formulation resulted in a nanosuspension with uniformly distributed particles averaging 233 nm in size, and only 3% precipitation. Physicochemical evaluations indicated that the formulation contained amorphous TICA and exhibited a supersaturation phenomenon, enhancing its dissolution rate when compared to the commercial equivalent. Additionally, pharmacokinetic profiling and intestinal absorption tests revealed a 2.8-fold improvement in gastrointestinal uptake and a 2.2-fold increase in oral bioavailability over the conventional formulation.	[53]

No	Strategies	Material	Methodology	Result	Ref.
6	Co-crystal	In order to improve solubility by co-crystal formation, this publication uses ticagrelor (TICA) as the active pharmaceutical ingredient (API) and nicotinamide (NCA) as the co-former. When Ticagrelor and Nicotinamide co-crystals were created in a 1:1 ratio, including a hydrated form, Ticagrelor's solubility and rate of dissolution were significantly improved over the unformulated drug.	The solution crystallization method (TICA-NCA hydrate, TICA-NCA, and single crystal) was used to create the co-crystal of TICA with Nicotinamide (NCA). Numerous analytical methods, such as powder X-ray diffraction PXRD, DSC, FTIR, SCXRD, transformation study, and solubility and dissolution experiments, were used to describe the co-crystal.	Co-crystals of ticagrelor (TICA) and nicotinamide (NCA) were created in a 1:1 molar ratio and examined using X-ray diffraction (XRD), differential scanning calorimetry (DSC), and Fourier-transform infrared spectroscopy (FTIR). When compared to the solubility of the free drug, the solubility of the co-crystals was significantly enhanced when tested in an acidic medium at pH 2. The co-crystal demonstrated a faster dissolution rate in vitro than the brand-name product. The solubility of TICA-NCA and TICA-NCA hydrate was approximately four and four-and-a-half times greater than that of the commercial formulation.	[10]
		The research utilized Ticagrelor as the active pharmaceutical ingredient and L-tartaric acid as the co-former to prepare co-crystals through a slow evaporation process, with the objective of enhancing solubility. Acetonitrile, methanol, and HPLC-grade water served as the solvents	Ticagrelor and L-tartaric acid co-crystals were synthesized in various ratios (1:1, 2:1, 1:2). To produce the final batches of Ticagrelor co-crystals, several methods were employed, including dry grinding, slurry conversion, and slow evaporation, among others. The formation of co-crystals was validated through analyses using Fourier-transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD). Subsequently, in vitro dissolution profiles and saturated solubility measurements were conducted to evaluate the resulting compounds.	In both 1:1 and 2:1 ratios, ticagrelor was successfully co-crystallized. When compared to the pure drugs, these co-crystals' dynamic solubility was increased by about 2.7 and 2.6 times, respectively. Compared to the active pharmacological ingredient of TICA and its physical mixture, in vitro dissolving experiments showed that the chosen TICA:L-TAR (1:1) co-crystal was 1.5 times more soluble.	[71]

of Capmul MCM as the oil component significantly enhances TICA solubility, allowing for a higher drug load in the formulation [7]. Second, the small droplet size (20–200 nm) of the microemulsion facilitates rapid drug dissolution and absorption due to the increased surface area [39]. Third, SMEDDS improves transcellular and paracellular absorption and facilitates lymphatic transport, which protects the drug from first-pass metabolism [40]. Fourth, the formulation increases cellular uptake and permeability in Caco-2 cells. In vitro permeability studies indicated that TICA SMEDDS exhibited a significantly higher apparent permeability compared to raw ticagrelor solution, suggesting improved transepithelial transport [7].

Nanostructured lipid carriers (NLC), also known as lipid-based nanoparticles, are proposed as an effective drug delivery system. NLC presents multiple benefits, such as a straightforward production process that eliminates the need for organic solvents and allows for easy scalability, exemplified by high-pressure homogenization. Furthermore, NLC utilizes a blend of solid and liquid lipids to create a disordered matrix that improves drug loading efficiency and reduces drug leakage over time. [41]. Nanostructured lipid carriers loaded with Ticagrelor (TICA-NLC) were developed to enhance the drug's bioavailability and antiplatelet activity. Using the Box-Behnken design, an optimized formulation was achieved with a particle size of 87.6 nm and an encapsulation efficiency of 92.1%. In vitro studies demonstrated a 1.56-fold increase in cellular uptake compared to raw TICA, while pharmacokinetic analysis revealed a 254.99% improvement in oral bioavailability for TICA-NLC. Additionally, TICA-NLC showed superior antiplatelet

activity, with an $AUIC_{0-24}$ of 1064.2%·h, representing a 1.73-fold increase compared to raw TICA. These results suggest that TICA-NLC is a potential formulation for increasing TICA oral absorption and therapeutic efficacy [42]. Nanostructured lipid carriers (NLC) combine solid and liquid lipids to create disordered matrices that improve drug loading efficiency and minimize drug loss during storage [43]. The selection of specific lipids, such as glycerol monostearate (solid lipid) and capmul MCM (Glyceryl Caprylate/Caprate, liquid lipid), is based on their strong solubility for Ticagrelor (TGL), enabling effective incorporation of the drug into the matrix. [42]. Besides that, the small particle size of the optimized TICA-NLC (87.6 nm) facilitates its transport across the intestinal membrane via both transcellular and paracellular pathways, thereby enhancing oral bioavailability. The nanoscale dimensions of the NLC increase the drug's contact surface area with the cell membrane, which improves cellular uptake [44]. Furthermore, the synergistic effect of lipids and surfactants in the NLC enhances drug absorption by increasing the formulation's affinity for cell membranes due to their lipophilic properties [45]. The NLC system demonstrates a controlled release mechanism that protects the drug from acid-induced degradation within the gastric environment and enhances intestinal uptake. This sustained release is driven by the gradual disintegration and erosion of the lipid matrix containing the drug, which promotes lymphatic absorption and circumvents cytochrome P450-mediated hepatic first-pass metabolism, thereby significantly improving bioavailability [46–48].

Nanosuspension (NSP) is a pharmaceutical technology designed to augment the properties of poorly soluble and permeable medicines, hence enhancing their oral bioavailability [49–51]. The nanosuspension technique comprises the manufacturing of nanosized medication particles, consisting of surfactants and polymers, which give a wide surface area, hence enhancing oral absorption [52]. Researchers formulated a nanosuspension of ticagrelor (TICA-NSP) using D-α-Tocopherol polyethylene glycol 1000 succinate (TPGS) and polyvinyl alcohol (PVA) as stabilizing agents, aiming to improve its aqueous solubility and oral bioavailability [53]. TICA-NSP had a particle size of 233 nm and a 3% precipitation rate. In vitro and pharmacokinetic tests revealed a 2.8-fold increase in gastrointestinal permeability and a 2.2-fold improvement in oral bioavailability over the commercial medication Brilinta®. The data indicate that TICA-NSP is a viable formulation for increasing TICA therapeutic efficacy, warranting future development into patient-friendly sustained-release tablets. The improved efficacy of drugs formulated as nanosuspensions is influenced by multiple factors. The greatly enlarged surface area of nanosized particles facilitates greater interaction with the gastrointestinal membrane, thereby enhancing absorption through both intracellular and paracellular routes. Stabilizers, such as surfactants, provide electrostatic stabilization by preventing particle aggregation, while polymers offer steric hindrance, further ensuring the physical stability of the system [54]. The careful selection of surfactants and polymers is essential to mitigate the risks of particle aggregation and Ostwald ripening, which can alter particle size distribution and compromise drug dissolution performance [55]. Nanosuspensions may also induce drug supersaturation, facilitating rapid dissolution rates. The increased hydrophilicity provided by incorporated surfactants and polymers prevents particle aggregation, enhances wettability, and promotes solubilization in the diffusion layer [56] Additionally, the amorphous state of the drug in the nanosuspension exhibits higher thermodynamic activity compared to its crystalline form, thereby enhancing its solubility [34]. The combined solubility and permeability advantages of TICA-NSP contribute to its increased oral bioavailability, highlighting its potential as an effective formulation for ticagrelor delivery [53].

The co-crystallization approach increases TICA solubility by producing new solid forms with improved physicochemical properties. Creating a co-crystal can alter various properties of a drug, such as its solubility, dissolution rate, stability, tendency to absorb moisture, compressibility, and bioavailability [57–59]. The primary benefits of the cocrystal formation strategy for modifying the properties of drugs are [60]: a) the coformer influences the physicochemical characteristics of the cocrystal, while the drug's molecular structure remains unchanged; b) there is no need to form or break covalent bonds; c) API molecules, both ionizable and non-ionizable, can form cocrystals; d) cocrystals exhibit stability; e) coformers may include food additives, preservatives, pharmaceutical excipients, and/or other APIs; and f) the physicochemical and pharmacokinetic properties of APIs can be enhanced without altering their pharmacological activity.

A new cocrystal composed of Ticagrelor (TICA) and Nicotinamide (NCA) was developed and analyzed with the aim of improving the solubility of TICA, which is significantly low at 10 µg/mL [10]. The co-crystals, formed in a 1:1 ratio, were confirmed through FTIR, DSC, and XRD analyses. Notably, TICA-NCA and TICA-NCA hydrate exhibited solubility improvements of approximately four to four and a half times compared to

the commercial product. The crystal structure of TICA-NCA hydrate was elucidated, revealing rich hydrogen bond interactions and a stable dihydrate form.

Cocrystals result from hydrogen bond interactions between the active pharmaceutical ingredient (API) and a coformer. In the solvent medium, these weak bonds are disrupted, allowing the hydrophilic conformer to dissociate from the crystal lattice and dissolve in the aqueous environment. In turn, hydrophobic drug molecules experience wetting and achieve supersaturation in the aqueous medium, characterized by a high lattice energy relative to their original crystalline form, a phenomenon commonly known as the "spring" effect. Nonetheless, the drug quickly forms loosely aggregated clusters. To fully utilize this supersaturation state, it must be sustained long enough to enable drug absorption. This effect can be attained by temporarily preventing precipitation through the use of pharmaceutical excipients or other substances that interfere with nucleation and crystal growth, often known as 'chutes' or 'precipitation inhibitors.' This phase generally persists for 120 to 300 minutes, allowing for enhanced solubility at high doses. This is because the transformation of these amorphous clusters into stable crystalline phases and/or their growth into larger crystals is a relatively slow process in the solvent medium [60].

Conclusion

Ticagrelor, a strong $P2Y_{12}$ receptor antagonist, encounters limited bioavailability because of its poor solubility and permeability, classifying it as a BCS Class IV drug. To improve its solubility and treatment effectiveness, several approaches have been investigated, such as solid dispersions (SD), self-microemulsifying drug delivery systems (SMEDDS), nanostructured lipid carriers, nanosuspensions (NSP), and co-crystal formation. Solid dispersion (SD) is widely employed to improve solubility, with the third-generation SD using surfactant polymers TPGS and Neusilin® US2 achieved a 2.2-fold and 34-fold increase in TICA release compared to physical mixtures and the commercial product Brilinta®, respectively, yet it faces limitations such as potential instability (amorphous phase), hygroscopicity, and manufacturing scalability issues. SMEDDS enhance bioavailability through solubilization, small droplet size, and lymphatic transport, but challenges include low drug loading capacity and the potential for precipitation upon dilution. NLC significantly improves bioavailability TICA (254.99%) and antiplatelet activity but may suffer from stability concerns, burst release, and complex optimization requirements. Nanosuspensions (NSP) offer increased solubility and permeability due to high surface area and amorphization, but issues such as Ostwald ripening, aggregation, and scalability must be addressed. Co-crystallization, as demonstrated with TICA-NCA hydrate, achieves a 4- to 4.5-fold solubility increase without altering the API's molecular structure, but co-crystals may be limited by stoichiometric constraints, conformer selection challenges, and potential recrystallization risk. Among these strategies, NLC and co-crystallization strategies emerge as the most promising approaches. NLC improves both solubility and permeability by increasing absorption and bypassing first-pass metabolism, whereas co-crystals boost solubility without changing the drug's molecular structure, providing stability and scalability benefits.

Conflict of Interest

No conflicts of interest are declared by the authors in relation to this research.

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