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ENHANCING THE DISSOLUTION RATE OF TICAGRELOR THROUGH PREPARATION WITH CYCLODEXTRINS – TABLET FORMULATION AND EVALUATION

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Abstract

This research investigates the effect of solid-state modification of ticagrelor (TICA) by combination with selected cyclodextrins (CDs) on the release of the active pharmaceutical ingredient from formulated tablets. Particle size distribution, flowability tests, and volumetric studies were conducted on the powders intended for compression. Based on the obtained results, new oral dosage forms utilising TICA-CD formulations were designed and evaluated. The use of TICA–CD binary systems enabled the preparation of direct compression tablets with reduced drug dosage (45 mg). It was demonstrated that the type of beta-cyclodextrin used did not significantly influence the dissolution rate. The release of the active substance from the tablets exceeded 90% after 75 minutes under conditions of varying pH. Thus, the complexation of ticagrelor with cyclodextrins resulted in significantly higher rates of active substance release. The results of the current study suggested that TICA–CD inclusion complexes can be incorporated into oral dosage forms that can subsequently be used in therapeutic practice.

Rezumat

Acest studiu cercetează modul în care modificarea stării solide a ticagrelorului (TICA) prin asocierea cu ciclodextrine (CDs) influențează eliberarea ingredientului activ farmaceutic din comprimatele formulate. Au fost realizate analize de distribuție granulometrică a particulelor, teste de fluiditate și studii volumetrice asupra pulberilor destinate procesului de comprimare directă. Pe baza rezultatelor obținute, au fost realizate și evaluate noi forme de dozare, utilizând formlările TICA-CD. Utilizarea sistemelor TICA–CD a permis obținerea comprimatelor cu doze reduse de medicament (45 mg), prin comprimare directă. S-a demonstrat că tipul de beta-ciclodextrină nu are un impact semnificativ asupra ratei de eliberare. Cedarea substanței active din comprimate a depășit 90% după 75 de minute, în condiții variabile de pH. Astfel, complexarea ticagrelorului cu ciclodextrine a condus la o eliberare semnificativ mai rapidă a substanței active. Rezultatele studiului sugerează că pulberile ce conțin complecșii de incluziune TICA–CD pot fi încorporate în forme formaceutice destinate administrării pe cale orală, care pot fi utilizate în practica terapeutică.

Keywords: ticagrelor, cyclodextrin, kneading, dissolution tests

Introduction

Oral administration is the most commonly used and convenient therapeutic method for drugs efficiently absorbed through the gastrointestinal membrane. The rate and extent of intestinal absorption are influenced by several factors, such as transit rate and the variable regional permeability of different sections of the gastrointestinal tract [1-3]. Therefore, a dynamic and elaborate system of factors associated with absorption, distribution, metabolism and excretion influences their pharmacokinetic profile [4]. The poor water solubility of about 90% of recently developed active pharmaceutical ingredients (APIs) limits their ability to dissolve in the gastrointestinal system [5], which leads to low and variable oral bioavailability [6-9]. Therefore, the API's solubility and, implicitly, its rate of dissolution are important

determinants of oral dosage forms' bioavailability [10, 11].

Ticagrelor (TICA), like most of the recently discovered APIs, is categorised as a Class IV drug by the Biopharmaceutics Classification System (BCS), due to its intrinsic low solubility and permeability [12, 13]. By preventing platelet aggregation and reducing ischemia risk, ticagrelor, a P2Y12 receptor antagonist with strong antiplatelet action, is recommended to avoid thrombotic effects [14]. It is primarily recommended for the treatment of serious cardiovascular events, such as myocardial infarction, ischemic stroke, unstable angina, atherosclerotic cardiovascular disease, and acute coronary syndromes [15-17].

Cyclodextrins (CDs) are crystalline, homogenous, and non-hygroscopic substances with a macrocyclic structure. They are cyclic oligosaccharides consisting of six, seven, or eight glucopyranose units connected by α (1–4) glycosidic bonds. Regardless of the number of glucose units, CDs have a relatively hydrophobic internal cavity and a hydrophilic external surface [18-21]. The three primary CDs utilised in the pharmaceutical industry are alpha (α)–, beta (β)– and gamma (γ)–cyclodextrins [22-24]. Chemically modified CDs, such as hydroxypropyl–β–cyclodextrin (HP–β–CD) and methyl–β–cyclodextrin (ME–β–CD), have been introduced in order to improve the solubility of drug–CD complexes. An additional advantage of incorporating these radicals is the reduction in nephrotoxicity previously associated with cyclodextrins that are poorly soluble in water [23, 25]. They have the ability to modify the physicochemical characteristics of APIs because of their amphiphilic structure, which enables them to form inclusion complexes [22, 23, 26, 27].

The main goal of this study was to investigate how the solid-state modification of TICA by inclusion in the cyclodextrin cavity affects the release of the API from tablets. The study aimed to formulate oral tablets containing TICA+β–CD, TICA+HP–β–CD and TICA+ME–β–CD, manufactured using the direct compression technique. Additionally, the study involved the qualitative and quantitative evaluation of the obtained tablets, in accordance with the standards established in pharmacopoeias and specialised literature, focusing on their physical characteristics, dissolution behaviour, and overall performance in terms of API release for oral administration.

Materials and Methods

Materials

Ticagrelor was generously supplied by Zentiva, Bucharest, Romania. β–CD, HP–β–CD and ME–β–CD were obtained from Hong Kong Guokang Bio-Technology Co., Limited, located in Baoji City, Shaanxi province, China. Prosolv®, silicified microcrystalline cellulose HD 90 (SMCC) and EXPLOTAB® sodium starch glycolate were provided by JRS PHARMA GmbH & Co. KG, Rosenberg, Germany. Undesa® magnesium stearate was provided by Unión Derivan S.A., Italy. Polysorbate 80 (Tween 80; analytical grade), potassium phosphate monobasic, sodium acetate, acetic acid, and hydrochloric acid were purchased from Merck KGaA (Darmstadt, Germany). Methanol (HPLC grade), formic acid (≥ 99.0%, Optima™ LC/MS Grade) and sodium hydroxide solution (extra pure, 50 wt.% in water) were obtained from Fisher Chemical (Thermo Fisher Scientific, Waltham, MA, USA). Ultrapure water (18.2 MΩ·cm at 25°C) was prepared using a Milli-Q purification system (Merck Millipore, Burlington, MA, USA). All other reagents were of analytical or HPLC grade and were used as received without further purification.

Methods

Preparation of ticagrelor inclusion complexes with β–CD, HP–β–CD and ME–β–CD. To achieve optimal drug absorption across biological membranes, it is crucial to incorporate the correct quantity of cyclodextrins into the formulation, ensuring the complete solubilisation of the drug [28, 29]. Consequently, inclusion complexes of TICA and CDs were created in a molar ratio of 1:1, in order to have 45 mg of TICA in addition to 100 mg of CD. The kneading technique was used to prepare the inclusion complexes. A ceramic mortar was used to physically knead each CD with the required amounts of TICA for an hour at room temperature. The samples were wetted with 10 mL of a 50:50 v/v ethyl alcohol:water mixture during this step. The resulting paste was left to dry at room temperature for twenty-four hours. Once the product had dried, it was ground into a powder and passed through an 800-micrometer sieve.

Preparation of direct compression material containing ticagrelor inclusion complexes with β–CD, HP–β–CD and ME–β–CD. The tablets were obtained using direct compression technique. The qualitative and quantitative composition of the powder mixture containing 45 mg TICA are presented in Table I. F0 is the control formulation, while F1-F3 contain inclusion complexes formed between TICA and β–CD (F1), HP–β–CD (F2) and ME–β–CD (F3). Prosolv®, SMCC, SSG and MGS were selected as major excipients.

All the ingredients were screened through an 800-micrometer sieve and mixed at room temperature for 20 min at 30 rpm speed in a CMP 12 Plexiglas cube blender (Pharmag GmbH, Klipphausen, Germany).

Table I

Qualitative and quantitative composition of the direct compression material containing ticagrelor inclusion complexes with β–CD, HP–β–CD, and ME–β–CD

Ingredients	Ingredient amount in tablet (%)			
	F0	F1	F2	F3
TICA	9.00	-	-	-
TICA+β–CD	-	9.00 + 19.52	-	-
TICA+HP–β–CD	-	-	9.00 + 23.64	-
TICA+ME–β–CD	-	-	-	9.00 + 22.44
SMCC	85.00	65.48	61.36	62.56
SSG	3.00	3.00	3.00	3.00
MGS	3.00	3.00	3.00	3.00

The pharmacotechnical properties of the inclusion complexes and direct compression blends containing inclusion complexes with β–CD, HP–β–CD and ME–β–CD. The flowability of the direct compression blends was assessed by measuring the time required for 60 g of each blend to pass through a 10-millimeter diameter orifice. The evaluations were conducted using an automated powder and granulate testing system, PTG-S3 (Pharma Test Apparatebau GmbH, Hainburg, Germany). For the particle size distribution determination, a CISA Sieve Shaker Mod. RP 10 (Cisa Cedaceria Industrial, Barcelona, Spain) was used. The Vankel Tap Density Tester (Vankel Industries Inc., Atlanta, GA, USA) was used for the volumetric investigations of the powders. Each powder mixture's previously weighted mass (m) was put into the apparatus's graded cylinders. Firstly, for each powder, a measurement was made to determine the initial bulk volume (V_0). Subsequently, the set parameters included 500 mechanical shocks for each determination. Then, upon completion of the tapping process, the final volume (Vf) was recorded. Based on the obtained data, the following characteristics were determined: the tapping capacity, which is the difference between the initial and final volume (V_0 - Vf); the bulk density before and after the tapping process (ρ_0 and ρf), which represents the ratio between the powder mass and the initial volume ($\rho_0 = m/V_0$), and respectively the final volume ($\rho f = m/Vf$); the Hausner ratio (HR), which represents the ratio between the final and initial bulk density ($\rho f / \rho_0$); and the Carr index (CI), which provides information on the percentage of powder compressibility, which is calculated using the formula: $[(\rho f - \rho_0)/\rho f] \times 100$.

Development and manufacturing of the tablets containing inclusion complexes with β–CD, HP–β–CD and ME–β–CD. Drawing upon the results from precompression studies, the decision was made to proceed with the compression of the four powder mixtures represented in Table I. The tablets containing ticagrelor inclusion complexes with β–CD, HP–β–CD and Me–β–CD were prepared using the direct compression method. A single-post (single punch) eccentric Erweka EP-1 Tablet Press (Heusenstamm, Germany) equipped with 12 mm flat punches was used to obtain the tablets, using a compression force of 30 kN.

Quantitative and qualitative control of the obtained tablets. The obtained tablets were investigated according to the compendial recommendations [30-33]. Mass uniformity was accomplished by weighing the tablets individually and calculating their average weight. A Mettler Toledo AT261 balance (Columbus, OH, USA) with a sensitivity of 0.01 mg was used to make the measurements. A VK 200 mechanical strength tester (Vanderkamp, New York, NY, USA) was used to measure the tablet's diameter, thickness and hardness. The Vankel friabilator (Vankel Ind., USA) was used to test the tablets' friability by centrifuging them for five minutes at a speed of 25 rpm. In order to ensure a representative and uniform assessment of their properties, each determination was carried out on a sample of 20 tablets from each formula. The dissolution profiles of the ticagrelor tablets were determined using a Vision G2 Classic 6 Dissolution Tester (Teledyne Hanson, Chatsworth, CA, USA) using USP Apparatus II (paddles). Experiments were conducted in six replicates (n = 6), following established pharmacopeial guidelines. The dissolution vessels contained 900 mL of dissolution medium, preheated to 37.0 ± 0.5°C, and the paddle rotation speed was set at 75 rpm. Four different media were evaluated: pH 1.2 hydrochloric acid buffer, pH 1.2 hydrochloric acid buffer containing 0.2% (w/v) Polysorbate 80, pH 4.5 acetate buffer containing 0.2% (w/v) Polysorbate 80, and pH 6.8 phosphate buffer containing 0.2% (w/v) Polysorbate 80. Aliquots of 5.0 ± 0.1 mL were sampled at predetermined intervals (10, 15, 20, 30, 45, 60 and 75 minutes). After each withdrawal, the volume was immediately replenished with an equal amount of preheated, fresh dissolution medium to ensure sink conditions. The collected samples were subsequently diluted using a water:methanol mixture and filtered through a 0.45 µm polyethersulfone filter prior to HPLC analysis. Chromatographic analysis was performed using a Jasco 4000 Series HPLC system (JASCO Corporation, Tokyo, Japan), equipped with a Kinetex® C18 analytical column (100 mm × 3 mm, 2.6 µm particle size; Phenomenex, Torrance, CA, USA), at 45°C. The mobile phase consisted of an

isocratic mixture of 0.1% aqueous formic acid and acetonitrile–methanol (1:1, v/v). Detection was carried out at 300 nm. The analytical method was validated according to the ICH Q2(R2) guidelines, in terms of linearity, accuracy, precision, specificity and sensitivity [34]. Calibration curves were prepared with ticagrelor standards spanning concentrations from 1 to 100 µg/mL, facilitating accurate quantification of the drug dissolved in the dissolution samples. Dissolution profiles were generated by converting chromatographic responses (area under the peak) into the percentage of ticagrelor dissolved, relative to the nominal tablet content.

Results and Discussion

The pharmacotechnical properties of the direct compression blends

The flow time determination analysis was performed to evaluate the ability of the powders, formed from the mixtures, to be subjected to the direct compression process (Table I), to flow in a vertical plane. Based on the determinations performed for each powder mixture, it was found that the flow time was approximately 15 seconds, more specifically 15.59 seconds for the mixture containing, in addition to excipients, inclusion complexes formed from TICA and β–CD, 15.43 seconds for the mixture containing inclusion complexes formed from ticagrelor and HP–β–CD and 15.02 seconds for the mixture containing inclusion complexes formed from ticagrelor and ME–β–CD (Table II). Thus, it can be concluded that the powders formed by the inclusion complexes of the active pharmaceutical ingredient with the three types of cyclodextrins exhibit favourable flow properties for the direct compression process.

Table II

The flow properties were obtained for the powders containing both the inclusion complexes and the excipients

Powder	Flow time (s)
TICA+β–CD + excipients	15.59
TICA+HP–β–CD + excipients	15.43
TICA+ME–β–CD + excipients	15.02

The results obtained from the analysis of the volumetric characteristics for the powders containing only inclusion complexes, as well as for those containing both the inclusion complexes and the excipients mentioned in Table I, are presented in Table III and Table IV.

An analysis of the initial volume occupied in the cylinder by the powders containing inclusion complexes highlights that the mixture containing β–CD occupies a smaller volume, indicating a more compact structure, in contrast to the powders formed from the other two cyclodextrins, which occupy a significantly larger volume. Consequently, the first mixture's initial bulk density value is bigger than the others.

The powder containing ME–β–CD has low flowability, which indicates a larger tendency for compaction compared to the other combinations. Furthermore, when compared to the other mixes, ME–β–CD has the highest compressibility index.

Therefore, the three mixtures reveal different volumetric properties. The inclusion complexes made from ticagrelor and ME–β–CD have higher compressibility and lower flowability than the powders made from ticagrelor and β–CD or ticagrelor and HP–β–CD.

Table III

The volumetric characteristics of the powders containing inclusion complexes between ticagrelor and the three types of cyclodextrins

Volumetric characteristics	TICA+β–CD	TICA+HP–β–CD	TICA+ME–β–CD
mass (g)	15.02	15.97	15.51
V_0 (mL)	34	56	58
V_f (mL)	21	31.5	29
$V_0 - V_f$ (mL)	13	24.5	29
ρ_0 (g/cm³)	0.44	0.29	0.27
ρ_f (g/cm³)	0.72	0.51	0.53
HR	1.62	1.78	2.00
CI %	38.24	43.75	50.00

Analysing the results presented in Table IV, which refers to the powders to be subjected to the direct compression process, it can be observed that the initial bulk density is lower than that of the powders containing only inclusion complexes, suggesting that the addition of excipients leads to a reduction in the bulk density of the powders. The final bulk density increases after tapping, suggesting a more significant compaction. In the case of the tablets containing inclusion complexes formed with β–CD, the Hausner ratio value is higher compared to the powder formed exclusively from inclusion complexes, in contrast to the Hausner ratio values observed in the mixtures containing the tablet powders with HP–β–CD and ME–β–CD. Additionally, the mixture containing β–CD is also distinguished by its compressibility index, showing higher values than the other mixtures. Analysing the obtained results, all three powders exhibit similar behaviour, with poor flowability, which is characteristic of fine, free-flowing powders.

Table IV

The volumetric characteristics of the powders containing both the inclusion complexes and the excipients

Volumetric characteristics	TICA+β–CD + excipients	TICA+HP–β–CD + excipients	TICA+ME–β–CD + excipients
mass (g)	23.98	27.45	27.75
V_0 (mL)	58	76	75
V_f (mL)	31	49	46
V_0 - V_f (mL)	27	27	29
ρ_0 (g/cm³)	0.41	0.36	0.37
ρ_f (g/cm³)	0.77	0.56	0.60
RH	1.87	1.55	1.63
IC %	46.55	35.53	38.67

For this study, the granulometric analysis of the powders is critical, providing significant information regarding flowability and compressibility, important properties for characterizing the consolidation behaviour of powder systems [35]. The particle size distribution histograms for the powdered TICA-CDs ICs obtained by the kneading method and the final formulation mixtures (ICs and excipients) to be directly compressed (Table I) are shown in Figure 1a and Figure 1b, respectively.

From the analysis of the granulometric histograms obtained for the powders containing ticagrelor inclusion complexes with the three types of cyclodextrins (Figure 1a), it can be observed that they contain a considerable percentage of particles with sizes ranging between 250 and 600 micrometres. This is especially noticeable for the inclusion complexes formed with β–CD and ME–β–CD.

Most of the particles in the powders that contain the final formulation mixtures (Figure 1b) are under 250 micrometres. The presence of excipients, which improve the powder's average flowability, is responsible for the increased proportion of smaller particles.

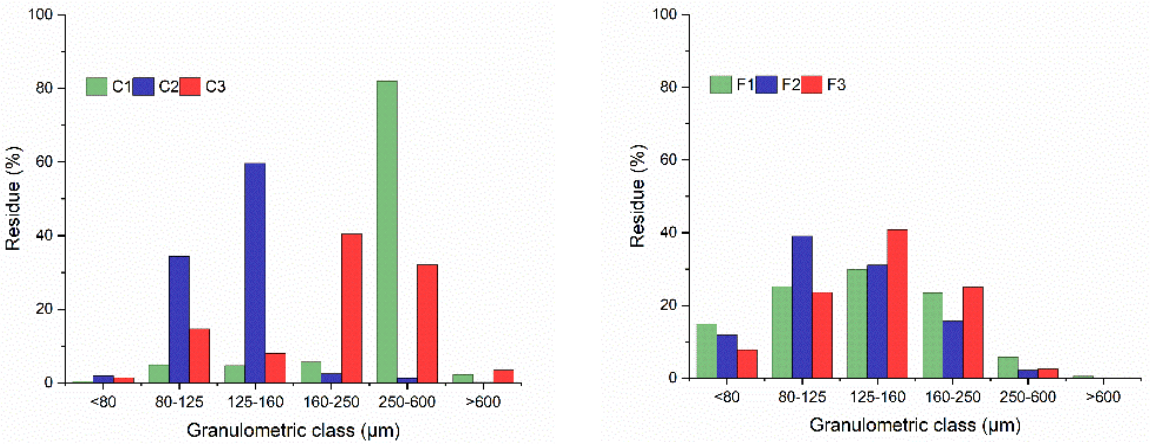

Figure 1.

Granulometric analysis of (a) TICA and β–CD (C1), TICA and HP–β–CD (C2), TICA and ME–β–CD (C3) ICs powders obtained by kneading methods; and (b) final formulation mixtures (Table I) containing: β–CD (F1), HP–β–CD (F2) and ME–β–CD (F3)

Quality assessment of tablets

Tablets represent the most commonly used solid oral dosage form, offering advantages both in terms of formulation, such as efficient manufacturing, long-term storage stability, and good temperature tolerance, as well as from the patient's perspective, due to ease of administration and low cost [36, 37]. Excipients may include binders, fillers, disintegrants, lubricants and other auxiliary substances necessary to ensure the desired bioavailability of the drug and the physico-mechanical properties of the tablets [35, 37-39]. Binders and fillers are used to provide cohesive properties to powders, thus facilitating the formulation of granules, as well as to add volume and increase the strength of tablets [37]. Microcrystalline cellulose (MCC) is an excipient used as a diluent, lubricant and disintegrant agent. It is hygroscopic in nature and frequently employed in direct compression. It swells when in contact with liquid, absorbing a substantial amount of moisture [40]. Lubricants represent an especially important class of excipients, added to reduce friction between particles, prevent powder adhesion to the surfaces of punches and dies, and facilitate tablet ejection from the die. One of the most commonly used lubricants in tablet formulation is magnesium stearate (MGS). However, its proportion must be

carefully chosen, as it can negatively affect the tablet's mechanical strength. Disintegrants are incorporated to facilitate the rapid breaking and disintegration of tablets after administration [37]. Sodium starch glycolate (SSG) is widely used in the preparation of tablets *via* direct compression. The typical concentration in a formulation ranges between 2% and 8%, with an optimal concentration of approximately 4%. It imparts good disintegration properties to tablets by rapidly absorbing water from the gastrointestinal tract, followed by rapid swelling and disintegration [41, 42]. The chosen excipients are presented in Table I.

To prevent the influence of high temperatures on the powders, the direct compression technique was the chosen method for obtaining the tablets. Tablets can be produced in a wide variety of sizes and shapes, depending on the design of the punches and dies [43]. Direct compression has a number of significant advantages over the wet granulation approach for creating tablets. One of the advantages is that it involves only the necessary processing steps – blending, lubricating and compressing the powders – making the process quicker and more effective. It also uses fewer excipients and minimizes stability problems for active components that are sensitive to heat. Additionally, compared to wet granulation, the direct compression method is less expensive. Direct compression does have a few disadvantages, though, such as the limited quantity of active ingredient that can be utilised, which limits the capacity to produce tablets with a high active ingredient content. Furthermore, since the final tablets could be quite thin or fragile, the process might not be appropriate for materials with low bulk volume. Drugs with poor flow characteristics also present processing challenges because, during blending, static charges can accumulate on the drug or excipient particles, causing agglomeration and insufficient mixing that can compromise the homogeneity of the formula [44].

The ultimate tablets must meet quality requirements for hardness, friability, disintegration time and consistency in weight and content. Thus, each of these important characteristics is affected by both the formulation ingredients and the processing method used [31, 43].

Studies for active ingredient release are used to evaluate *in vitro* performance for solid oral dosage forms. Therefore, determining the release rate is an essential step in confirming the pharmacological activity of drugs. The active substance's characteristics (particle size, solid state – crystalline or amorphous, powder density), the pharmaceutical product's composition (mass ratio between active substance and excipients, type of excipients), the manufacturing process (compression forces, equipment used), and storage conditions (temperature, humidity) are some of the factors that may affect this process. The USP Apparatus 2 with paddles is often utilized to evaluate the rate at which the active ingredient is released from tablets [45-48].

Uncoated tablets were obtained, which exhibit similar organoleptic characteristics, having a white colour and a flat disc shape, with a compact and homogeneous structure and bevelled edges. The appearance of the obtained tablets is shown in Figure 2.

Figure 2.
The appearance of the tablets containing ticagrelor formulations with: (b) β–CD, (c) HP–β–CD and (d) ME–β–CD, compared to the control formula, without cyclodextrin (a)

As described in Table V, tablet compression leaded to tablets with similar sizes, a diameter of 12 mm with a variability below 1% between the tablets of the same batch, and a thickness of around 4 mm with slight differences between the batches. The weight loss of each tablet was less than 1%, therefore we obtained an acceptable friability of the tablets.

The studied materials manifested high hardness with excellent compression and low friability levels, not significantly different from zero, therefore with values in compliance with the pharmacopeial requirements (smaller than 1%) [31]. Hardness varied between batches and decreased in the following order F0 > F3 > F2 > F1. As expected, the hardness of the control tablets had much higher values compared to the others.

Table V

Quality properties of the studied tablets

Parameter	Formulation			
	F0	F1	F2	F3
Mass uniformity (mg)	482.65 ± 4.82	484.8 ± 4.39	483.68 ± 4.79	486.25 ± 4.87
Thickness (mm)	3.85 ± 0.02	3.88 ± 0.03	3.73 ± 0.05	3.99 ± 0.04
Diameter (mm)	12.12 ± 0.03	12.11 ± 0.03	12.07 ± 0.01	12.06 ± 0.02
Friability (%)	0.1 ± 0.02	0.09 ± 0.03	0.16 ± 0.02	0.21 ± 0.02
Hardness (N)	141.22 ± 4.34	66.19 ± 2.54	91.20 ± 5.31	116.70 ± 4.28

The dissolution profiles of the experimental ticagrelor tablets (F0, F1, F2, F3) were evaluated across four distinct media (pH 1.2, pH 1.2 + Polysorbate 80, pH 4.5 + Polysorbate 80 and pH 6.8 + Polysorbate 80) to assess the impact of cyclodextrin inclusion complexes on drug release behaviour.

The inclusion of Polysorbate 80 in dissolution media for low aqueous solubility drugs is an effective strategy to maintain sink conditions during *in vitro* testing. Polysorbate 80 acts as a surrogate for endogenous surfactants and bile salts present in the gastrointestinal (GI) tract, thereby mimicking the solubilizing environment found *in vivo*. This surfactant facilitates enhanced solubilization and prevents drug precipitation at higher concentrations, which is critical for obtaining reliable and predictive dissolution profiles for poorly soluble drugs, including ticagrelor [49]. The use of multiple dissolution media with distinct pH values and surfactant compositions is a well-established approach for simulating the various GI environments encountered by orally administered drugs [50]. Testing at pH 1.2 without surfactant can mimic the fasted stomach environment, whereas the inclusion of surfactants such as Polysorbate 80 at the same pH has been shown to emulate fed-state conditions due to the increased concentration of endogenous lipids and bile salts present after food intake [51]. Likewise, employing media at pH 4.5 with Polysorbate 80 seeks to replicate the conditions during the transition phase between the stomach and early intestinal tract, while at pH 6.8 with Polysorbate 80, the dissolution medium closely parallels the near-neutral environment of the small intestine, where absorption processes are predominant for many BCS Class II drugs [52].

Furthermore, incorporating Polysorbate 80 in the dissolution media significantly enhances the apparent solubility of poorly water-soluble drugs by facilitating wetting and micellar solubilisation, thereby preventing the formation of drug precipitates that might otherwise hinder the accurate assessment of release kinetics and dissolution rate [53]. This strategy ensures the maintenance of sink conditions, which is critical for reliably simulating the rapid drug partitioning and absorption observed *in vivo* [54, 55]. Studies have demonstrated that the proper selection of surfactant concentration is instrumental not only in solubilising the drug but also in stabilizing supersaturated solutions and providing a more predictive *in vitro - in vivo* correlation [56, 57]. The relevance of this approach becomes particularly pronounced for drugs such as TICA, where intrinsic challenges associated with low aqueous solubility can complicate formulation development and bioavailability enhancement efforts [58]. By utilizing biologically-relevant media with tailored pH and surfactant levels, researchers can gain insights into the pH-dependent changes in solubility and the surfactant-mediated improvements in dissolution. This dual investigation provides a more robust understanding of the factors that govern drug release in the GI tract and, consequently, aids in the rational design and optimisation of drug delivery systems for poorly soluble compounds [58].

The dissolution profiles for experimental formulations under different pH and surfactant conditions are presented in Figure 3.

At pH 1.2 without surfactant (Figure 3a), dissolution rates were generally low, with less than 30% of TICA released after 75 minutes, highlighting ticagrelor's inherently limited solubility in acidic media. Among the tested formulations, F3 (TICA+ME–β–CD) exhibited most favourable dissolution characteristics, demonstrating a slightly faster and higher release compared to the other formulations. The introduction of 0.2% Tween 80 at pH 1.2 significantly enhanced the dissolution rates (Figure 3b). In these conditions, formulations containing inclusion complexes (F1, F2, F3) released more than 50% of the active substance within 20 minutes and exceeded 90% dissolution at 75 minutes. This marked improvement emphasizes the critical role of surfactants in facilitating TICA solubilization, likely by mimicking physiological surfactant-rich gastrointestinal environments. Notably, the control formulation F0, without cyclodextrin complexation, lagged behind, underscoring the effectiveness of cyclodextrin complexes in promoting dissolution.

In mildly acidic conditions (pH 4.5 with Tween 80, Figure 3c), TICA release profiles closely mirrored those observed at pH 1.2 with surfactant. Although all cyclodextrin-containing formulations rapidly reached high dissolution percentages, formulation F1 (TICA+β–CD) demonstrated a slightly faster initial dissolution compared to formulations containing modified cyclodextrins (F2, F3). This observation suggests that under moderately acidic conditions, the non-modified β–CD may offer a marginal advantage during early dissolution stages.

At near-neutral intestinal conditions (pH 6.8 with Tween 80, Figure 3d), all formulations displayed robust and comparable dissolution performance after the initial 30 minutes. Despite early variability, by 45 minutes, differences between formulations became minimal. Nevertheless, the inclusion complex with ME–β–CD (F3) consistently provided superior early-stage dissolution compared to other formulations, confirming the benefit of methylation in enhancing solubility.

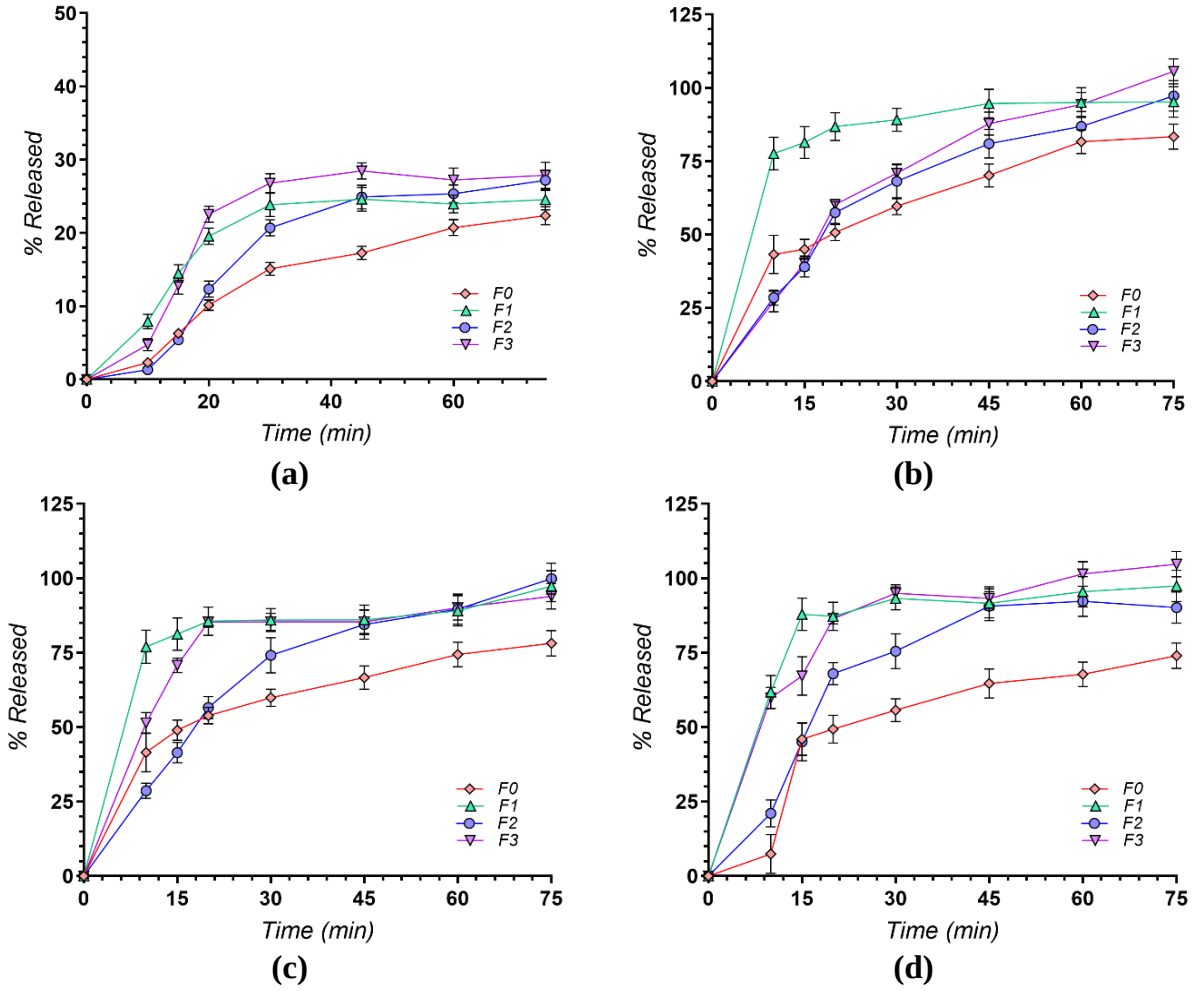

Figure 3.

In vitro release profiles of TICA from the experimental formulations, under different pH conditions: (a) pH 1.2 HCl buffer; (b) pH 1.2 HCl buffer containing 0.2% (w/v) Polysorbate 80; (c) pH 4.5 acetate buffer containing 0.2% (w/v) Polysorbate 80; and (d) pH 6.8 phosphate buffer containing 0.2% (w/v) Polysorbate 80

As a result, the dissolution profiles of the experimental TICA tablet formulations demonstrate the significant role of cyclodextrin inclusion complexes and the use of Polysorbate 80 in enhancing drug release.

Conclusions

The current study concentrated on developing and evaluating innovative oral pharmaceutical formulations with improved bioavailability that contain ticagrelor. Therefore, the kneading technique was used to create the inclusion complexes of ticagrelor with β–CD, HP–β–CD and ME–β–CD, in order to use them as the active ingredient in the tablets. Pre-formulation investigations were carried out on powders that had only the inclusion complexes and powders that also contained the excipients added for the preparation of the compression blends. Based on the results obtained, it was decided to proceed with the direct compression technique of tablet production.

The experiments conducted on the obtained tablets clearly indicated that the inclusion of ticagrelor in β–cyclodextrin complexes substantially improved dissolution characteristics across a broad spectrum of physiologically relevant pH values, especially in surfactant-containing media.

The utilisation of cyclodextrin complexes can therefore significantly enhance oral bioavailability, potentially reducing dosage requirements and associated adverse effects.

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Conflict of interest

The authors declare no conflict of interest.

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