

Solubility Enhancement of Ticagrelor by Different Complexation Methods

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Abstract

The antiplatelet medication ticagrelor is taken orally and found as a crystalline powder with a water solubility of approximately 3.5 µg/ml at room temperature. Within the physiological range, ticagrelor has no pKa value. The Biopharmaceutics Categorization defines ticagrelor as a "poor solubility, low permeability medication" because it lacks pH-dependent solubility (Class IV). The average unmodified bioavailability of ticagrelor in healthful volunteers is 36%.

The research seeks to enhance the solubility and dissolution of ticagrelor by utilizing various methods. It aims to prepare the cyclodextrin inclusion complex.

Physical trituration, kneading, and solvent evaporation were all employed to create nine formulas of cyclodextrin inclusion complex with HPβCD. Saturated solubility, FTIR, and DSC were used to characterize the produced formulations.

In terms of the ticagrelor inclusion complex with hydroxyl propyl beta cyclodextrin (HPβCD). All complexes enhanced solubility by forming an inclusion complex with HPβCD. However, the solvent evaporation process proved the most effective for ticagrelor solubilization. The optimum inclusion complex formula (F9) demonstrated a tenfold increase in saturated solubility over the pure drug.

1. INTRODUCTION

Only 8% of the new medication candidates have increased permeability and solubility. Recent tests showed that 70% of the novel medication candidates lacked adequate water solubility. 40% of all commercially available immediate-release oral medications are being classified as insoluble (<100 µg/ml).⁽¹⁾

On the other hand, drug research is hampered by the inadequate solubility of medication candidates. How quickly the medicine dissolves depends on how it is soluble in water. Orally administered medicines with low solubilities frequently have low bioavailability and mixes with aqueous solubilities below 100 µg/ml experience dissolution-limited absorption. Raising the dose amount would be needed to get the blood medication concentration into the therapeutic drug concentration capacity in these conditions^{(2), (3)}

One of these various methods to increase solubility is nanotechnology, which uses attractive nanoparticles and has gained much interest in the past ten years. Polymeric nanoparticles are stable particles or particulate distributions with sizes between 10 and 1000 nm (PNPs). Due to these particles' microscopic size and enormous surface area, the number of atoms or molecules on the exterior can be significantly grown^{(4), (5)}.

Ticagrelor has the molecular weight and formula C₂₃H₂₈F₂N₆O₄S (522.57 gm/mole). Ticagrelor is a crystalline powder with 3.5 µg/ml water soluble at room temperature⁽⁶⁾.

Thus, the research goal is to enhance the solubility of the inadequately water-soluble drug ticagrelor. It is accomplished by developing and testing a ticagrelor inclusion complex with HPβCD⁽⁷⁾.

2. MATERIALS AND PROCEDURES

The Ticagrelor and HPβCD powders were acquired from China, AOPharm, and Methanol from UK, GCC Analytical Reagents.

Drug Characterization

Determination of Ticagrelor powder's melting point was determined using the capillary tube technique. The tube was sealed at one end, plunged in drug powder, and positioned within the melting point apparatus, where the temperature gradually increased. The melting point was determined by recording the temperature at which powder became liquid⁽⁸⁾.

Ticagrelor λ Max Determination

The drug's λ maximum effective concentration (max) was ascertained by scanning the solutions spectrophotometrically between 200 and 400 nm with ticagrelor solutions of 5 $\mu\text{g/ml}$ in methanol, HCl solution (pH 1.2) with 1% Brij. 35, and phosphate buffer solution (pH 6.8) with 1% Brij. 35.⁽⁹⁾

Ticagrelor Calibration Curves

By making serial dilutions of the medication from stock solutions (5 $\mu\text{g/ml}$ to 100 $\mu\text{g/ml}$) and analyzing the prepared samples spectrophotometrically at the drug's maximum concentration, calibration curves for ticagrelor in methanol, distilled water with 1% Brij. 35, HCl buffer pH (1.2) with 1% Brij. 35, and phosphate buffer solution (pH 6.8) with 1% Brij. 35 were created. The calculated absorbance was recorded and plotted against the concentration⁽¹⁰⁾.

Ticagrelor Solubility Determination

The equilibrium solubility of ticagrelor in three distinct test media—water, HCl buffer solution pH 1.2 with 1% Brij 35, and phosphate buffer solution pH 6.8 with 1% Brij 35—was ascertained using the shaking flask method. A test tube containing 10 ml of medium and an excess of the drug was agitated for 48 hours in a water bath at 37°C while using a shaker. Drug content was determined spectrophotometrically using filtered samples⁽¹⁰⁾.

Preparation of Ticagrelor inclusion complexes

Utilizing 3 distinct processing techniques, physical trituration, kneading, and solvent evaporation, cyclodextrin inclusion complex/ticagrelor at weight ratios of 1:1, 1:2, and 1:4 employing HP β CD (Hydroxypropyl β -cyclodextrin).⁽¹²⁾

Method of physical trituration

By gradually incorporating ticagrelor into HP β CD in a mortar while lightly pulverizing it, the two substances (HP β CD and Ticagrelor) were weighed, sieved, and evenly combined. For an hour, the mixture was continually combined (magnetic stirrer) until it became homogeneous. The mixes were stored in a sealed container after filtering through a #65 mesh sieve (0.211 mm)⁽¹³⁾.

Method of Kneading

In a mortar, HP β CD was moistened with enough water (10% w/w) to form a paste, and ticagrelor was carefully counted to the paste. An appropriate dose of water was intermittently added while manually kneading for an hour to keep the paste's consistency. In an oven set to 50 °C, the mixture was dried for 24 hours. Using a mortar and pestle, the dried complex was ground. The inclusion complex was sieved through a #65 mesh and stored in a sealed container⁽¹⁴⁾.

Method of Solvent evaporation

HP β CD was disintegrated in distilled water (50 mL), while Ticagrelor was disintegrated in methanol (25 mL). The two solutions were combined and swirled for an hour (Magnetic stirrer). Methanol was removed with continual stirring and heating at 50 °C. A rotary evaporator was then applied to remove water under low pressure. The combination was heated to 50 °C for 24 hours in an oven to evaporate any remaining solvent. Mortar and pestle

were used to grind the inclusion complex. The inclusion complex was sieved through a #65 mesh sieve and maintained in a covered container ⁽¹⁵⁾.

Table 1: Composition of Ticagrelor Inclusion Complexes.

Formula No.	Method of Preparation	Ticagrelor/ HPβCD (Ratio)
F1	Physical trituration	1:1
F2	Physical trituration	1:2
F3	Physical trituration	1:4
F4	Method of kneading	1:1
F5	Method of kneading	1:2
F6	Method of kneading	1:4
F7	solvent evaporation	1:1
F8	solvent evaporation	1:2
F9	solvent evaporation	1:4

Study of Phase solubility

Higuchi and Connors' method was used to study phase solubility. A surplus of ticagrelor (1 g) was counted to 50 mL of filtered water, including diverse concentrations of HPCD (2–20 mM). The flasks continuously bounced at 25 °C for a few days to reach equilibrium. A 0.45 m nylon membrane filter was used to filter 3 mL of sample liquid. The filtrate (100 L) was tested at the maximum ticagrelor concentration after the proper dilution. Each measurement was performed three times ⁽¹⁰⁾.

Study of Solubility

Solubility was investigated using extra stable dispersions in 50 mL of pure water. After being vortex-mixed for three minutes, the flasks were stirred at 120 contests per minute for 72 hours in a water bath at 30 °C. Three millilitres of samples were obtained and passed through a nylon membrane filter with a 0.45-micron pore size. Before performing a spectrophotometric analysis at ticagrelor's maximum, the filtrate (100 μL) was adequately diluted. Each measurement was performed three times ⁽⁹⁾.

Study of Inclusion efficiency

All ticagrelor inclusion complexes and physical mixtures (25 mg) were taken individually in 25-ml ml of volumetric flask. It was then thoroughly mixed with ten milliliters of methanol before being sonicated at room temperature for 30 minutes. The volume was filled to the proper level with methanol. To obtain the final drug concentration of 10 μg/ml and perform a spectrophotometric analysis for drug content, an aliquot from each solution was appropriately diluted with methanol. The formula was used to calculate inclusion efficiency ⁽¹⁵⁾.

$$\text{Inclusion efficiency} = \frac{\text{estimated \% drugcontent}}{\text{theoretical \% drugcontent}} \times 100 \quad \text{eq. 1}$$

Spectroscopy of Fourier Transform Infrared (FTIR)

The FT-IR spectra were obtained using a spectroscopy of Fourier transform infrared (FT-IR) Shimadzu 8300 from Japan. Potassium bromide was used to compress samples of pure Ticagrelor, Ticagrelor HPβCD complex of the chosen formula, and HPβCD. The gained spectrum ranged from 4000-400 cm⁻¹ in wave number ⁽¹⁶⁾⁽¹⁷⁾.

Differential Scanning Calorimetry (DSC)

When the drug is transformed into nanoparticles, DSC can be used to assess the drug's crystalline state as well as the compatibility between the drug and excipient. A system of automatic thermal analyzer determined the thermal properties of the same samples used in the FTIR studies. Five milligrams of precisely weighed samples were placed in aluminum pans that weren't hermetically sealed and heated at a rate of 20 °C per minute in comparison to a pan that was empty to cover a temperature range of 50 °C to 300 °C^{(18) (19)}.

3. RESULTS AND DISCUSSION

Characterizations of Ticagrelor

Determination of Melting Point

The Ticagrelor melted at 140-142° C. This study result that indicates the purity of drug powder has the sameness with the one reported ^(20,21).

λ Max Determination

The analysis of UV spectra of ticagrelor in methanol, Phosphate buffer pH 6.8 with 1% Brij. 35 and HCl buffer pH 1.2 with 1% Brij. 35, shows the same λ max at 254 nm, as illustrated in figure 8,9, and 10 respectively which like the published one ⁽¹¹⁾.

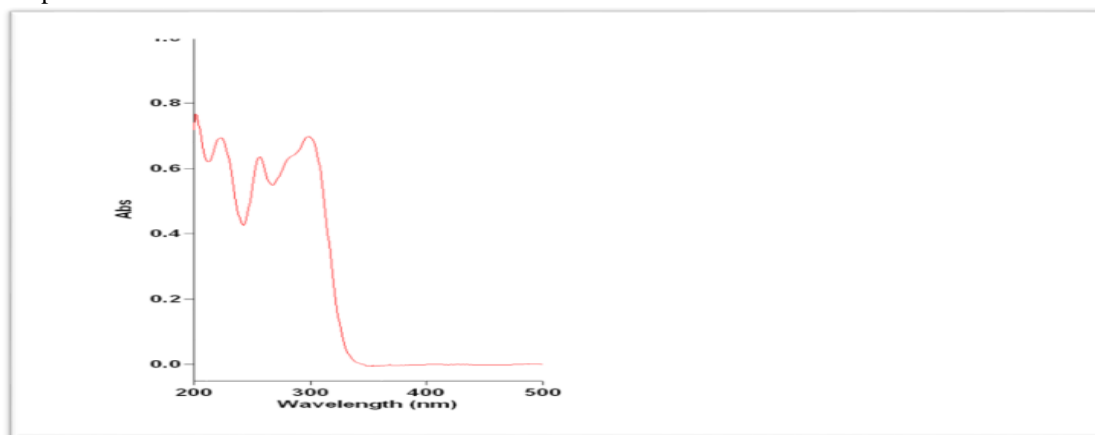


Figure 1: Ticagrelor in Methanol UV Spectrum

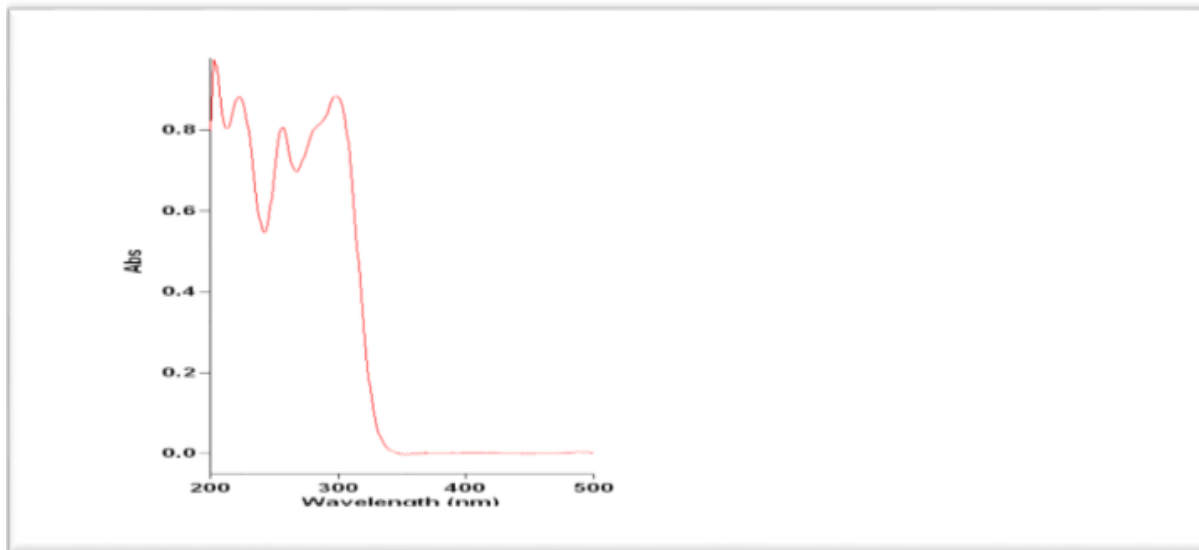


Figure 2: Ticagrelor in HCl Buffer pH 1.2 with 1 % Brij. 35 UV spectrum

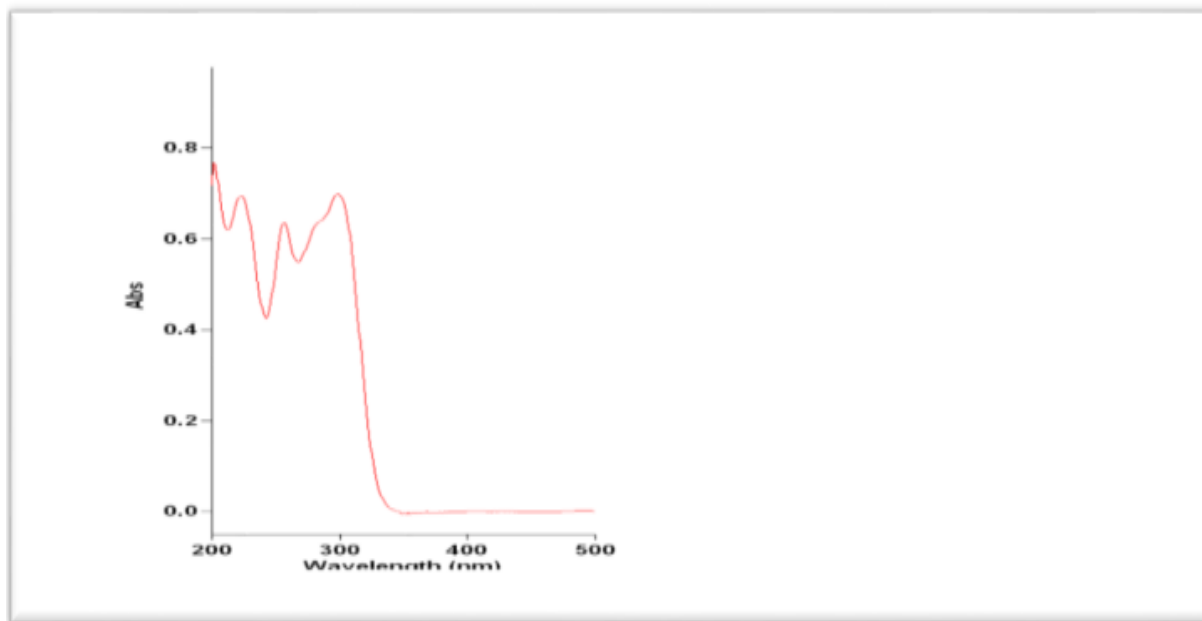


Figure 3: 1 % Brij. 35 in Phosphate Buffer pH 6.8 with 1 % Brij. 35 UV spectrum

Ticagrelor Calibration Curves

Figures 4, 5, 6, and 7 exhibit the Ticagrelor calibration curves in methanol, distilled water with 1% Brij. 35, HCl buffer pH 1.2 with 1% Brij. 35, and Phosphate buffer pH 6.8 with 1% Brij. 35. By plotting absorbance versus concentration in micrograms with a high coefficient of determination, a straight line was generated. It illustrates that, for the used range of attention, the calibration curve follows Beer's law ⁽¹⁰⁾.

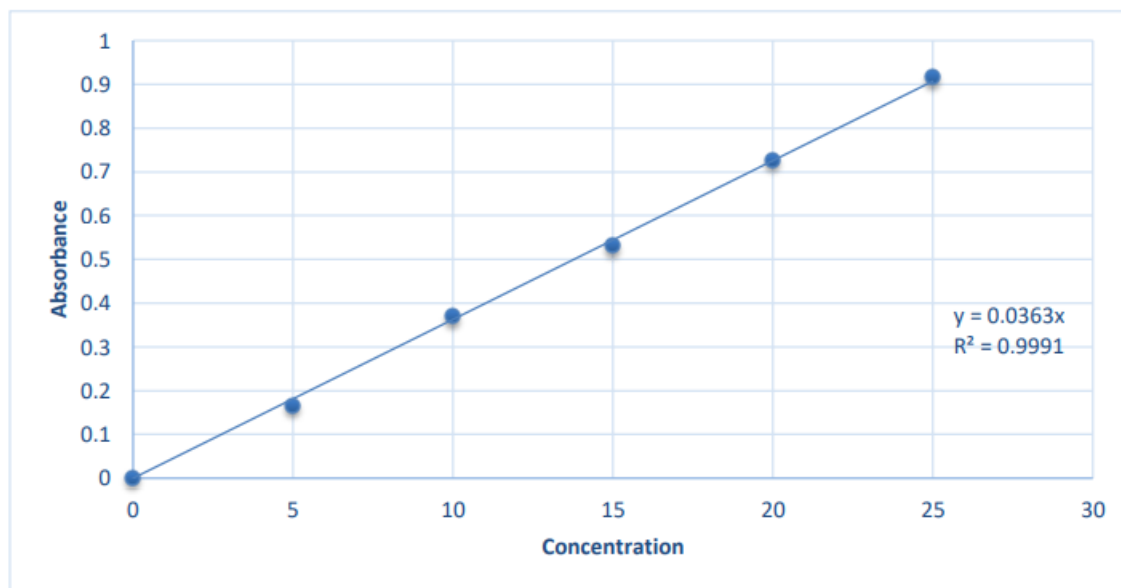


Figure 4: Ticagrelor Calibration Curve in Methanol

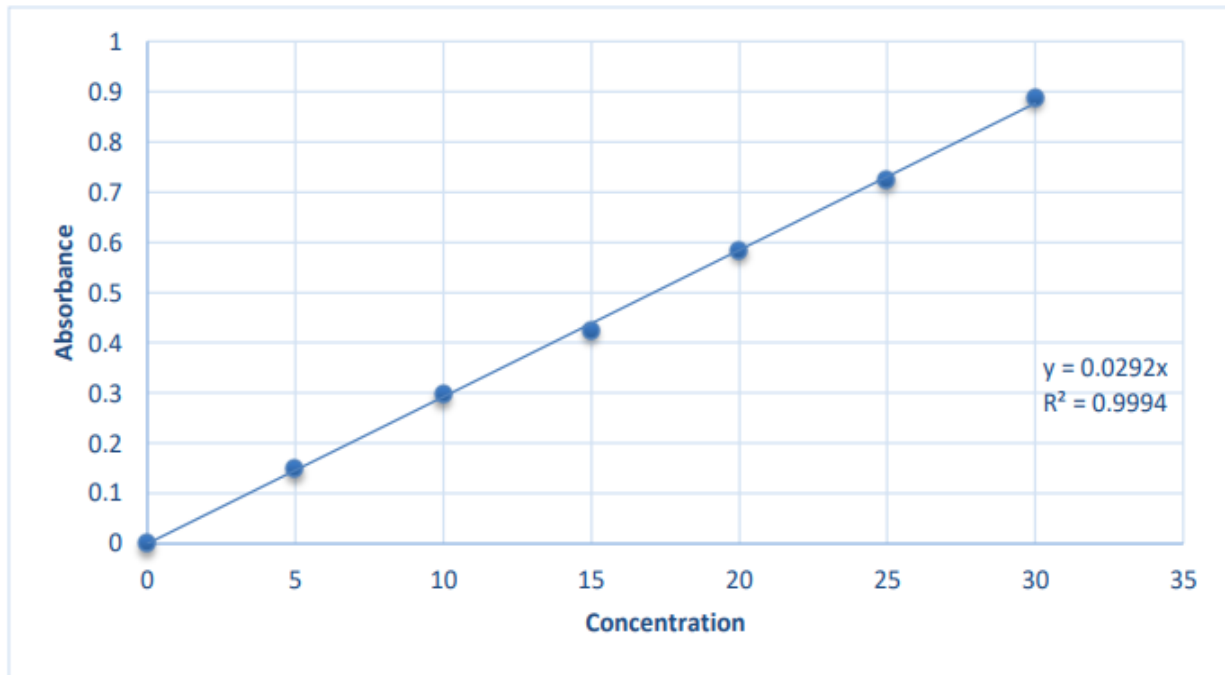


Figure 5: Ticagrelor Calibration curve in DW with 1 % Brij 35.

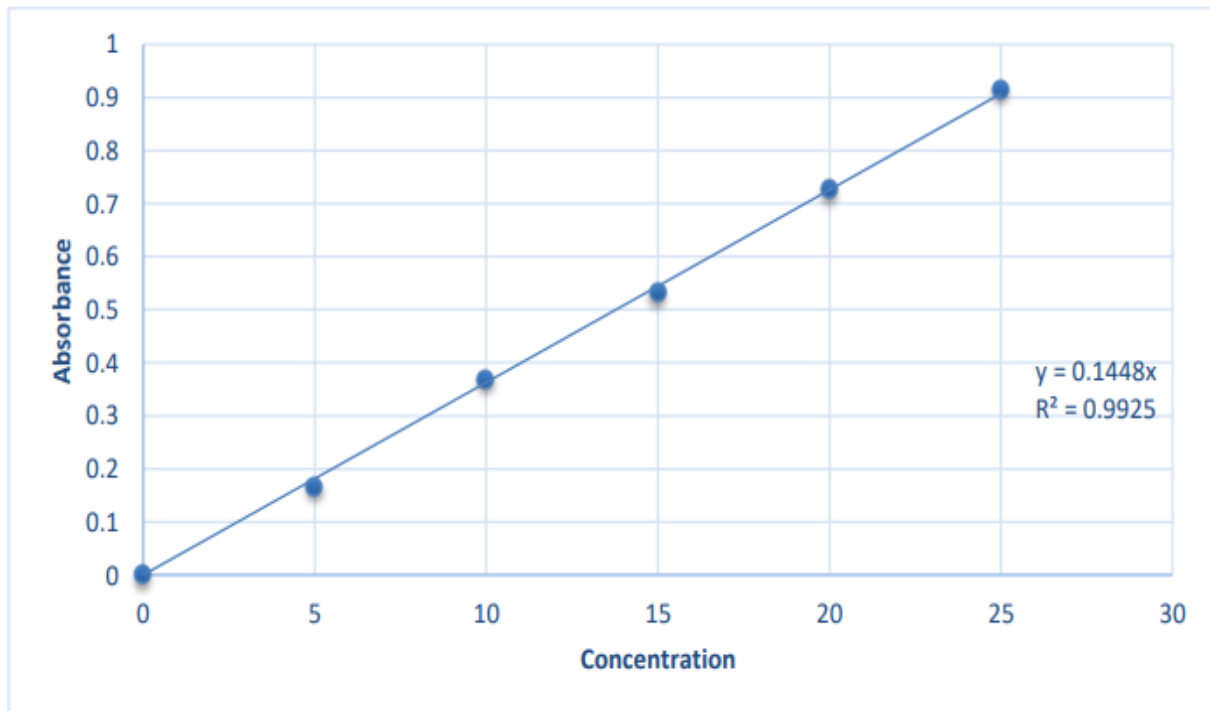


Figure 6: Ticagrelor in HCl Buffer pH 1.2 with 1 % Brij. 35 Calibration Curve

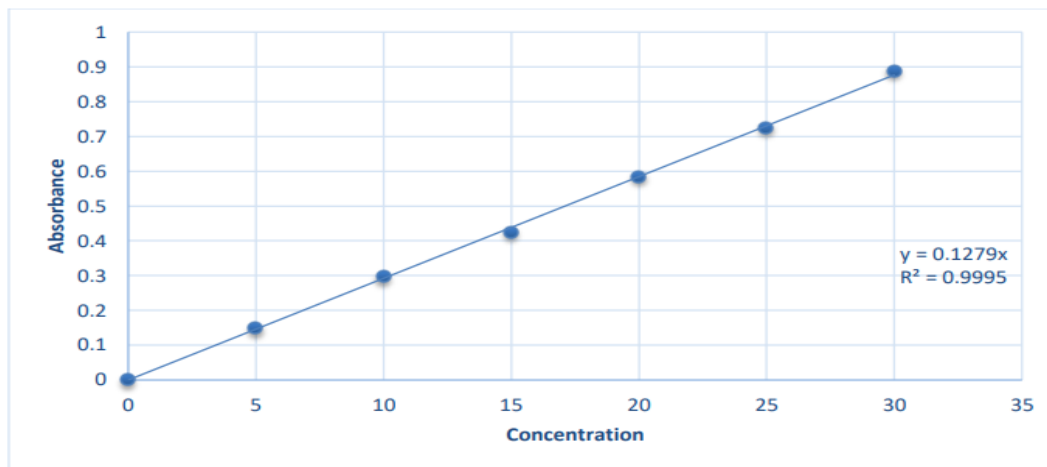


Figure 7: Ticagrelor in Phosphate Buffer pH 6.8 with 1 % Brij. 35 Calibration Curve

Ticagrelor Saturation Solubility in Different Media

Ticagrelor's poor solubility was defined to be consistent with published research, as shown in table (2); additionally, the findings demonstrate that it does not exemplify pH-dependent solubility. According to the Biopharmaceutics Classification System, ticagrelor categorized as having "low solubility low permeability" (BCS). Ticagrelor belongs to the BCS class IV of drugs ⁽²²⁾.

Table 2: Ticagrelor Saturation Solubility in Different Media

Solubility(mg/L)	Solvent
3.2	Distilled water
3.6	HCl solution pH 1.2
3.5	Buffer solution pH6.8

Study of Phase solubility

To investigate the solubility of the ticagrelor: HPβCD inclusion complex, a study of phase solubility was carried out. Figure 8 illustrates how ticagrelor's solubility increased proportionally as the concentration of HPβCD increased, with an AL-type curve ⁽²³⁾.

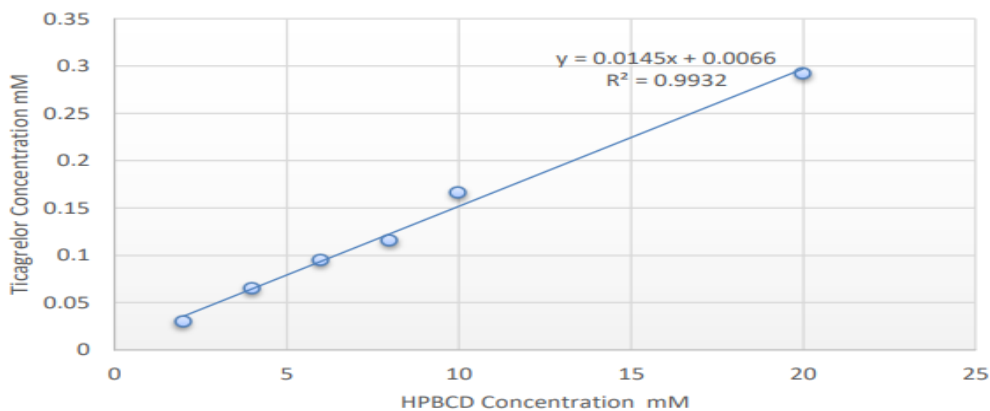


Figure 8: Ticagrelor Phase-Solubility Diagram and HPβCD in an Aqueous Solution

Study of Solubility

The HP β CD inclusion complexes/solubility values of ticagrelor and ticagrelor are listed in Table 3. No matter the preparation technique, adding HP β CD significantly (P 0.05) increased the solubility of ticagrelor. The solubility of ticagrelor may be elevated to varying degrees by each of the three preparation techniques. After physical trituration and kneading, the solvent evaporation process came up with the most significant solubility of ticagrelor in HP β CD (P 0.05). The solubility of ticagrelor/HCD prepared by kneading was 14 mg/L at a weight ratio of 1:1, which was roughly twice as much as that prepared by physical trituration (7 mg/L at a similar ratio)—as a result, kneading increased solubility better than physical trituration. Solvent evaporation generated the highest ticagrelor solubility out of the three preparation techniques at similar ratios of 28 mg/L. (24).

Table 3: Ticagrelor Inclusion Complex Formula Composition

Formula No.	Ticagrelor/ HP β CD (Ratio)	Solubility Mg/L
F1	1:1	7
F2	1:2	11
F3	1:4	12
F4	1:1	14
F5	1:2	20
F6	1:4	24
F7	1:1	28
F8	1:2	30
F9	1:4	41

Different preparation method Comparison

Physical trituration, kneading, and solvent evaporation is the easiest and quickest to get ready when the three preparation techniques are compared. HPCD could improve the solubility and dissolution of ticagrelor through a straightforward physical trituration procedure. The solubility of ticagrelor increased by about 2, 2.57, and 3.428 times with HP β CD (F1, F2, F3). When water was added to cyclodextrin, the kneading method produced a wet paste (25).

The addition of ticagrelor increased the paste's consistency. How simple it was to knead the paste depended on how much water was in it. Drying produced a dry, hard mass; milling was necessary to turn it into a finely powdered version of the complex (26). When the two approaches were contrasted, it was shown that the kneading approach resulted in a higher level of ticagrelorsolubilization than physical trituration. With HP β CD, ticagrelor's solubility increased by roughly 4, 4.569, and 6.285 times, respectively (F4, F5, F6). In the solvent evaporation process, ticagrelor was melted in methanol, an organic solvent, and HP β CD was dissolved in water. When the two solutions were mixed, they became miscible. Following drying, the complex was finely powdered. The solubility of ticagrelor increased by about 8.58, 9.43, and 12 times with HP β CD, respectively (F7, F8, F9) (27).

Study of Drug Compatibility with HP β CD

Infrared Spectroscopy Using Fourier Transforms

Operational parties interacting with the excipient while formulating are visible in the FT-IR spectra. Figure (9) displays the usual IR peak of ticagrelor. The spectra of the chosen formulas, F9 and HPCD, are shown in Figures (10) and (11). They illustrate the presence of the drug's central heights and show no apparent exchange between the medicine and polymer during the production of the nanoparticles (19).

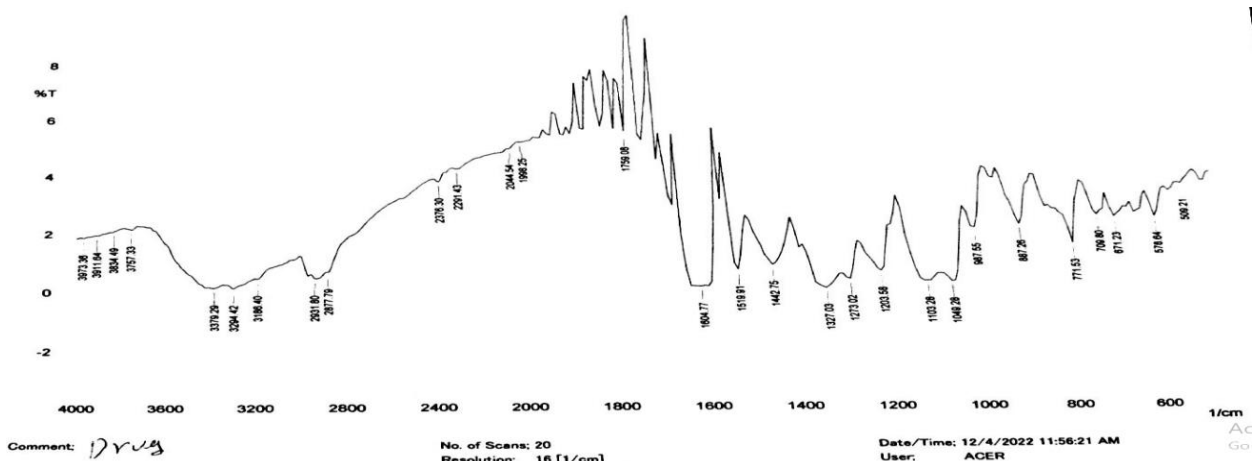


Figure 9: FTIR spectrum of ticagrelor

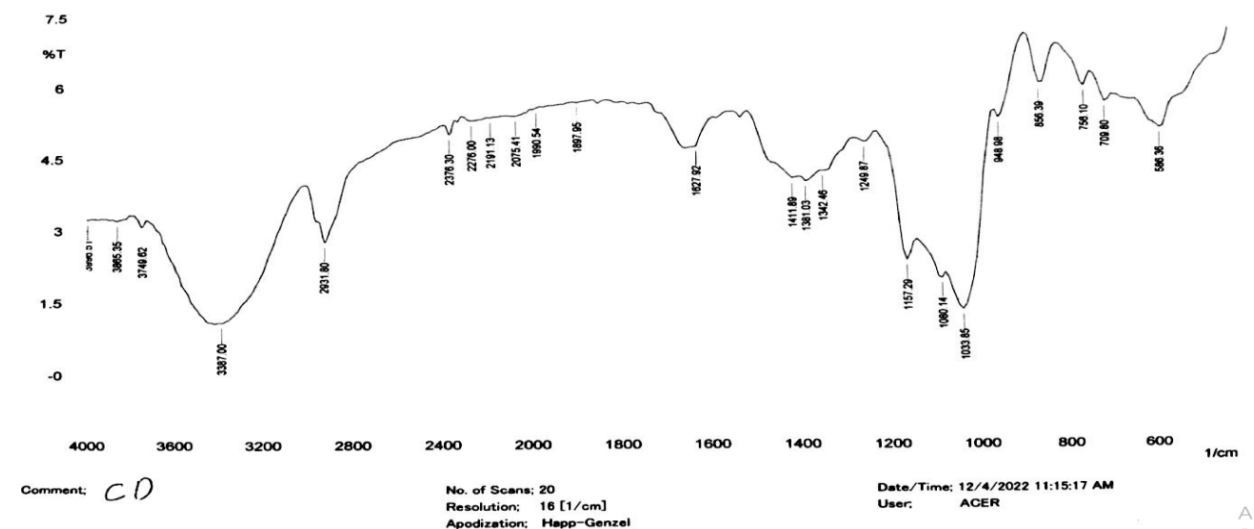


Figure 10: FTIR spectrum of HPβCD

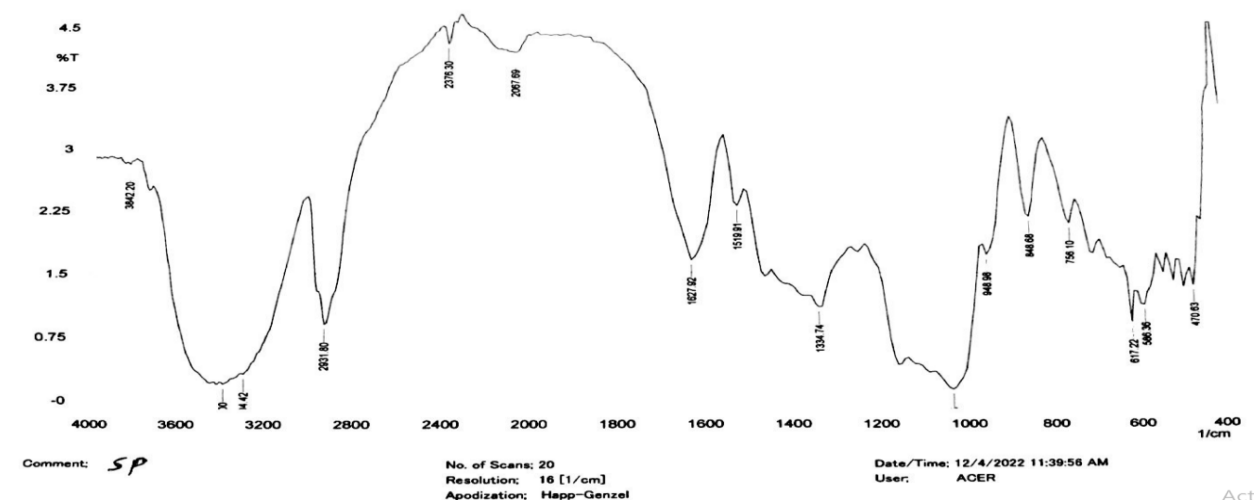


Figure 11: FTIR spectrum of ticagrelor - HPβCD complex

Differential Scanning Calorimetry (DSC)

As shown in figure, the DSC thermogram of ticagrelor displays a sharp endothermic peak correlating to its dissolving time, implying that the drug is in a pure crystalline state fig.(12). Despite the thermograms of the inclusion complex of of HP β CD and the chosen formula F9, as shown in figures (13) and (14) ⁽²⁰⁾.

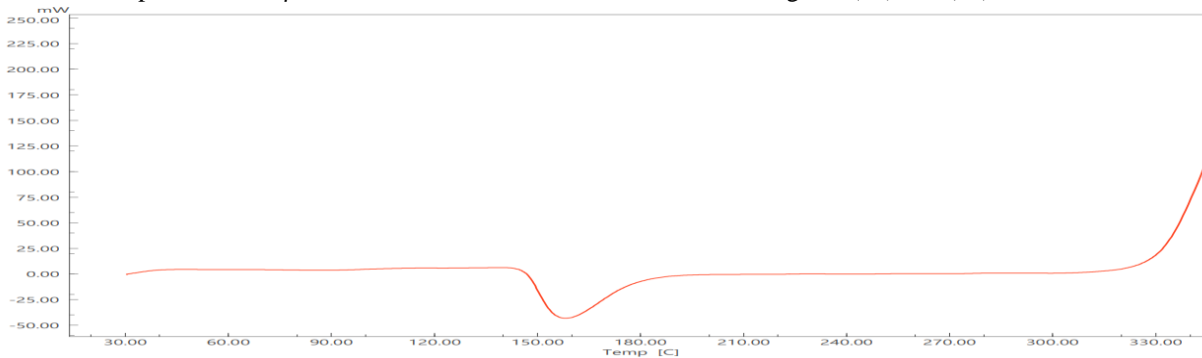


Figure 12: DSC thermogram of ticagrelor

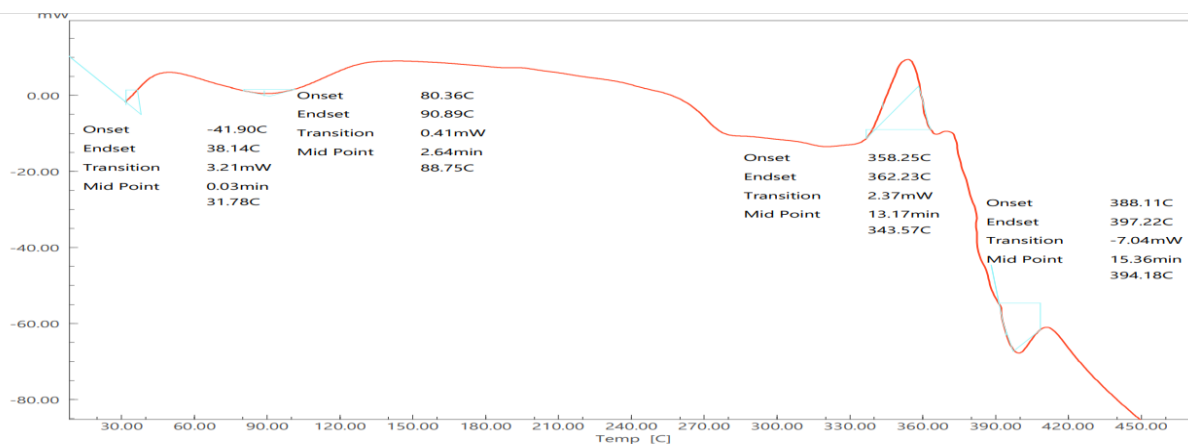


Figure 13: DSC thermogram of HP β CD

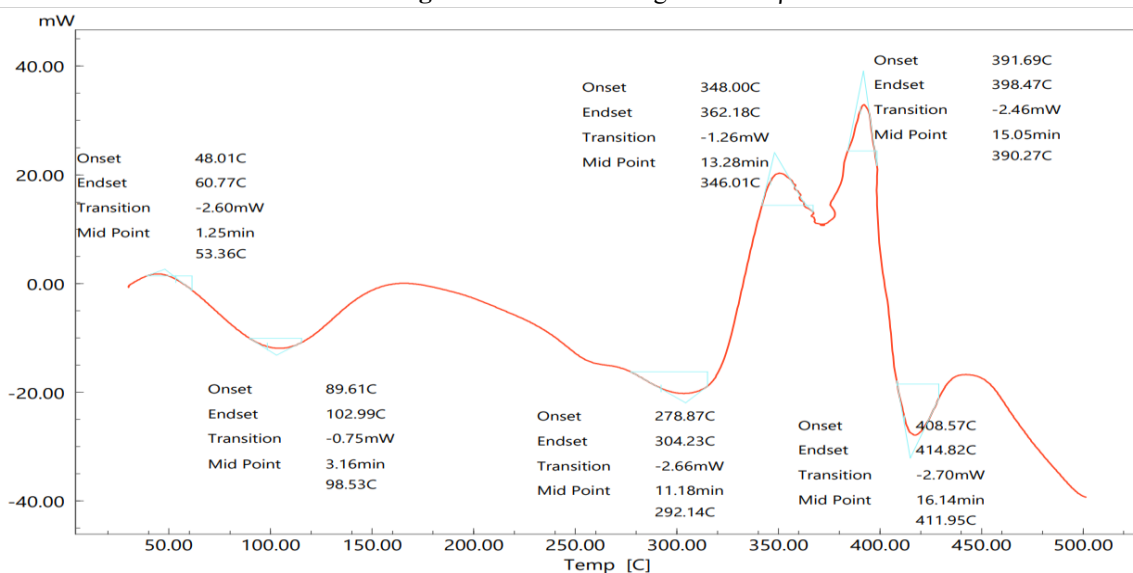


Figure 14: DSC thermogram of ticagrelor – HP β CD complex

CONCLUSION

The following conclusions based on the findings of the studies.

The three ticagrelor HPCD inclusion formulation process, complex physical trituration, kneading, and solvent evaporation might significantly raise ticagrelor's dissolution rate and solubility. The solvent evaporation process is the most efficient as ticagrelorsolubilization.

The optimum inclusion complex formula (F9) exhibits a tenfold increase in saturated solubility over pure drugs. DSC analysis of nanoparticles of a specific formula (F9) shows that the drug's crystallinity and amorphization are reduced.

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