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Enhancement of Ticagrelor solubility by comparative study of solid dispersion techniques: Hot melt extrusion and solvent evaporation

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Abstract
Ticagrelor (TCG) is a BCS Class IV antiplatelet agent that exhibits low aqueous solubility and poor intestinal permeability, both of which significantly limit its oral bioavailability. In an effort to overcome these biopharmaceutical challenges, the present research aimed to enhance the solubility and dissolution behavior of TCG through the solid dispersion (SD) technique. Five different polymers–Kollidon® VA64, Kollidon® K17, Kollidon® K30, Soluplus®, and PEG 6000–were selected based on their solubilizing potential and process compatibility. Solid dispersions were prepared using two widely employed methods: solvent evaporation and hot-melt extrusion (HME). The prepared SDs were subjected to comprehensive characterization to assess drug-polymer interactions, physical state, and in vitro dissolution performance. Among all tested combinations, the formulation based on Kollidon® VA64 prepared by HME demonstrated the most significant improvement in solubility and dissolution rate compared to the pure drug and physical mixtures. This optimized solid dispersion was further processed into immediate- release (IR) tablets using the direct compression method. Physicochemical analyses such as Differential Scanning Calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR), and X-ray Diffraction (XRD) confirmed the successful conversion of the drug to an amorphous state and the absence of any incompatibility with selected excipients.The study highlights the effectiveness of Kollidon® VA64 as a carrier and the advantages of the HME technique in improving drug release. The developed IR formulation presents a promising strategy for enhancing the oral bioavailability and therapeutic potential of Ticagrelor.
Keywords: *Solid dispersion, HME, Solubility enhancement, BCS Class IV, Solvent Evaporation.*

INTRODUCTION

One of the most widely used method of administration of dosage form is the oral route for delivering medications intended to have systemic effects through absorption in the gastrointestinal (GI) tract. Despite their preference, the oral route can be problematic and inefficient for many drugs due to various challenges. One major issue is limited drug absorption, which can lead to poor bioavailability (Fordtran JS etal. 1973.,) (Kobayashi M etal, 2001.,) (Erni et al. (1987). Several factors can restrict drug absorption from the GI tract, with the most significant being the drug's poor solubility in water and/or poor permeability through the GI membranes.When a drug is administered orally, it must initially solubilize in the git fluids before it can traverse to the membranes of the epithelial lining and reaches to the systemic circulation. Because generally drugs possessing the Inadequate aqueous solubility results in hampering the initial dissolution phase, and then results in limiting the extent of absorption. Similarly, insufficient permeability of the drug across git membranes concludes the difficulty in absorption, as the drug molecule is unable cross biological barriers to reach the bloodstream. To address these issues, pharmaceutical research focuses on two main areas to enhance the bioavailability of the poorly soluble drugs are increasing their aqueous and thus by rate of dissolution and enhancing the permeability of drugs that have difficulty passing through membranes. (Iqbal et al. (2002.,) (Habib et al. (2000)).Drugs which are classified under the BCS Class IV low solubility and low membrane permeability. Low solubility often results and related to the limited absorption which concludes the poor absorption into the body (Salunke et al. (2022). So, enhancing the drug's solubility and thus dissolution is now becoming a major concern, therefore to resolve this issue a key strategy is needed that aims to improve the bioavailability of such compounds. The selected drug, Ticagrelor is a BCS Class IV drug, characterized by having nature of both low solubility and low permeability, having an oral bioavailability measured approximately 36% (Teng et al. (2010)). As it is an antiplatelet drug that falls into the category of a reversible P2Y12 receptor antagonist, it acts by inhibiting binding of adenosine diphosphate (ADP) to the P2Y12 receptor, results into the inhibition of aggregation of platelets (Van Giezen et al. (2009.,) (Armstrong et al. (2014).,) (Husted et al. (2009)). Ticagrelor and its metabolites both have the antiplatelet platelet which are basically similar and also comparable in nature. Recently FDA

launches a notice which states that to exert the dual antiplatelet therapy, Ticagrelor is now given in combination with aspirin to decrease the risk of ACS-acute coronary syndromes like myocardial infarction and stroke (AstraZeneca et al. (2011)).Solid dispersions refer to those preparation in which poorly soluble drug is dispersed in an inert carrier or matrix to enhance the solubility and dissolution of the embedded molecular drug (Punitha et al. (2011)). It produces several benefits like enhancement of the wettability and dispersibility of the drug thus improving its dissolution rate Solid dispersion preparation usually consists of merging the drug having low solubility into an inert carrier or matrix or so that it results into enhancement of its physicochemical properties. This method significantly enhances the drug's potential to dissolve into the dispersion media via improving its wettability and convenience of dispersion. Solid dispersions are extensively having 4 types of classification according to the characteristics of the carrier material:
First-generation systems consist of the crystalline carriers.
Second-generation systems having the carriers which are amorphous in nature so that they can prevent the crystallization (Modica de Mohac et al. (2018)).
Third-generation basically focuses on carriers having surfactant nature or surfactants to improve the solubilization.
Fourth-generation systems consist of agents which are used to modify the release pattern and profile of the drug.
Among all different formulation techniques available, the two most widely accepted techniques of solid dispersions are solvent evaporation and hot-melt extrusion (Van den Mooter et al. (2006)). However, the exact mechanism by which solid dispersions works is not completely understood but various theories are proposed to demonstrate to enhance the solubility and dissolution of solid dispersion. Such theories are based on the reduction in the size of molecular particle so that its surface area will gradually increases that contributes to the enhancement of the dissolution behavior of the drug (Djukaj et al. (2022)).
Reduction in the size of particles has been shown to Particle size reduction is known to boost the drug absorption via enhancement of the overall area of surface exposed to the absorption site, hence enabling faster dissolution and uptake (Liversidge et al. (1995)). One of the most widely accepted techniques used is the state conversion of a drug from crystalline to an amorphous form; this method is commonly known as amorphization. This conversion usually takes place by change encounters in the crystal lattice and its perfectly order of the molecules arrangements which brings into the solubility increment due to the higher internal energy and disruption of their orderly arrangement into the randomization. Moreover, it is proven that if there is amplification in the surface wettability of the particles of drug it considerably affects its solubility. This is due to the greater interaction that occurs between the drug and dissolution media which in turns broadens the actual surface area which comes in its contact and boosts the process of dissolution (Malkawi et al. (2022)).In the present research, a comparative analysis of solid dispersion techniques has been conducted using two widely adopted methods: solvent evaporation and hot melt extrusion, both were selected by vast literature review and effectiveness in enhancing the solubility of poorly water-soluble drugs [17].The basic principle involves in Solvent evaporation is to dissolve the drugs and an appropriate polymer or carrier in a common organic solvent, then remove the solvent to create a solid dispersion while the basic concept of hot-melt extrusion is the melting, mixing, and extrusion principle. The barrels' high temperature causes the material to melt. The material is mixed uniformly and moved forward by the screw rotation. Extrusion is the final step, in which the melted material is pushed out of a die and cooled by passing it through chilled rollers before being gathered. The physical characteristics of the material undergo modification by extrusion (Davis et al. (2018)).Comparative studies are crucial in pharmaceutical research to determine the most effective methods for improving drug solubility and bioavailability. These studies help clarify the strengths and weaknesses of various techniques, offering insights into the best approaches for specific drugs. Our study is focused on the enhancement of the solubility of the Ticagrelor, a BCS Class IV drugs that have very low solubility and low permeability, so the technique used involves the formation of an amorphous solid dispersion which is a solid dispersion technique results into the enhancement of solubility and dissolution rate of the poorly soluble drug. Two techniques of solid dispersion are used namely Solvent evaporation and Hot-melt extrusion technique (HME). Out of them one is HME technique used further for the formulation preparation due to its better results outcome results in greater increase in solubility and hence effective in achieving the improved bioavailability as compared to the solvent evaporation. Basic concept underlying is the conversion of the drug from its crystalline form to its amorphous form via integrating the drug into a suitable polymer matrix to overcome the solubility and dissolution limitations.

MATERIALS AND METHODS MATERIALS

S. No	Ingredients	Manufacturer
1	Ticagrelor	Sun Pharmaceutical Industries
2	Kollidon VA64	BASF
3	Soluplus	BASF
4	PEG 6000	Clariant
5	Kollidon K17	BASF
6	Kollidon K30	BASF

The Laboratory facility, both the drug and polymers utilized in this study were of good analytical grade and materials were procured from the Research and Development Facility of the Sun Pharmaceuticals Pvt. Ltd., located at Gurugram, Haryana.

METHODS

Selection of Polymer

The polymers were selected on the basis of vast review literature. The criteria were set up to select the polymers that it should not modify the release pattern of the drug as the formulation is meant to be an immediate-release dosage form, the melting temperature of the selected polymers must not be too high or too low so that it can facilitate the processing of hot-melt extrusion. The hot-melt process is a solvent free process. So, a suitable solvent was selected that possess high solubility, non- reactive, non- toxic to the human and liquid polymer/plasticizers such as polysorbate were not to be selected. Waxy solids were removed from the selection criteria as they did not mix properly.

Hot stage microscopy

Hot stage microscopy used smart components like a microscope made by (Nikon Eclipse E600 POL), heating system and cooling system, and the digital camera (Moticam 1080)—were launched. Live characterization of sample was done by the attached Motic Image Plus software in the hot stage microscopy system connected to the computer (Šimek et al. (2014)). The sample holder was perfectly cleaned before loading the sample, and then a small amount of sample was positioned on the plate, by gently removing the excess amount through the brush. The holder was then placed on the hot stage system, and then the magnification of the microscope was configured to 10X. The heating unit was automatically set to gradually increase the temperature by the rate of 10°C per minute, and then the nature of the sample was visually monitored in real-time. The melting point was determined and noted down on the basis that their transition occurs during heating.

Solvent Evaporation

Solvent evaporation method is done by using the oven that was preheated at the temperature below the melting point of drug and all polymers used. The temperature in the oven was maintained at 80°C for all polymers except PEG 6000, for which the temperature was set at 30°C to prevent thermal degradation.

Hot-melt Extrusion

The hot-melt extrusion process was initiated by launching the extruder unit (Steer Engineering, Model:
Omicron 12P), and then zone and die heating systems were turned on. After That the chiller was started in automatic mode to ensure uniform cooling. The temperature of the adjacent zones should not variate at maximum 40°C by each other so to ensure this firstly the polymer's melting point was estimated and then temperature settings for the screw zones and die were set up. Moreover, the gap between the actual operating temperature and the preconfigured value should not deviate within 10°C.The screw rotations were not started until the barrel zones reached their set temperatures. The screw rotation speed was increased gradually, first in increments of 1 RPM to reach 20 RPM, after that direct jump of 20 RPM intervals unless the speed of 100 RPM was achieved. The mixture of the prepared solid dispersion of drug and polymer was firstly introduced into the feed hopper manually by using a spatula. When this mixture approached the die section, the vacuum of the instrument was turned on to remove the excess trapped air. The extrudes are then collected by the end of this process using the attached conveyor belt (Yadav et al. (2021)).

Preparation of trial batches for Solvent Evaporation and HME

The formulation then utilized equal proportions of 1:1 drug to polymer ratio for both the methods in the same ratio. After the suitable polymer was selected the level of the polymer is optimized to proceed for the optimization batches in the higher ratios 1:3 and 1:5. To enhance the flow property and processability of the solid dispersion blend in the hot melt

extruder, Cabosil used a glidant.

Solvent Evaporation

For solvent evaporation equal parts of TCG and each polymer were dissolved in an appropriate volume of methanol. This process utilized a mechanical stirrer to ensure thorough mixing and uniform dissolution. The mechanical stirring was critical to achieving a homogeneous solution, which is essential for the consistent formation of solid dispersions. Then, the homogeneous solution was then transferred to a vacuum oven. The vacuum environment facilitated the efficient removal of methanol through evaporation, leaving behind the solid dispersions. This step was carefully monitored to ensure complete solvent removal, which is crucial for the stability and performance of the solid dispersions. Following the complete removal of the solvent, the resulting solid dispersions were collected and processed further. The solid mass was crushed in a mortar to break down any large aggregates. This step ensured that the solid dispersions were in a manageable form for subsequent processing and analysis. The crushed dispersions were then sieved using ASTM #60 to obtain a uniform particle size distribution, which is important for consistent dissolution behavior. The prepared solid dispersions were then subjected to further research and analysis to evaluate their solubility and dissolution enhancement properties.

Hot melt extrusion

Dispensed the required amount of API and each excipient in a polybag. Transferred all of the dispensed material to a larger polybag and mixed it in the polybag mimicking the V- cone blender for a duration of 5 minutes. All the batches were formulated using the hot-melt extruder.For the preliminary batches, the drug and polymers were combined in the ratio of 1:1. Following this, the most appropriate polymer was identified that meets all the required criteria and gradually results in increased solubility. The concentration of the chosen polymer was then optimized and subsequent batches of formulation were prepared in the ratio of 1:3 and 1:5. To improvise the blend's flow properties for better processing in the hot-melt extruder, Cabosil was incorporated in the formulation having the function of glidant.

Screening Batches for TCG Solid Dispersions by Solvent Evaporation

S. No	Ingredients	Screening Batches (in gm)				
		SD1	SD2	SD3	SD4	SD5
1.	TCG	1	1	1	1	1
2.	Povidone VA64	1	-	-	-	-
3.	Soluplus	-	1	-	-	-
4.	PEG 6000	-	-	1	-	-
5.	K17	-	-	-	1	-
6.	K30	-	-	-	-	1

Unit Formula of Trial Batches for TCG Solid Dispersions Prepared by Hot Melt Extrusion (HME)

TCG Solid Dispersions Prepared by Hot Melt Extrusion (HME)					
S. No	Ingredients	Drug: Polymer Ratio (1:1)			
		SD8	SD9	SD10	SD11
		Quantity/Unit (mg)	Quantity/Unit (mg)	Quantity/Unit (mg)	Quantity/Unit (mg)
1	TCG	90	90	90	90
2	Colloidal Silicon Dioxide	4.6	4.6	4.6	4.6
3	Kollidon VA64	90	-	-	-
4	PEG 6000	-	90	-	-
5	Kollidon17	-	-	90	-

		Temperature (in °C)								
S.No.	Solid Dispersion	Polymers	Zone- 1	Zone- 2	Zone- 3	Zone- 4	Zone- 5	Zone- 6	Zone- 7	Die Zone
1.	SD8	Kollidon VA64	50	70	90	105	130	180	180	180
2.	SD9	PEG 6000	30	30	40	55	70	85	100	100
3.	SD10	Kollidon17	60	70	90	120	140	140	165	170
4.	SD11	Kollidon30	60	70	100	120	145	160	180	180

Characterization FTIR

FTIR plays an important role in the characterization of the drug-excipients interactions. It is the most widely and commonly used technique for the analysis of the materials. Drug and its mixture with polymers were taken around 2-3 mg and then mixed with 250mg of pure KBr which was previously dried at temperature around 300-400^{o}C. the pellets formed by applying the pressure of 10 tons force- weight and then scanned over range of 4000-400cm-1 by using Shimadzu, FTIR-1700 Japan (Forato et al. (1998)).

XRD

X-Ray Diffraction usually known as XRD is the non- destructive technique and most widely used to determine the crystallinity in the structure of material such as phases, defects, orientation of the materials (El Bourakadi et al. (2021)). XRD based on principle of Bragg's law ($n\lambda = 2d\sin\theta$) where λ is the wavelength of the incident X-Rays, d is the interplanar space,θ is the angle of incidence.This method basically used a monochromatic beam of X-Rays that is aimed at the sample, these beams reflected back and generate a diffraction pattern which is unique and identifies to the individual material. It generally determine about the percentage crystallinity that is contained in any material. By getting an XRD graph, it can be easily interpreted that amorphous regions of a sample usually have broad peaks while crystalline regions have sharp peaks (Patel et al. (2017)).

Solubility studies

Ticagrelor along with its prepared batches of solid dispersions via solvent evaporation and hot melt extrusion techniques were taken 50 mg and the transferred to 10 ml of media selected. Solubility assessment of the Ticagrelor pure drug and its respective solid dispersions was done in 0.1 N HCl buffer, acetate buffer at pH 4.5, phosphate buffer at pH 6.8 and water to evaluate their performance at varying physiological conditions of body.The dispersions were kept at 150 rpm for 24hrs in a bio shaker maintaining the temperature 37 °C. after 24 hrs the samples were collected via using a 0.45 µm syringe filter. The collected filtrate then used for scanning in UV Spectrophotometer (Shimadzu UV 1800) in appropriate dilutions. All these samples were prepared in triplicate for the accuracy and precision of the results.

Stability study

A pharmaceutical drug product may undergo various changes on storing as in appearance, consistency, CU, clarity of the solution, variation in moisture contents limit, effect of particle size and shape, pH, and also the physical condition of packaging material, thus affecting its stability. So, to ensure that no such change has occurred in the formulation, we need to conduct the stability testing of the final finished product. The optimized batch of TCG formulation packed in blisters and kept in humidity condition i.e., 40± 2°C/75 ± 5 RH and 25± 2 ° C/60 ± 5 RH conditions for 1 months. For the purpose of analysing the drug content, the sample was tested once for three months. Q1C stability tests were executed as per ICH guidelines for the most optimum formulation. Stability studies were conducted under 2 conditions accelerated (40± 2 °C/75 ± 5 % RH) and also at long term (25 ± 2 ° C/60 ± 5% RH). Samples were assessed for the analyzing the drug content, and in-vitro dissolution behavior, once the experiments were completed.

Dissolution study

For the in vitro dissolution study, USP dissolution II a paddle type apparatus is employed under the following predefined conditions such as the OGD media 0.2%w/v polysorbate 80 in water with 900ml of volume was selected. The apparatus was operated at the 75rpm with maintain a standard temperature at 37 ± 0.5°C. 7ml of sample was withdrawn at each pre-set points 5, 10, 15, 30, 45, and 60 minutes with immediate replacement by fresh dissolution media to measure the drug

release profile by using cuvette of 2mm size.

Analysis Method- The withdrawn samples were filtered, and the amount of drug dissolved was quantified using UV spectrophotometer (Shimadzu UV 1800) at the appropriate wavelength. Each same was then filtered through membrane filter (0.4µ). The samples were analyzed for the drug release by measuring the absorbance at 301nm using UV- visible spectrophotometer after suitable dilutions having dilution factor 5.

RESULT AND DISCUSSION

Selection of polymer and plasticizer

Polymers were selected on the basis of the criteria mentioned above, that aligned with the drug's thermal compatibility and stability. The selected combinations of polymers result in excellent performance and suitability for the intended formulation. Based on the mentioned criteria, below are the polymers selected:

Polymers: Kollidon 17, Koliidon 30, Polyethylene Glycol 6000, Kollidon VA64

Soluplus is only selected for Solvent Evaporation and not selected for Hot Melt Extrusion Method as this polymer is previously used for this technique.

Hot-stage microscopy

The thermal nature of the API and Polymers were analyzed by using hot-stage microscopy and the observations are detailed in table below:

Table 1: Melting point analysis by hot-stage microscopy

S. No.	Ingredient	M.P. (in °C) (Literature)	M.P. (in °C) (Observed)	Selected for work
1.	TCG	140 -142	144	Yes
2.	Kollidon 17	129-130	145	Yes
3.	Koliidon 30	131 (Tg)	134 (Tg)	Yes
4.	Polyethylene Glycol 6000	58 – 63	70	Yes
5.	Kollidon VA64	140	160	Yes

Solubility studies

The model drug was found to have great solubility in methanol but practically insoluble in 0.1 N HCl, and buffer solutions of pH 4.5, 6.8 and water. Notably, the solid dispersion (screening batch) prepared via both the techniques showed the significant enhancement in solubility in water compared to other media. presents the solubility profiles of the solid dispersion in 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer along with the respective fold increase relative to the pure API and Table 7 shows the data of solubility of the optimization batches of solvent evaporation and HME respectively in various selected media. Both the tables show the increase in solubility of the optimization batches in water as compared to the screening batches solubility. To conform the media that enhance the solubility, a further repeat of all the buffers again as done for screening batches. Results show the water is suitable media that results in enhancement of solubility of both techniques solid dispersion.Based on the solubility data of TCG: Kollidon VA64 solid dispersions in different buffer media of solvent evaporation from Table 6, the optimal polymer ratios vary depending on the pH of the medium. In pH 0.1N HCl buffer, the solubility increases with the polymer ratio, peaking at the 1:5 ratio (SD7) with a solubility of 0.8954 mg/ml. Therefore, the optimal ratio for acidic conditions is 1:5. In pH 4.5 acetate buffer, the solubility reaches its highest value at the 1:5 ratio (SD7) with a solubility of 0.7653 mg/ml. Hence, the optimal ratio for mildly acidic conditions is 1:5. For pH 6.8 phosphate buffer, the highest solubility is observed at the 1:3 ratio (SD6), with a solubility of 0.2547 mg/ml. Therefore, the optimal ratio for slightly basic conditions is 1:3.Finally, in water, the solubility shows the most significant enhancement at the 1:5 ratio (SD7), with a solubility of 4.435 mg/ml. Thus, the optimal ratio for aqueous environments is also 1:5.

Based on the solubility data across various buffer media for Hot Melt Extrusion from Table 7, the optimal polymer and ratio for the final formulation of TCG solid dispersions can be identified as follows: In pH 0.1N HCl Buffer: The 1:3 ratio (TCG: Kollidon VA64) showed the highest solubility of 0.4367 mg/ml, making it the most effective formulation for acidic conditions. In pH 4.5 Acetate Buffer: The 1:5 ratio (TCG: Kollidon VA64) achieved the highest solubility of 0.6974

mg/ml, suggesting it performs best in mildly acidic environments. In pH 6.8 Phosphate Buffer: The 1:5 ratio (TCG: Kollidon VA64) resulted in the highest solubility of 0.8932 mg/ml, proving to be the most effective in neutral to slightly basic conditions. In Water: The 1:3 ratio (TCG: Kollidon VA64) provided the highest solubility of 1.803 mg/ml, indicating that this formulation works best in an aqueous environment.

Overall, Kollidon VA64 consistently improves TCG solubility across different pH conditions, with the1:5 ratio being the most effective in pH 6.8 Phosphate buffer and pH 4.5 Acetate buffer, and the 1:3 ratio showing the best performance in pH 0.1N HCl buffer and water. If a single formulation is to be selected for the final product, the 1:3 ratio in water provides the highest overall solubility and would be the most suitable choice for the final formulation.

Solubility of Model drug in different solvent media

S. No.	Solvent System	Solubility (mg/ml)
1.	Water	0.0044
2.	0.1 N HCl	0.0274
3.	pH 4.5 Acetate buffer	0.0293
4.	pH 6.8 Phosphate buffer	0.0044

Solubility Comparison of TCG Solid Dispersions-Screening Batches by Solvent Evaporation with Various Polymers in Different Buffer Media

S.No.	Screening Batches (1:1)	Solubility (mg/ml)			
		pH 0.1N HCl Buffer	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer	Water
	TCG (API)	0.0245	0.0193	0.0269	0.0469
SD1	TCG: Kollidon VA64	0.0892	0.0852	0.1862	0.2589
SD2	TCG: Soluplus	0.0276	0.0591	0.0299	0.0578
SD3	TCG: PEG 6000	0.0675	0.0245	0.1346	0.0543
SD4	TCG: Kollidon17	0.0342	0.0278	0.0945	0.0574
SD5	TCG: Kollidon30	0.0492	0.0575	0.0334	0.0454

Solubility Analysis Of TCG: Kollidon VA64 Solid Dispersions					
S.No.	Drug: Polymer Ratio	Solubility (mg/ml) in Different Buffer Media			
		Ph 0.1N HCl	pH 4.5 Acetate	pH 6.8 Phosphate	water
SD6	[1:3]	0.1589	0.1654	0.2547	0.8051
SD7	[1:5]	0.8954	0.7653	0.4645	1.035

Solubility of Trial Batches of TCG Solid Dispersions Prepared by Hot Melt Extrusion (1:1 Drug- to-Polymer Ratio) in Different Buffer Media

Solubility of Trial Batches of TCG Solid Dispersions Prepared by Hot Melt Extrusion					
S.No.	Screening Batches (1:1)	Solubility (mg/ml)			
		pH 0.1N HCl Buffer	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer	Water
	TCG (API)	0.0245	0.0193	0.0269	0.0469
SD8	TCG: Povidone VA64	0.1737	0.1676	0.2452	0.4634
SD9	TCG: PEG 6000	0.1592	0.1234	0.1432	0.1264
SD10	TCG: K17	0.1059	0.0924	0.2882	0.3218
SD11	TCG: K30	0.0735	0.0353	0.0931	0.1132

Overall Comparative Solubility of TCG: Kollidon VA64 Solid Dispersions by HME in Different Buffer Media

Solubility Analysis Of TCG: Kollidon VA64 Solid Dispersions					
S.No.	Drug: Polymer Ratio				
		pH 0.1N HCl Buffer	pH 4.5 Acetate Buffer	pH 6.8 Phosphate Buffer	water
SD12	[1:3]	0.4367	0.3469	0.2398	1.803
SD13	[1:5]	0.1965	0.6974	0.8932	1.029

Tablet Thickness and Hardness for TCG IR Tablets (n=10)

Tablets (n=10)	Thickness (mm)	Hardness (kp)
1	4.91	8.1
2	4.86	8.5
3	4.85	9.0
4	4.83	8.6
5	4.81	9.1
6	4.86	8.2
7	4.91	8.8
8	4.87	9.1
9	4.82	8.7
10	4.88	8.4

Table No.	Weight (mg)
1	400.5
2	399.9
3	398.5
4	400.7
5	400.3
6	400.7
7	400.4
8	399.3
9	399.8
10	400

Tablet Weight and Deviation from Average for TCG IR Tablets (n=10)

Stability study

Physical observation of final optimized formulation when kept at Accelerated (40± 2°C/75 ± 5 % RH) and long term at 25 ± 2 ° C/60 ± 5% RH)

S.no	Parameter	Initial	(40± 2 °C/75 ± 5 % RH)	25 ± 2 ° C/60 ± 5% RH).
1	Pink to off pink, Oval shaped tablet, with 776 embossing on oneside and plane from other side of the tablet	Pink to off pink	No change	No change

2	Assay	Drug A	Drug B	Drug A	Drug B	Drug A	Drug B
		99.89	100	99.9	99.9	100	99.99

Table. 7.46. Physical observation of optimized formulation initial after 3-month stability

DISSOLUTION STUDY

Dissolution of optimized batches IR tablets in 0.2% Polysorbate 80 in water.

Tablets formed by direct compression method and set up for comparative dissolution study with reference marketed product. SD12 was selected for final tablet formulation. In house formulated IR tablet release profile was observed in comparison of reference marketed formulation over a period of 90- minutes. Varying concentrations of sodium starch glycolate (SSG) and without SSG formulations were used to confirm that the release was due to the formulation matrix or specifically influenced by the superdisintegrant (SSG), a systematic optimization study was performed. The drug release for the market formulation at 15 minutes observed 35.8% (0 mg SSG), 38.4% (2 mg), 39.4% (4 mg), 40.9% (6 mg), and 41.2% (8 mg), respectively. This clearly shows the significant role of SSG in improving the drug disintegration and thus release profile. This similar trend is shown by the formulation at all time points.

However, when 8mg SSG was used, the improvement in dissolution profile reaches to minimal or slightly reduced (e.g., 99.5% at 60 minutes), suggesting a plateau, saturated or potential negative effect due to excessive swelling. On the basis of this observation, 6 mg of SSG was selected as the optimal concentration for final formulation, provides the most suitable balance between rapid drug release and formulation stability. As compared to the market formulation, which gradually released the drug over 90 minutes, the optimized IR formulations, particularly with 6 mg SSG, demonstrated a significantly faster and more efficient release profile, indicating its potential for improved therapeutic response and patient compliance.

Table: % drug release of final formulation in 0.2% Polysorbate-80 in water

% drug release of final formulation in 0.2% Polysorbate-80 in water						
Time (minutes)	**% Drug Dissolved (Market Formulation)**	**% Drug Dissolved (IR Product without SSG)**	**% Drug Dissolved (IR Product with 2mg SSG)**	**% Drug Dissolved (IR Product with 4mg SSG)**	**% Drug Dissolved (IR Product with 6mg SSG)**	**% Drug Dissolved (IR Product with 8mg SSG)**
15	28.2	35.8	38.4	39.4	40.9	41.2
30	62.4	68.3	67.8	70.8	72.2	71.9
45	75.7	87.3	88.5	90.3	92.9	93.8
60	80.3	90.3	93.5	96.2	99.9	99.5
75	84.6	94.3	94.9	98.3	100.3	102.9
90	95.7	98.5	98.9	99.1	101.7	103.9

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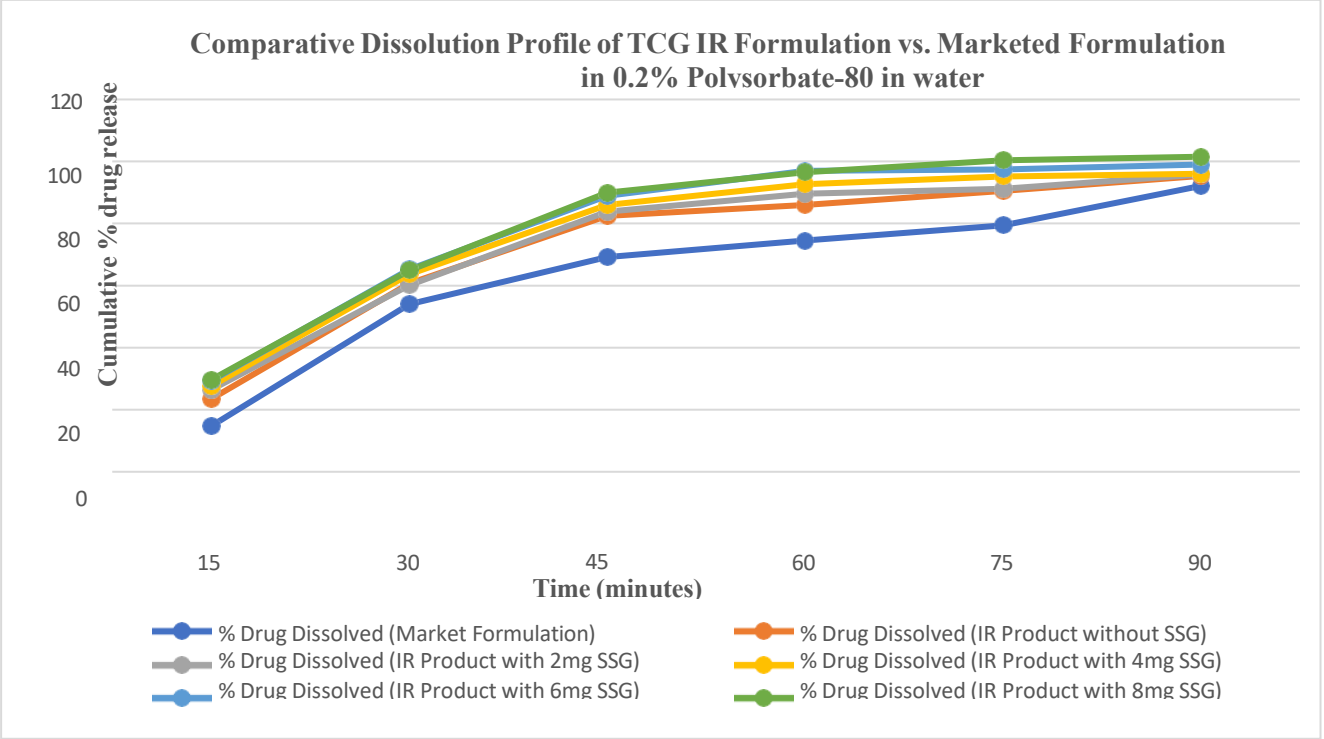
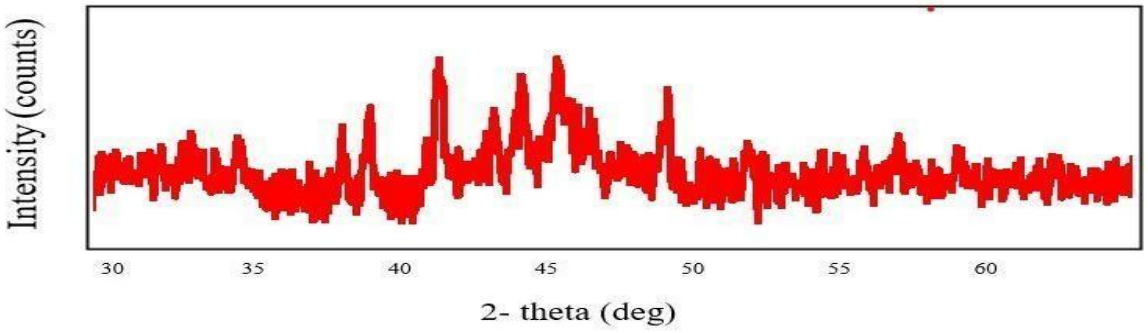


ray Diffraction (XRD) Analysis

The XRD pattern of the final optimized solid dispersion (API:Kollidon® VA64 in 1:3 ratio) prepared by hot-melt extrusion (HME) shows a broad halo and absence of sharp crystalline peaks in the 2θ range of 30° to 65°. This indicates a significant reduction in crystallinity and suggests successful transformation of the API into an amorphous form.

The lack of distinct diffraction peaks confirms molecular dispersion of the API within the polymer matrix. Kollidon VA64 likely played a key role in stabilizing the amorphous state, which is beneficial for enhancing solubility and dissolution. This reduction in crystallinity aligns with the goal of improving the bioavailability of poorly soluble drugs through solid dispersion systems.



CONCLUSION

This study confirms that **Kollidon VA64** is a highly effective polymer for enhancing the solubility of **Ticagrelor (TCG)**, with the solubility improvement varying depending on both the **polymer ratio** and **media** used. Based on the findings, the following key observations can be made:

Best Polymer: **Kollidon VA64** is the **most effective polymer** for enhancing **Ticagrelor's solubility**. Its performance across various ratios (1:3 and 1:5) in both **Solvent Evaporation** and **Hot Melt Extrusion** techniques suggests that it can be successfully used for solubility enhancement in multiple environments. **Kollidon VA64** provides an ideal balance between improving **Ticagrelor's** solubility and maintaining the stability of the drug-polymer system.

Best Media: **Water** emerged as the **most favorable medium** for solubility enhancement, particularly in the **Hot Melt Extrusion** technique. This is evidenced by the highest solubility of **1.803 mg/ml** achieved at the **1:3 ratio** (SD12) in **water**. However, for targeted formulations in **acidic** or **mildly acidic environments**, both **pH 0.1 N HCl Buffer** and **pH 4.5**

Acetate Buffer provided optimal results when combined with the **1:5 ratio** (SD7 for Solvent Evaporation and SD13 for HME). **pH 6.8 Phosphate Buffer** also proved to be effective in **neutral conditions**, where the **1:5 ratio** again yielded the best solubility.

Best Method: Both **Solvent Evaporation** and **Hot Melt Extrusion** proved effective in improving **Ticagrelor's** solubility. However, **Hot Melt Extrusion** was particularly beneficial in enhancing solubility in **water** and **mildly acidic conditions**. For **acidic conditions**, **Solvent Evaporation** at a **1:5 ratio** yielded the best solubility

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