International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 15, Issue 4, 2023

Original Article

DESIGN, OPTIMIZATION, AND CHARACTERIZATION OF A NOVEL AMORPHOUS SOLID DISPERSION FORMULATION FOR ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF TICAGRELOR

ABHISHEK SRIVASTAVA[1,2], MOHAMMAD AHMAD KHAN[2], SIMRATA BEDI[1], UMA BHANDARI[2*]

[1]Formulation Research and Development, Sun Pharmaceutical Industries Ltd. Gurugram-122015 Haryana, India. [2]Department of Pharmacology, SPER, Jamia Hamdard University, New Delhi-110062, India
[*]Corresponding author: Uma Bhandari; [*]Email: ubhandari@jamiahamdard.ac.in

Received: 18 Feb 2023, Revised and Accepted: 13 Apr 2023

ABSTRACT

Objective: The study aims to enhance the solubility and dissolution of ticagrelor by formulating an amorphous solid dispersion using the hot melt extrusion technique.

Methods: Solubility of ticagrelor is very limited in water and buffers of pH 1.2 to 6.8, which is one of the prime reasons for its low oral bioavailability. Amorphous solid dispersions were prepared using the Hot Melt Extrusion technique using different polymers, plasticizers, and surfactants. The formulation is optimized based on the level of polymer in the formulation. The final formulation of Ticagrelor Amorphous Solid Dispersion is made with a drug-polymer ratio of 1:3, keeping the plasticizer level at 10% of the polymer along with a surfactant Sodium Lauryl Sulfate.

Results: The formulation showed an increase in solubility of 193.95-times in water, 50.71-times in 0.1 N HCl, 332.74-times in pH 4.5 acetate buffer, and 85.20-times in pH 6.8 phosphate buffer as compared to the pure drug. The drug release of the final formulation was found to be 70.0±4.4%, 55.4±1.1%, 35.5±2.1%, and 30.0±0.8% at 90 min, while the reference product showed a release of 9.4±1.1%, 20.7±0.5%, 8.4±0.3%, and 7.8±0.2% at 90 min in water, 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 Phosphate Buffer respectively. The drug release of the final formulation was found to be 99.1±3.8% at 60 min in 0.2% w/v Polysorbate-80 in water.

Conclusion: In the present study, the amorphous solid dispersion of the poorly-soluble drug ticagrelor was successfully prepared. The polymer, Plasdone S630, is considered the most suitable with ticagrelor for formulating amorphous solid dispersion using Hot Melt Extrusion technology to increase the solubility and dissolution of the drug.

Keywords*:* BCS Class-IV drug, Amorphous solid dispersion, Hot melt extrusion, Ticagrelor

DOI: https://dx.doi.org/10.22159/ijap.2023v15i4.47618. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Poorly-soluble drugs (BCS Class II and IV) may tend to show dissolution-limited absorption. Improving solubility and dissolution is one way for the formulators to improve the bioavailability of such molecules [1]. Ticagrelor is a BCS class IV molecule with low solubility and low permeability and a reported oral bioavailability of 36% [2, 3].

It is classified as an anti-platelet aggregator, which reversibly binds to the $P2Y_{12}$ receptor and directly acts by antagonizing the binding of adenosine phosphate to the $P2Y_{12}$ receptor resulting in decreased uptake of adenosine. Both the active drug and its metabolite have approximately equal potencies [4]. The newly discovered and FDA-approved ticagrelor is taken orally in dual antiplatelet therapy along with aspirin [5-7] to manage risks associated with ACS, such as strokes and myocardial infarctions.

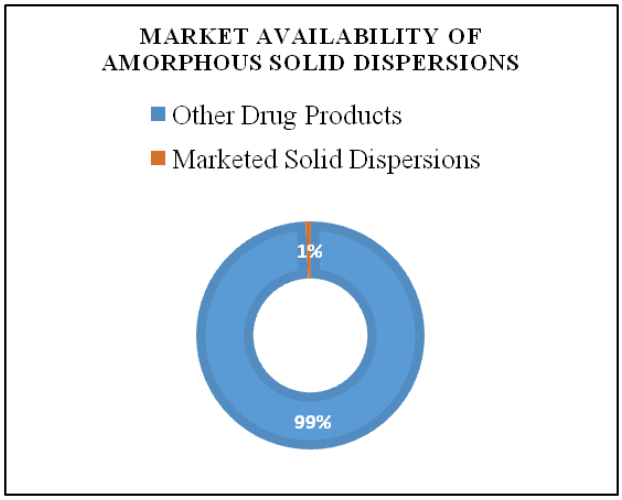
Solid dispersion is a formulation where the active drug is dispersed in a solid carrier, usually a polymer [8-10]. Based on the carrier used in the solid dispersion, they can be classified into four categories; i.e., first-generation (employs crystalline carriers), second-generation (employs amorphous carriers), third-generation (employs surfactant carriers), and fourth-generation (employs release modifying carriers) [11]. The mechanism of action of solid dispersions has not been confirmed, but various theories which are considered the reason for enhanced solubility and dissolution of solid dispersion are discussed as follows [12]: Decrease in particle size of the drug: The decrease in particle size increases the effective surface area available for the dissolution of the drug. The decrease in particle size may also increase the rate of absorption in some cases [13]. Amorphization of the drug: Conversion of the crystalline drug into its amorphous form increases the solubility, changing the crystal lattice's range order [14, 15]. Increase in wettability of the drug: This increases the area of contact between the solvent and the drug thereby increasing the solubility [16].

Firstly, the production of solid dispersions is a very complex process and the stability of dispersion stands as a second factor [17]. Among various methods employed for the formulation of solid dispersion, such as the fusion method [18], melt method [19], solvent evaporation [20, 21], and lyophilization [22], the most common methods used in pharmaceutical industries are spray drying and hot-melt extrusion. Hot-melt extrusion is one of the most efficient and most valued techniques involved for the formulation of solid dispersion. It avoids the use of solvent in the formulation and has maximum scalability [23]. The physical property of the substance under extrusion is altered when the substance is forced through the die or orifice. The drug becomes molecularly dispersed in the polymer under specified conditions of temperature and pressure [24]. Amongst different types of extruders (radial screen extruders, ram extruders, screw extruders), screw extruder is the most widely used in the pharmaceutical industry with three subtypes [17, 18]. The study aims to enhance the solubility and dissolution of ticagrelor by formulating an amorphous solid dispersion using the hot melt extrusion technique.

MATERIALS AND METHODS

Material

Ticagrelor was obtained from Sun Pharmaceutical Pvt. Ltd. Compritol 888 ATO was procured from Gattefosse, India. Plasdone S630 was obtained from Ashland, Mumbai. Methocel E5 was purchased from Dupont, India. PEG 4000 was obtained from SPIL, Paonta, H. P. Soluplus, Kolliphor P 188, Kolliphor P 407, and Kolliphor SLS were kindly gifted from BASF, Mumbai. All the other reagents used in the experiment were of analytical grade, available in Sun Pharmaceuticals Pvt. Ltd. (Research and Development), Gurugram, Haryana.



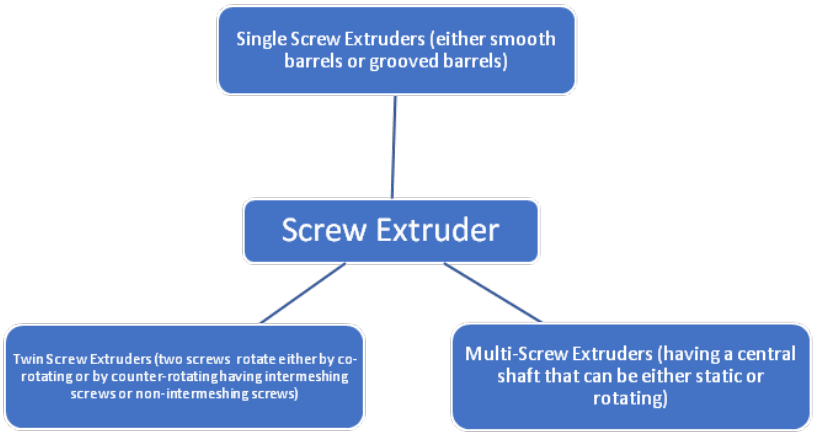


Fig. 1: Screw extruder and market availability of amorphous solid dispersions. Among the 3732 registered drugs in 2015, only 24 were amorphous solid dispersion formulations which shows that the formulations are not readily marketed

Methods

Selection of polymer and plasticizer

The polymer and plasticizer were selected based on the literature. The criteria for the selection of polymer were: The polymer should not modify the release pattern of the drug as the formulation is meant to be an immediate-release dosage form. The polymer's melting temperature must not be too high or too low to facilitate the processing of hot-melt extrusion. The hot-melt process is a solvent-free process. So liquid polymer/plasticizers such as polysorbate were not to be selected. Waxy solids did not mix properly and were not used in the study.

Hot stage microscopy

Hot stage components, including the microscope (Nikon Eclipse E600 POL), heating unit, cooling unit, and camera (Moticam 1080) were turned on. The Motif Image Plus software on the computer showed a live preview of the sample under observation [25]. The sample holder was cleaned, sampling was done and excess samples were brushed off. The sample holder was placed on the hot stage and magnification (10X) was set. The heating unit was set to a temperature of 10 °C/min and the sample was observed in the live preview. The melting temperature of the sample was noted down.

Design of experiment approach

The Design of the experimental approach was used to finalize the screening of polymers for the Solid Dispersion process. JMP software was used for the DoE.

The screening study was done for the selection of polymers that increased the solubility and dissolution of the model drug. The custom design was used for the screening design for the selected excipients basis outcome of pre-formulation studies and the minimum number of trials was run. The trial batches were executed based on their solubility and dissolution. Optimization batches were planned using a 2-factorial design. In the optimization design, the level of the polymer was optimized. After the formulation was optimized, the final optimized batch was processed with the addition of a surfactant (1%-5%), one factor at a time [21].

Preparation of physical blends for HME

For the trial batch, the drug and polymer was taken in the ratio-1:1. After the selection of a suitable polymer, the polymer level was optimized and the optimized batches were prepared in the API: Polymer ratio of 1:3 and 1:5. The plasticizer level was kept constant at 10% of polymer content in all the trials. Cabosil was added as a glidant which was intended to increase the flow property for better processing of the blend in the hot-melt extruder.

Hot-melt extrusion

The twin screw co-rotating hot-melt extruder (Steer Engineering, Model-Omicron 12P) was switched on. Zone heating and Die heating were enabled on the machine. The chiller temperature was set to automatic mode. The temperature of the screw zones and die were set according to the polymer's melting temperature. The melting pressure was kept at 1 bar and the chiller temperature at 7 °C. The physical mixture was extruded at 100 RPM under a vacuum. The extrude was milled using a quadro co-mill with a screen size of 34R (rounded, 990 µm) at 1200 RPM for five min. The milled extrude was mixed with a diluent and lubricant was added to extrude, filled in suitable size capsules for the *in vitro* release studies [16].

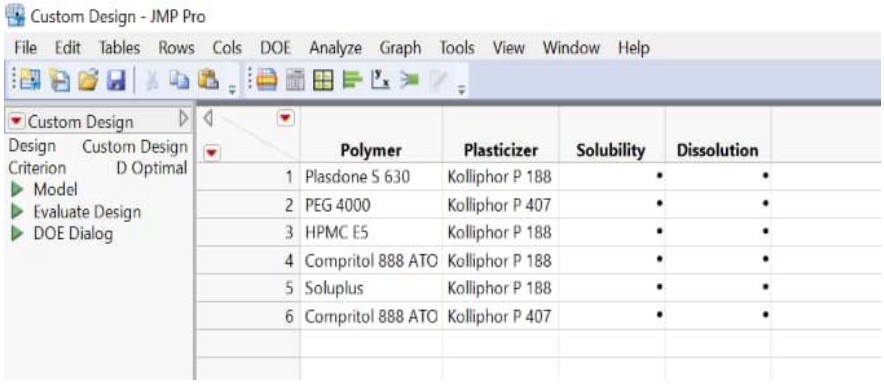


Fig. 2: Number of trials as per custom design (DoE)

Table 1: Represents the formula for a unit dose of solid dispersion of the model drug

S. No.	Ingredients	Trial batch (in mg)			Optimization batch (in mg)									
		SD-1	SD-2	SD-3	SD-4	SD-5	SD-6	SD-7	SD-8	SD-9	SD-10	SD-11	SD-12	SD-13	SD-14
1.	Ticagrelor	90	90	90	90	90	90	90	90	90	90	90	90	90	90
2.	Compritol 888 ATO	90	-	90	-	-	-	-	-	-	-	-	-	-	-
3.	Plasdone S630	-	90	-	-	-	-	-	270	450	-	-	270	270	270
4.	Methocel E5	-	-	-	90	-	-	270	-	-	-	-	-	-	-
5.	PEG 4000	-	-	-	-	-	90	-	-	-	-	-	-	-	-
6.	Soluplus	-	-	-	-	90	-	-	-	-	270	450	-	-	-
7.	Kolliphor P 188	9	9	-	9	9	-	-	-	-	-	-	-	-	-
8.	Kolliphor P 407	-	-	9	-	-	9	27	27	45	27	45	27	27	27
9.	Cabosil-M	0.47	0.47	0.47	0.47	0.47	0.47	0.97	0.97	1.46	0.97	1.46	0.97	0.97	0.97
10.	Sodium Lauryl Sulphate	-	-	-	-	-	-	-	-	-	-	-	0.9	2.7	4.5

Table 2: Presents the temperature of different zones in the hot-melt extruder

S. No.	Solid dispersion	Temperature (in °C)							
		Zone-1	Zone-2	Zone-3	Zone-4	Zone-5	Zone-6	Zone-7	Die zone
1.	SD-1, SD-3	30	30	60	90	120	150	150	150
2.	SD-2		30	60	90	120	150	150	160
3.	SD-4		30	60	90	120	150	150	160
4.	SD-5, SD-10, SD-11		30	40	55	70	85	110	115
5.	SD-6		30	40	55	70	85	110	115
6.	SD-7		35	65	100	130	160	190	200
7.	SD-8, SD-9, SD-12, SD-13, SD-14		40	65	90	115	140	150	150

Characterization

FTIR

Infrared spectroscopy was conducted using a Perkin Elmer (Model-Spectrum One) FTIR instrument and the spectrum was recorded in the region of 4000 to 400 cm^{-1}. The procedure consisted of dispersing a sample (2-3 mg) in KBr (200-400 mg) using a mortar and pestle and compressing it into discs by applying a pressure of 8-10 tons in a hydraulic press or a pellet press (Kimaya Engineers). After the pressing, the sample-KBr mixture turns into a thin, transparent disc. The disc was kept in the sample holder and scanned in the 4000 to 400 cm^{-1}. All spectra were collected as an average of three scans [26].

XRD

The X-ray Diffraction is based on Bragg's equation, $n\lambda = 2d \sin\theta$, where λ is the wavelength of the X-ray beam and n is any positive integer. The inherent arrangement of molecules within a crystal dictates the resulting pattern of diffraction peaks, both position and intensity. The data obtained from a powder diffractometer is typically presented as intensity, either as counts per second or relative to the highest peak, vs diffraction angle, typically as °2θ (degrees two-theta).

The powder X-ray patterns of API and Solid dispersion were recorded. X-ray diffractograms were generated using an X-ray diffractometer (Bruker, Karlsruhe, Germany) equipped with a Copper anode, Cu Ka radiation, 40 kV voltage, 15 mA current, and 20 over 3°-35° range with 0.02° step size at a rate of 10°/min. XRD results are interpreted based on the peaks of the compound. The crystalline molecules show sharp peaks. Amorphous compounds instead show broad peaks instead of sharp peaks [27].

Solubility studies

50 mg of Pure Drug and Solid Dispersions equivalent to 50 mg of API were transferred to a vial containing 10 ml of media, which was kept in a shaker at 150 rpm for 24 h, maintaining the temperature of 37 °C. The samples were filtered after 24 h using a 0.45 µm syringe filter. The filtrate was used to make appropriate dilutions and the samples were scanned in UV Spectrophotometer (Shimadzu UV-1800). The samples were made in triplicate and the mean was calculated. Solubility of the model drug and solid dispersions was estimated in water, 0.1 N HCl, Acetate buffer pH 4.5, and Phosphate buffer pH 6.8.

Dissolution study

Dissolution was performed using USP dissolution apparatus II (Paddle type) with 900 ml of water at 75 RPM at 37 °C±0.5 °C. The sampling time points were 15, 30, 45, 60, 75, and 90 min. Withdraw 7 ml of the sample medium and filter through a 0.45-µm syringe filter. Measured the absorbance of filtrate at 301 nm, 2 mm cuvette

using water as blank in a UV-spectrophotometer (Shimadzu UV-1800).

Determination of drug content

The assay method of the model drug was developed in 0.2% Polysorbate-80 in water. The drug shows the maximum response in the solvent when compared to other solvents. Solid dispersions (equivalent to unit dosage form) will be weighed and dissolved in 100 ml methanol. Pipette out the stock solution and transfer it to a volumetric flask, volume makeup with 0.2% Polysorbate-80 in water to make a solution with a concentration of 18 µg/ml. Sample observed in the UV spectrophotometer for the absorbance [28].

RESULTS AND DISCUSSION

Selection of polymer and plasticizer

Based on the selection criteria, the polymers and plasticizers selected are mentioned below:

- Polymer: Compritol 888 ATO, Methocel E5, PEG 4000, Plasdone S 630, and Soluplus.
- Plasticizer: Kolliphor P 188 and Kolliphor P 407.

Hot-stage microscopy

The hot-stage microscopy results of the drug and excipients are mentioned below.

Solubility studies

The model drug is soluble in methanol. The model drug is practically insoluble in water, 0.1N HCl, and buffers of pH 4.5 and 6.8. The increase in solubility of the solid dispersion (screening batch) formulation was the highest in water as compared to other media. The solubility of Solid dispersion in water, 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer has been mentioned in table 5. The table also contains the respective increase in solubility of solid dispersion compared to that of the API.

Table 1: Hot-stage microscopy results

S. No.	Ingredient	M. p. (in ^{o}C) (Literature)	M. p. (in ^{o}C) (Observed)	Selection for research work
1.	Model drug	140-142	144	Yes
2.	Compritol 888 ATO	69–74	76	Yes
3.	Methocel E5 Premium	154 (Tg)	262	Yes
4.	Polyethylene Glycol 4000 IH	53–58	61	Yes
5.	Plasdone S 630	198–200	163	Yes
6.	Soluplus	70 (Tg)	143	Yes
7.	Docusate Sodium	153	188	Yes
8.	Kolliphor P 188	52–57	56	Yes
9.	Kolliphor P 407	53–54	56	Yes

Table 4: Demonstrates the solubility of the drug in different solvent media

S. No.	Solvent system	Solubility (mg/ml)
1.	Water	0.0115
2.	0.1 N HCl	0.0274
3.	pH 4.5 Acetate buffer	0.0030
4.	pH 6.8 Phosphate buffer	0.0094

Table 5: Presents the solubility of screening batches of Solid dispersion in different media

Solid dispersion	Water		0.1 N HCl		pH 4.5 acetate buffer		pH 6.8 phosphate buffer	
	Solubility (mg/ml)	Increase in solubility w. r. t API	Solubility (mg/ml)	Increase in solubility w. r. t API	Solubility (mg/ml)	Increase in solubility w. r. t API	Solubility (mg/ml)	Increase in solubility w. r. t API
SD-1	0.016	1.96	0.026	1.02	0.007	1.45	0.008	1.65
SD-2	0.206	25.81	0.061	2.37	0.035	7.36	0.048	9.73
SD-3	0.035	4.34	0.048	0.89	0.025	5.30	0.065	13.10
SD-4	0.112	14.04	0.070	2.75	0.017	3.63	0.009	1.82
SD-5	0.050	6.26	0.103	4.01	0.050	10.48	0.028	5.79
SD-6	0.045	5.59	0.118	4.61	0.070	14.68	0.055	11.21

The solid dispersion of model drug SD-2 (Plasdone S 630) and SD-4 (Methocel E5) in the ratio of 1:1 show an increase in solubility in water up to 26 times and 14 times, respectively.

Table 2: Solubility of optimization batches of solid dispersion in different media

Solid dispersion	Water		0.1 N HCl		pH 4.5 acetate buffer		pH 6.8 phosphate buffer	
	Solubility (mg/ml)	Increase in solubility w. r. t API	Solubility (mg/ml)	Increase in solubility w. r. t API	Solubility (mg/ml)	Increase in solubility w. r. t API	Solubility (mg/ml)	Increase in solubility w. r. t API
SD-8	1.172	101.69	2.323	84.53	1.091	355.16	1.889	199.59
SD-9	2.124	184.26	2.009	73.12	1.695	551.47	1.567	165.58
SD-10	0.951	82.74	0.998	36.30	0.334	111.42	0.183	19.35
SD-11	1.898	165.12	1.358	49.38	0620	206.88	0.516	54.38
SD-12	1.723	149.86	1.278	46.47	0.484	161.58	0.634	66.67
SD-13	2.230	193.95	1.394	50.71	0.998	332.74	0.809	85.20
SD-14	2.173	188.99	1.433	52.11	0.876	292.17	0.676	71.21

Table 6 depicts the solubility of the optimization batches of the solid dispersion in water, 0.1 N HCl, pH 4.5 acetate buffer, and pH 6.8 phosphate buffer. The table also contains the respective increase in solubility of solid dispersion when compared to that of the API. The solubility of the optimization batches increases in all the media. The solubility in water increased by a minimum of 82.74 times in the case of SD-10, API: Soluplus (1:3 ratio), while the maximum increase of 193.95 times was seen in the case of SD-13, formulation with API: Plasdone S 630 (1:3 ratio) with 3% SLS. The SD-13 formulation showed optimum results in case of an increase in solubility. The formulation showed a rise of 193.95 times in water, 50.71 times in 0.1 N HCl, 332.74 times in pH 4.5 acetate buffer, and 85.20 times in pH 6.8 phosphate buffer.

All the formulations of optimization batches showed the solubility range of 1.172-2.173 mg/ml, 2.323-1.433 mg/ml, 1.091-0.876 mg/ml, and 1.889-0.676 mg/ml in water, 0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer respectively which were 101.69 to 188.99 times increased in water media, 84.53 to 52.11 times increased in HCl media, 355.16 to 292.17 times increased in acetate buffer and 199.59 to 71.21 times extended in phosphate buffer concerning the solubility of pure ticagrelor in those 4 media. The solubility of all batches was seen to be raised in all the media as compared to that of the reference drug, but amongst all, SD-13 exhibited the highest water solubility, which was 193.95 times increased due to significant hydrophilicity of Plasdone S 630. This water-soluble, pharmaceutical oral care polymer with a Tg value of around 106 °c and degradation temperature of about 270 °C provides induced solubility and dissolution rate of Ticagrelor solid dispersion. The existence of hydrogen bonding between the drug molecule's hydrogen donor sites (OH groups) and Plasdone S 630 carbonyl (C=O) moieties was observed to improve the physical stability of the formulation and reduce crystallization kinetics in the dispersion matrix. Along with polymer interaction, the incorporation of surfactant plays a key role in establishing the best-optimized formulation. In spite of the high polymer content in SD-9 (API: Plasdone S 630-1:5) it displayed a lower solubility than SD-13 (API: Plasdone S 630-1:3 with 3% Sodium lauryl sulfate). Sodium lauryl sulfate (SLS) acts as a strong inhibitor of drug agglomeration below its CMC and induces dissolution rate and amp; drug release kinetics stabilizing solid dispersion by hydrophilicity enhancement and good wettability. Also, it facilitates better interaction between the drug and polymer, good dispersion as well as adsorption. At an optimum concentration, SLS starts to adsorb on the polymer chains and its clusters get distributed to more than two polymer chains leading to higher stability of the formulation. Kolliphor P 407 at an amount of 10% of the polymer, was used as a plasticizer to lower the processing temperature and reduce the melt viscosity of formulation batches. Hence SD-13 batch was found to be the most desirable, optimized andamp; robust formulation.

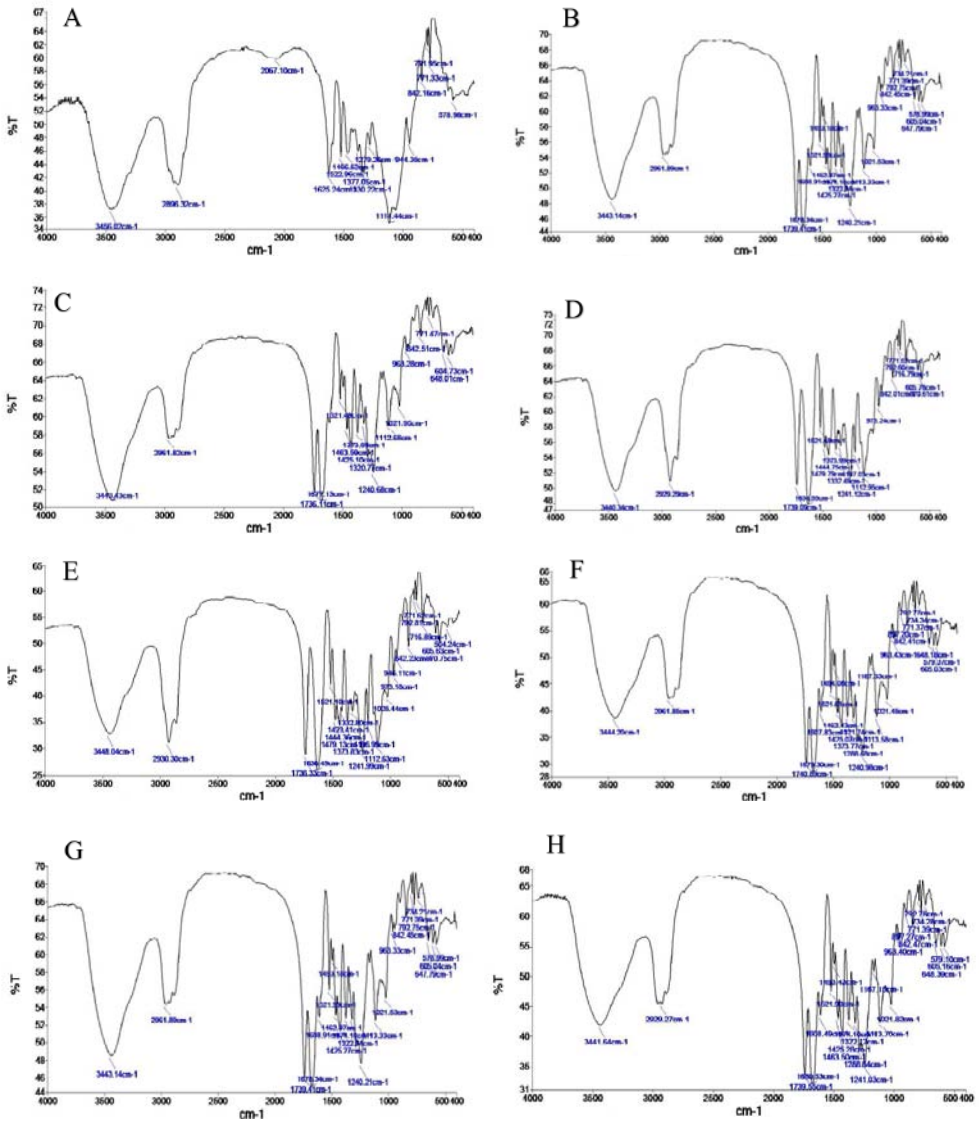


Fig. 3: FTIR graph of (A) SD-7, (B) SD-8, (C) SD-9, (D) SD-10, (E) SD-11, (F) SD-12, (G) SD-13, and (H) SD-14

FTIR

The FTIR spectra of Solid Dispersions (SD-7 to SD-14) given suggests the alteration in IR-radiation (% transmittance) corresponding to the frequency in the range of 3456-3441 cm^{-1}, 2896-2962 cm^{-1}, 1736-1625 cm^{-1}, 1625-1678 cm^{-1}, and 1522-1240 cm^{-1}.

The broad peak present in the range of 3456-3441 cm^{-1} corresponds to the presence of an alcoholic group, while the presence of a peak at 2896-2962 cm^{-1} corresponds to a C-H stretch. Peaks with strong intensity in the range of 1736-1625 cm^{-1}, and 1625-1678 cm^{-1} correspond to C=C bond vibrations, while the presence of peaks at 1522-1240 cm^{-1} indicates the presence of C-F stretch. FTIR spectra of the various samples have been presented in fig. 3.

XRD

X-ray diffractometry provides useful information about the physical state of API in its solid dispersions in polymeric carriers. As shown in fig. 4, the sharp peaks observed in the XRD pattern of the pure API are characteristics of its crystalline form. The XRD graph of the pure drug shows a characteristic peak at °2Θ values of 5.4103, 13.4052, 18.2185, 22.5089, and 24.1826.

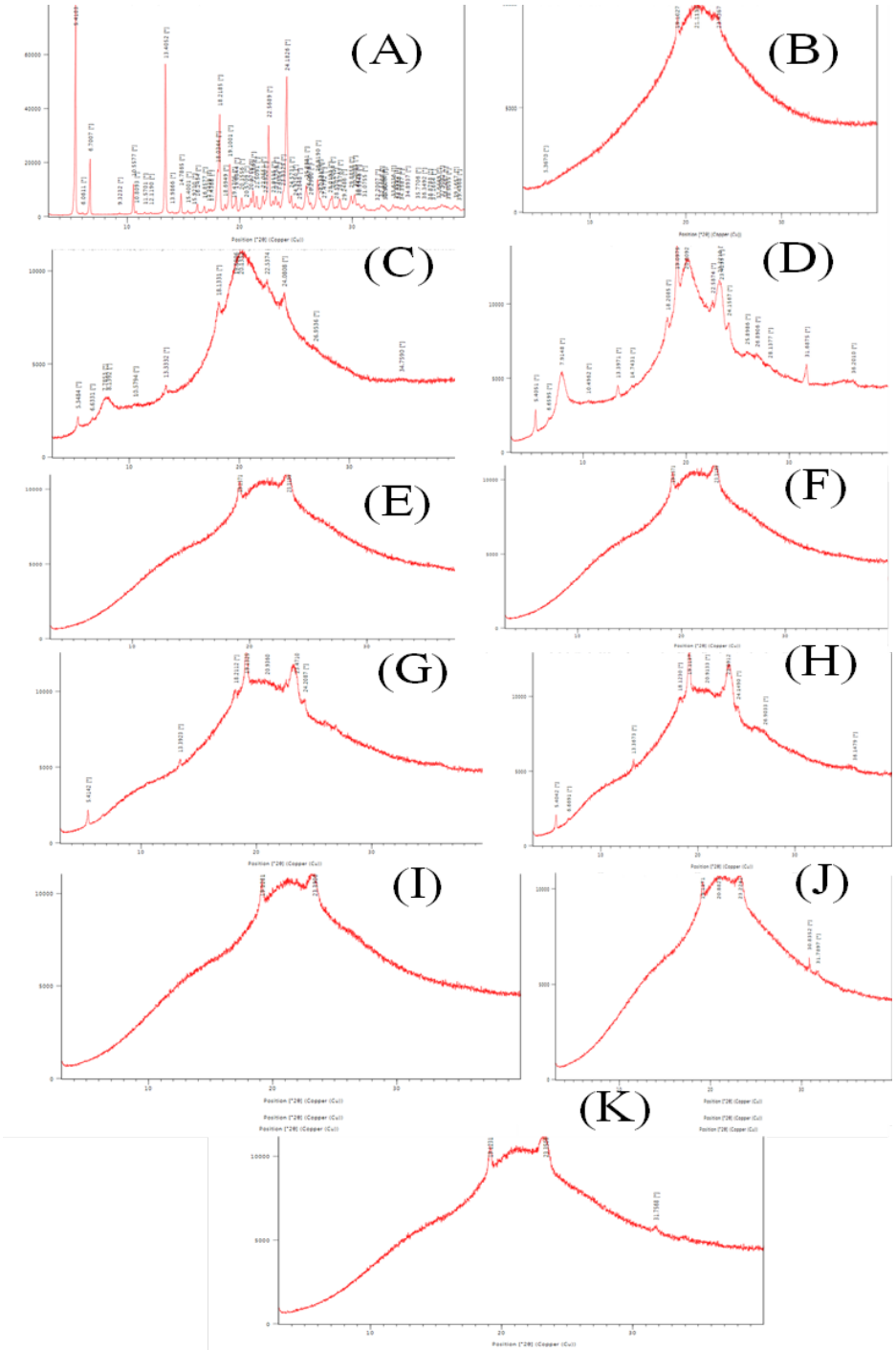


Fig. 4: XRD graph of (A) Pure drug, (B) SD-2, (C) SD-4, (D) SD-7, (E) SD-8, (F) SD-9, (G) SD-10, (H) SD-11, (I) SD-12, (J) SD-13, and (K) SD-14. On the other hand, pure carrier polymers exhibit characteristic broad, amorphous halos in the case of SD-2 and SD-4, as seen in fig. 7. This indicates the conversion of the crystalline state of the drug into the amorphous state. As the amount of polymeric carriers increases and exceeds a threshold level, amorphous halos start to appear, indicating the possible crystalline-to-amorphous transition

Table 3: Demonstrates XRD results of the screening batches of solid dispersion

Batch No.	Details	XRD results
-	Pure Drug	Crystalline
SD-2	API+Plasdone S 630 (1:1)	Amorphous+Crystalline
SD-4	API+Methocel E5 (1:1)	Amorphous+Crystalline

The sharp peaks of solid dispersion prepared using methocel E5, as seen in fig. 8(A) indicates that the drug is not converted into an amorphous form. The peak characteristic of the model drug could also be seen in the XRD graph. The amount and intensity of peaks determine the crystallinity of the solid dispersion. Sharp peaks could be seen in the case of the dispersion prepared using soluplus as seen. The peaks seen in the graph are the characteristic peaks of the model drug. In the X-ray diffractometer, it produced a broad continuous peak with a weak intensity which indicates the conversion of crystalline state to amorphous and it resulted in an appropriate immediate release formulation with 99.1±3.8% drug release at 60 min in 0.2% w/v polysorbate-80 solution in water; 70.0±4.4% drug release at 90 min in water. Patel *et al.* have shown that the solubility of poorly soluble NSAID Tenoxicam was enhanced by amorphous spray-dried dispersion using l-arginine and PVP [29].

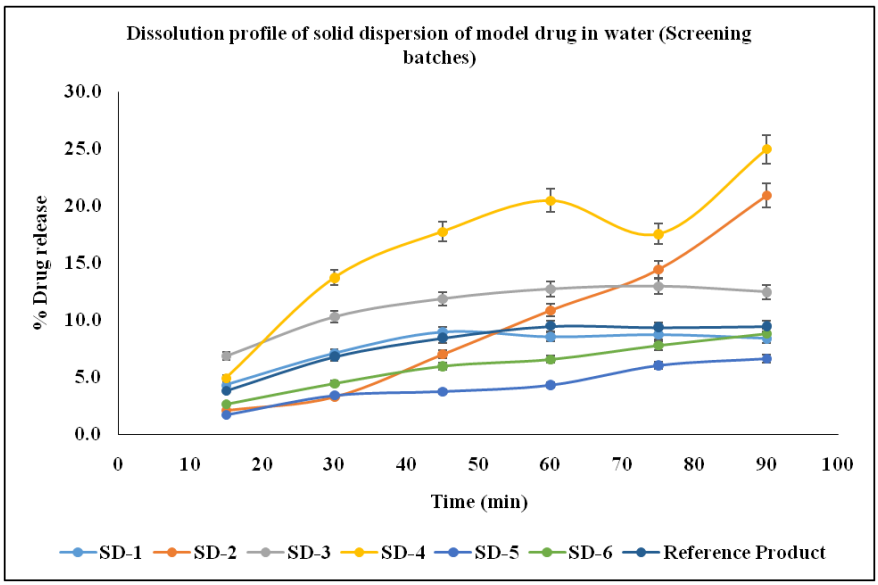


Fig. 5: Comparison of % drug release of screening batches of model drug in water; the values are presented as mean±SD (n = 3)

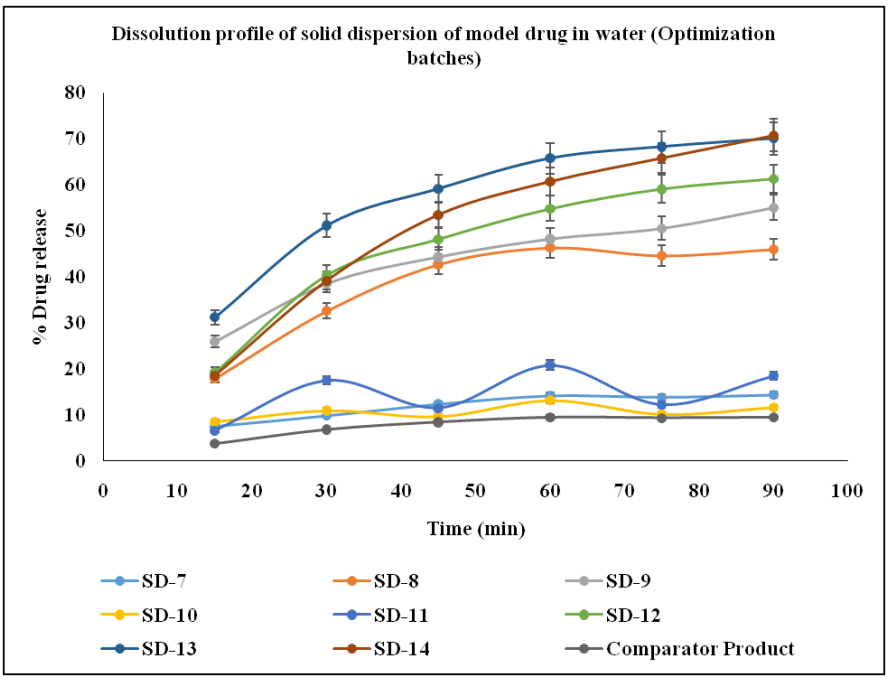


Fig. 6: Comparison of % drug release of optimization batches of model drug in water; the values are presented as mean±SD (n = 3)

Dissolution study

Dissolution of solid dispersion capsules in water

In vitro drug release of different SDs was compared with the reference products. Dissolution studies were performed in water which acted as a discriminatory media. As compared to the drug release of the reference product (9.4±1.1%), drug release of solid dispersion (SD-2, SD-3, and SD-4) was in the range of 12.5±0.8%-25.0±1.2% within 90 min of dissolution studies. The formulations were in the API: Polymer ratio of 1:1 containing polymers Plasdone S 630, Compritol 888 ATO, and Methocel E5, respectively. Methocel E5 and Plasdone S 630 showed a maximum release of 20.9±4.2% and 25.0±1.2%, respectively. The solid dispersions using these two polymers significantly increased the dissolution profile.

Dissolution of solid dispersion (optimization batches) capsules in water

In vitro drug release of different SDs was compared with the reference product in water. SD-7 showed a modified-release pattern and was not used in further studies as the formulation is an immediate-release formulation. A comparison of the % drug release of screening batches of Model drugs in water has been presented in fig. 5.

As compared to the drug release of the reference product (9.4±1.1%), the drug release of solid dispersion of the optimization batches was higher within 90 min of dissolution studies. The formulation SD-13 and SD-14 showed the maximum drug release of 70.0±4.4%, and 70.7±2.9%, respectively, within 90 min of dissolution studies. The comparison graph can be seen in fig. 4, where the % drug release of optimization batches of solid dispersion versus time (in min) are graphically represented. Comparison of % drug release of Optimization batches of Model drugs in water has been presented in fig. 6.

The increase in dissolution of the final optimized batch (SD-13) is up to 7 times (70.0±4.4%) when compared to the reference product (9.4±1.1%). The distinguished release pattern of the final formulation and reference product was an indication of water being the discriminatory media.

Multimedia dissolution of the final formulation

The *in vitro* release study of the final formulation (SD-13) was done in multiple media to record the dissolution pattern of the formulation across various GI pH. The dissolution data could be seen below graphically in terms of % drug release vs time. The drug release of final formulation SD-13 was found to be 70.0±4.4%, 55.4±1.1%, 35.5±2.1%, and 30.0±0.8% at 90 min while the reference product showed a release of 9.4±1.1%, 20.7±0.5%, 8.4±0.3%, and 7.8±0.2% at 90 min in water, 0.1 N HCl, pH 4.5 Acetate Buffer and pH 6.8 Phosphate Buffer respectively. The increase in drug release of solid dispersion is an indication of the formulation of solid dispersion. *In vitro* release profile of the Final formulation (SD-13) and Comparator product in different dissolution media is depicted in fig. 7.

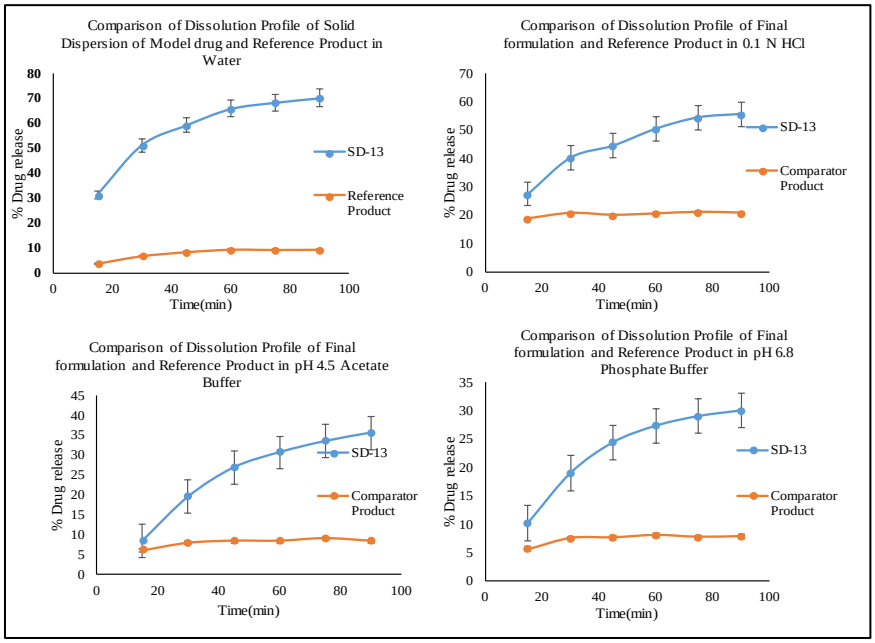


Fig. 7: *In vitro* release profile of final formulation (SD-13) and comparator product in different dissolution media; the values are presented as mean±SD (n = 3)

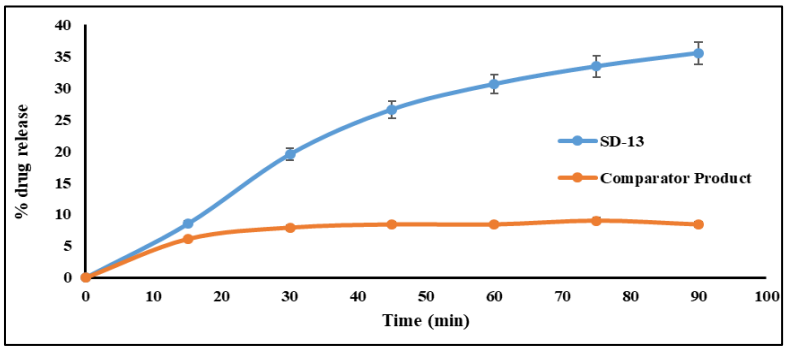


Fig. 8: Comparison of drug release of final formulation and the reference product in 0.2% w/v Polysorbate-80 in water; the values are presented as mean±SD (n = 3)

Drug release of final formulation in 0.2% polysorbate-80 in water

The drug release of the final formulation SD-13 was found to be 99.1±3.8% at 60 min in 0.2% w/v Polysorbate-80 in water. The media is the OGD media for the model drug recommended by the FDA. The graphical representation of a comparison of the drug release of the final formulation and reference product can be seen in fig. 8. The final formulation fits into the category of immediate-release drug formulations.

In a study, Lauretta *et al.* have reported that amorphous ternary solid dispersion of poorly soluble gliclazid (used in the treatment of patients with type 2 diabetes) with crosslinked PVP and SLS by co-milling technique exhibited a higher dissolution rate (90% in 2 h) compared to the commercial product Diabrezide [30]. Additionally, Saha Sumit *et al.* have stated that third-generation solid dispersion of alectinib hydrochloride by solvent evaporation technique resulted in increased drug solubility and dissolution using soluplus and different surfactants [31].

Assay

The sample solution of concentration 18 µg/ml was scanned for absorbance in UV-Spectrophotometer. The drug content in Solid dispersion (API: Plasdone S 630-1:3 without SLS) was found to be 17.45 µg/ml and the drug content in Solid dispersion (API: Plasdone S 630-1:3 with 3% SLS) was found to be 17.81 µg/ml. The assay was found to be 96.91% and 98.92%, respectively.

CONCLUSION

The highlight of the study is the potential of Hot Melt Extrusion technology to convert the crystalline ticagrelor into its amorphous form using Plasdone S 630 as a carrier. The Amorphous Solid Dispersion of Ticagrelor showed an increase in solubility and dissolution over a varying pH range (1.2-6.8). The amorphous solid dispersion drug release is higher than that of the conventional formulation (tablet) of ticagrelor available on the market. The method employed for the formulation i.e. hot melt extrusion-is easily scalable and works well with Plasdone S 630 due to its melting point being in range with that of the drug. The conversion of the drug was confirmed by X-ray Diffraction and Fourier Transform Infrared Spectroscopy shows the interaction between the drug and polymers. The aim of the research to improve the solubility and dissolution of ticagrelor by conversion of the drug into its Amorphous form by formulating a Solid dispersion was successfully attained.

ACKNOWLEDGMENT

Authors acknowledge Sun Pharmaceutical Industries Ltd. Gurugram-122015 Haryana, India for providing infrastructure to conduct experiments.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

REFERENCES

1. Daeihamed M, Dadashzadeh S, Haeri A, Akhlaghi MF. Potential of liposomes for enhancement of oral drug absorption. Curr Drug Deliv. 2017;14(2):289-303. doi: 10.2174/1567201813666160115125756, PMID 26768542.
2. Kim SJ, Lee HK, Na YG, Bang KH, Lee HJ, Wang M. A novel composition of ticagrelor by solid dispersion technique for increasing solubility and intestinal permeability. Int J Pharm. 2019;555:11-8. doi: 10.1016/j.ijpharm.2018.11.038, PMID 30448313.
3. Bayoumi AA. Enhancement of solubility of a poorly soluble antiplatelet aggregation drug by cogrinding technique. Asian J Pharm Clin Res. 2018;11(10):340-4. doi: 10.22159/ajpcr.2018.v11i10.27136.
4. Niazi M, Wissmar J, Berggren AR, Karlsson C, Johanson P. Development strategy and relative bioavailability of a pediatric tablet formulation of ticagrelor. Clin Drug Investig. 2019;39(8):765-73. doi: 10.1007/s40261-019-00800-w, PMID 31140114.
5. Spina E, Barbieri MA, Cicala G, Bruno A, de Leon J. Clinically relevant drug interactions between newer antidepressants and oral anticoagulants. Expert Opin Drug Metab Toxicol. 2020;16(1):31-44. doi: 10.1080/17425255.2020.1700952, PMID 31795773.
6. Sharma R, Kumar P, Prashanth SP, Belagali Y. Dual antiplatelet therapy in coronary artery disease. Cardiol Ther. 2020;9(2):349-61. doi: 10.1007/s40119-020-00197-0, PMID 32804330.
7. Mehata AK, Dehari D. Bradford assay as a high-throughput bioanalytical screening method for conforming pathophysiological state of the animal. J Drug Delivery Ther. 2020;10(1-s):105-10. doi: 10.22270/jddt.v10i1-s.3921.
8. Bhide P, Nachinolkar R. Formulation development and characterization of meclizine hydrochloride fast dissolving tablets using solid dispersion technique. Int J App Pharm. 2018;10(4):141-6. doi: 10.22159/ijap.2018v10i4.26493.
9. Bhairav BA, Jagtap LR, Saudagar RB. Solubility and dissolution enhancement of pioglitazone using solid dispersion technique. Int J Curr Pharm Sci. 2017;9(5):186-93. doi: 10.22159/ijcpr.2017v9i5.22326.
10. Jagdale S, Dangat Y, Kuchekar B. Improvement of dissolution rate of ramipril by solid dispersion technique and development of buccal patch. Int J Pharm Pharm Sci. 2012;4:309-18.
11. Emara LH, Abdelfattah FM, Taha NF. Hot melt extrusion method for preparation of ibuprofen/sucroester WE15 solid dispersions: evaluation and stability assessment. J Appl Pharm Sci. 2017;7(8):156-67.
12. Khaleel NY, Abdulrasool AA, Ghareeb MM, Hussain SA. Solubility and dissolution improvement of ketoprofen by solid dispersion in polymer and surfactant using solvent evaporation method. J Acad Sci IJPPS. 2011;3:431-5.
13. Enose AA, Dasan PK, Sivaramakrishnan H, Shah SM. Formulation and characterization of solid dispersion prepared by hot melt mixing: a fast screening approach for polymer selection. J Pharm (Cairo). 2014;2014:105382. doi: 10.1155/2014/105382, PMID 26556187.
14. Baghel S, Cathcart H, O'Reilly NJ. Polymeric amorphous solid dispersions: a review of amorphization, crystallization, stabilization, solid-state characterization, and aqueous solubilization of biopharmaceutical classification system class II drugs. J Pharm Sci. 2016;105(9):2527-44. doi: 10.1016/j.xphs.2015.10.008, PMID 26886314.
15. Mehata AK, Dehari D, Priya V, Muthu MS. Drug-releasing textile materials: current developments and future perspectives. Fiber and textile engineering in drug delivery systems. Elsevier; 2023. p. 1-38.
16. Yadav M, Sarolia J, Vyas B, Lalan M, Mangrulkar S, Shah P. Amalgamation of solid dispersion and melt adsorption technique: improved *in vitro* and *in vivo* performance of ticagrelor tablets. AAPS PharmSciTech. 2021;22(8):257. doi: 10.1208/s12249-021-02138-z, PMID 34676463.
17. Schittny A, Huwyler J, Puchkov M. Mechanisms of increased bioavailability through amorphous solid dispersions: a review. Drug Deliv. 2020;27(1):110-27. doi: 10.1080/10717544.2019.1704940, PMID 31885288.
18. Malviya R, Srivastava P, Bansal M, PKJIJPSR S. Improvement of dissolution behavior of paracetamol using solid dispersion technique. IJPSR. 2010;1:95-9. http://dx.doi.org/10.13040/IJPSR.0975-8232.1(7).95-99.
19. Tian Y, Jones DS, Donnelly C, Brannigan T, Li S, Andrews GP. A new method of constructing a drug–polymer temperature–composition phase diagram using hot-melt extrusion. Mol Pharm. 2018;15(4):1379-91. doi: 10.1021/acs.molpharmaceut.7b00445, PMID 29205040.
20. Shin SC, Kim J. Physicochemical characterization of solid dispersion of furosemide with TPGS. Int J Pharm. 2003;251(1-2):79-84. doi: 10.1016/s0378-5173(02)00586-0, PMID 12527177.

21. Dehari D, Mehata AK, Priya V, Parbat D, Kumar D, Srivastava AK. Luliconazole nail lacquer for the treatment of onychomycosis: formulation, characterization and *in vitro* and ex vivo evaluation. AAPS PharmSciTech. 2022;23(6):175. doi: 10.1208/s12249-022-02324-7, PMID 35750993.
22. Alwan RM, Raja NA, Alhagiesa AW. Formulation and optimization of lyophilized selexipag nanocrystals to improve the saturation solubility and dissolution rate. Syst Rev Pharm. 2020;11(11):596-605.
23. Roychowdhury R, Kara DD, Rathnanand M. Hot-melt extrusion technique: A novel continuous manufacturing method for enteric-coated pellets. J Appl Pharm Sci. 2021;11(7):13-9.
24. Li Y, Pang H, Guo Z, Lin L, Dong Y, Li G. Interactions between drugs and polymers influencing hot melt extrusion. J Pharm Pharmacol. 2014;66(2):148-66. doi: 10.1111/jphp.12183, PMID 24325738.
25. Kumar A, Singh P, Nanda A. Hot stage microscopy and its applications in pharmaceutical characterization. Appl Microsc. 2020;50(1):12. doi: 10.1186/s42649-020-00032-9, PMID 33580349.
26. Aparna A, Kumar YS, Bhikshapathi DVRN. Formulation and *in vivo* evaluation of ticagrelor self-nanoemulsifying drug delivery systems. Pharm Nanotechnol. 2021;9(1):61-9. doi: 10.2174/2211738508666200708150151, PMID 32640972.
27. Mehata AK, Dehari D, Ayyannan SR, Muthu MS. X-ray powder diffraction spectroscopy as a robust tool in early predicting bioavailability of pharmaceutical formulation containing polymorphic drug substance. Drug Deliv Lett. 2020;10(3):250-4. doi: 10.2174/2210303110999200519074306.
28. Kumar Mehata A, Bharti S, Singh P, Viswanadh MK, Kumari L, Agrawal P. Trastuzumab decorated TPGS-g-chitosan nanoparticles for targeted breast cancer therapy. Colloids Surf B Biointerfaces. 2019;173:366-77. doi: 10.1016/j.colsurfb.2018.10.007, PMID 30316083.
29. Patel JR, Carlton RA, Yuniatine F, Needham TE, Wu L, Vogt FG. Preparation and structural characterization of amorphous spray-dried dispersions of tenoxicam with enhanced dissolution. J Pharm Sci. 2012;101(2):641-63. doi: 10.1002/jps.22800, PMID 22095696.
30. Maggi L, Canobbio A, Bruni G, Musitelli G, Conte U. Improvement of the dissolution behavior of gliclazide, a slightly soluble drug, using solid dispersions. J Drug Deliv Sci Technol. 2015;26:17-23. doi: 10.1016/j.jddst.2015.01.002.
31. Saha SK, Joshi A, Singh R, Jana S, Dubey K. An investigation into solubility and dissolution improvement of alectinib hydrochloride as a third-generation amorphous solid dispersion. J Drug Deliv Sci Technol. 2023;81:104259. doi: 10.1016/j.jddst.2023.104259.