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Development and in Vitro Characterization of Trimetazidine Fast Dissolving Tablets using Direct Compression Method

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ABSTRACT

Background: Trimetazidine has good water solubility and is known to be anti-anginal and anti-ischemic. However, the bioavailability of trimetazidine in its traditional forms is low. Potentially better treatment effectiveness and patient compliance could be achieved by using fast dissolving tablets (FDTs) to increase their dissolve rate.

Objective: This study aimed to develop and test Trimetazidine fast-solving tablets by means of a solid-dispersion technique, a direct compression method, and a factorial design for optimization.

Methods: By kneading PEG 6000 and HPMC E5, solid dispersions were produced. The medication content, disintegration time, wetting time, physicochemical qualities, and in vitro drug release were assessed in tablets that were made by direct compression. For optimization, we used response surface methodology (RSM), and for solid-state characterizations, we used scanning electron microscopy (SEM), dynamic surface spectroscopy (DSC), and XRD.

Results: Solid dispersions based on PEG 6000 demonstrated improved drug content (up to $96.41 \pm 0.44\%$) and solubility (up to 98.37%) among the formulations. Faster disintegration (~30.95 sec), better wetting time, and nearly full drug release (~100% in 30 min) were all features of the optimized FDT (FDT 10). Amorphization was confirmed by solid-state experiments, which led to better solubility. When compared to the pure active pharmaceutical ingredient (API), the drug release rate is dramatically increased by Trimetazidine fast-dissolving formulations. With its exceptional performance compared to all other formulations examined, FDT 10 is a strong contender for further research and in vivo testing.

Conclusion: Using PEG 6000 and direct compression, researchers were able to create optimized Trimetazidine FDTs that have far better dissolving behavior and provide a more patient-friendly option for managing angina with a quick onset of action. These results lend credence to the need for more clinical and in vivo studies.

Keywords: Trimetazidine, Fast Dissolving Tablets, Solid Dispersion, PEG 6000, Factorial Design, In Vitro Characterization, Direct Compression, Bioavailability

INTRODUCTION

A classic symptom of angina pectoris is a sharp, abrupt, and excruciating pain in the chest that spreads outward, affecting the jaw, back, and arms. Ischemia occurs when blood flow to the heart muscle from the coronaries is inadequate to meet its oxygen needs. An anti-anginal and anti-ischemic drug, trimetazidine improves the state of the [1] ischemic myocardium and displays anti-ischemic actions without producing hemodynamic alterations. Because of its high solubility in water, it finds therapeutic application in the long-term management of angina pectoris. It is a one-of-a-kind medicine that prevents cardiac cells from suffering damage caused by ischemia. Unlike nitrates, beta blockers, and calcium channel blockers, trimetazidine works by a distinct mechanism [2]. Trimetazidine protects myocardial cells from damage during an ischemia episode, in contrast to these anti-anginal medicines that influence hemodynamic factors of the supply-demand balance in the heart. It takes 5.4 hours for it to reach its maximal concentration after absorption via the intestinal mucosa. At 89 µg/L, the maximum concentration is detected. There is an 11-hour window in which the maximum 75 plasma concentration stays

higher than 75% of C max. The reason for increasing the dosage of [3] trimetazidine is that its bioavailability is 87%, which is somewhat lower with the modified release formulation compared to the immediate release formulation. One metabolic anti-ischemic medication that helps the heart and muscles use glucose better is trimetazidine dihydrochloride (TM) [4]. Among its many applications are the prevention and treatment of angina pectoris, neurosensorial tissue ischemia, and Meniere's illness [5]. According to [6], it is absorbed quickly and has a relatively short half-life ($t1/2 = 6.0 \pm 1.4$ h). It will be difficult to design it in a controlled release medication delivery system because it is a freely water-soluble substance. The tablet cores were prepared using the direct compression approach.

To enhance the therapeutic effectiveness of medications with short half-lives and to boost patient compliance, several forms of oral controlled release formulation have been created. The goal of these formulations is to provide controlled medication delivery over an extended period and in a variety of medical settings. Since matrix [7] tablets are simple to produce, they are frequently utilized in the development of sustained release formulations for medicinal substances. The matrix can be tableted using either the usual wet granulation process or direct compression with the help of a rate-controlling polymer.
One of the most straightforward methods of tablet processing is direct compression. Powder mixing, lubrication, and compaction are the three primary processes involved. Due to the lack of a granulation stage, excipients developed for direct compression and formulated to impart the required flow and compaction qualities are typically required to enhance the flow and compaction of components [8].

The use of hydrophilic non-cellulosic polymers in suitable combinations is widespread for oral controlled release dosage forms due to its affordability, simplicity, and efficacy. As a result, the pharmaceutical business has seen an enormous demand for sustained release products. The goal of medication delivery systems is to maximize therapeutic efficacy with minimal side effects. A relatively new method in the pharmaceutical sciences, sustained-release dose forms have already demonstrated their usefulness and compliance [9].

In this investigation, 2^3 factorial designs were utilized. When conducting studies to determine the relative contributions of multiple factors, a factorial design is among the most effective options. The term "factorial design" refers to an experimental setup in which every conceivable combination of factor levels is tested in every single trial or replication [10]. It is possible to navigate the experimental space and obtain the optimized formula with preset limitations for various components using an optimization strategy based on a response surface methodology (RSM) employing polynomial equations [11, 12]. For 12 hours, our optimization method will seek out the best TM zero order extended-release formulation.

The current research aims to find out how different processing conditions and modifications in the dissolving media impact the release properties of sustained release matrix tablets containing Trimetazidine Dihydrochloride in Kollidon SR, which are used as a rate retarding ingredient.

MATERIAL AND METHODS

Materials

Global Napi Pharmaceuticals Company kindly provided samples of trimetazidine dihydrochloride (Sharon Bio-Medicine, India), spray dried lactose (Molkerei MEGGLE Wasser burg GmbH & Co., KG, Germany), microcrystalline cellulose (avicel PH-102), supplied by F M C Biopolymer, Ireland, and PEG400, manufactured by BASF Fine Chemicals, Switzerland. "Magnesium stearate" manufactured by Witco Corp in the United States. Sigma-Aldrich Chemie of Steinhiem, Germany, in a 5% solution in toluene/ethanol 80:20. The Sigma-Aldrich Company in St. Louis, USA, produces dibutyl phthalate. Everything else was used exactly as it was received and was of analytical quality.

Preparation of Solvent Deposition System

Solid dispersion Method: Solvent Evaporation Method

Formulation of Solid Dispersion (SD)

A solid dispersion of TMT was produced by the kneading method with PEG 6000 and HPMC E5. The composition of TMT solid dispersions is as follows [13].

Table 1: Composition of different solid dispersion formulations

CODE	COMPOSITION	RATIO	METHOD
SD1	TMT: PEG 6000	1:4	Kneading method
SD2		1:2	
SD3		1:6	
SD4		1:8	
SD5	TMT: HPMC E5	1:1	Kneading method
SD6		1:2	
SD6		1:3	
SD7		1:4	

Procedure: The medication was dissolved in an adequate amount of methanol solvent. In this solution, an adequate quantity of polymer was added. The mixture was well agitated and thereafter subjected to evaporation using a water bath. The system underwent dehydration in a vacuum oven. Preserved in a hermetically sealed receptacle and stored in a desiccator [14].

Selection of Polymer: To identify the optimal polymer for producing solvent depositions, using lactose and MCC, solvent depositions were created.

EVALUATION OF SOLID DISPERSION

FTIR Spectroscopy
A comparison was made between the drug sample's recorded IR spectra and the conventional functional group frequencies of TMT using an FTIR Spectrometer. The IR spectra that were acquired confirmed that the drug sample in question was TMT, thanks to the presence of its distinctive group frequencies.

Percentage Yield: They collected and measured the created powders. In order to get the recipe's total weight, we divided it by the sum of all the non-volatile components.

$$\%\ yield\ = \frac{weight\ of\ powder}{weight\ of solid\ starting\ materials} X100$$

Drug content: A 50 ml volumetric flask was filled with precisely 100 mg of compounds that had been meticulously measured. After that, 40 millilitres of methanol were used to dissolve the formulations. Methanol was added to the solution to dilute it to the appropriate volume. After diluting the solution with 0.1N hydrochloric acid (HCI), A UV spectrophotometric technique operating at a wavelength of 281 nm was used to ascertain the drug concentration [15].

Percentage drug release: The entire product recipes were tested for solubility using the USP type I dissolving equipment. The conditions employed in the studies were a temperature of 37±0.5 °C, a rotation speed of 50 rpm, and a dissolving fluid of 900 cc 0.1N HCl. The samples were obtained at irregular intervals of 0, 10, 30, 45, and 60 minutes. Afterwards, the volume was raised by adding the same quantity of conventional dissolving medium. Filtration and dilution were applied to the specimens. Using a UV-visible spectrophotometer, determine the absorbance of the solution at 280 nm [16].

PREPARATION OF TABLETS WITH OPTIMIZED BOTH THE DRUGS FORMULATIONS

Direct compression method: Medicines underwent enhancements the direct compression technique was used to make tablets utilising SD and IC formulations. The direct compression approach made use of lactose, an easily compressible excipient, as filler. The substance was identified as crospovidone at a concentration of 5%. As lubricants, the researchers used talc (2% of the total) and as disintegrants, they used magnesium stearate (5% of the whole). The ingredients were combined in a plastic jar with a tight lid. Using a tablet press with a 7mm diameter, the powder mixture was compacted into tablets [17].

EVALUATION OF TABLETS

Physico-chemical properties
Thickness: The Vernier callipers were used to evaluate the thickness of the tablet; Millimetres (mm) are used as the unit of measurement [18].

Hardness: A Monsanto hardness tester was used to measure the hardness of the manufactured tablets. We picked three tablets at random from each batch of formulation and applied force in the opposite direction. The unit of measurement is kilogrammes per square centimetre, abbreviated as Kg/cm² [19].

Friability: A Roche friabilator was used to evaluate the produced fast-dissolving tablets' friability. The tablets were simultaneously abased and shocked for four minutes or one hundred revolutions in a revolving plastic chamber at a rate of 25 revolutions per minute. A tablet sample (Wi) that had been previously weighed was placed into the friabilator and rotated 100 times. A soft muslin cloth was used to dust off the pills before they were weighed once again (Wf). The formula below is used to calculate the friability (F).

$$F = \frac{Wi - Wf}{Wi} X100$$

Weight Variation test: The weight variation test included weighing 20 pills one by one, calculating their average weight, and then comparing the weights of each tablet to the mean. After calculating the weight change as a percentage, the IP Limits were compared. The variance was found to be within an acceptable range, passing the weight variation test [20].

Drug Content: A glass crusher and pestle were used to measure and break five pills. A carefully measured 100 mg of powder was added to a 50 ml volumetric flask, diluted in methanol, and filtered using Whatmann filter paper no. 41. The liquid that passed through the filter was collected and appropriately mixed with a phosphate buffer solution with a pH of 1.2. A UV spectrophotometer was used to quantify the drug concentration at a wavelength of 281 nm [21].

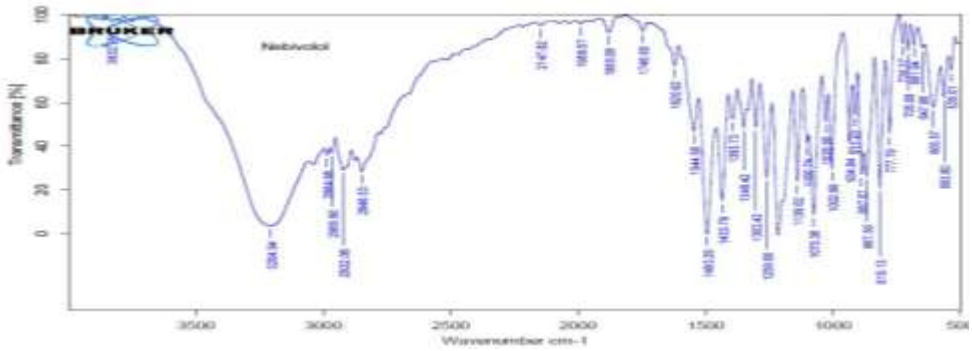
Disintegration time: The Indian Pharmacopoeia was used to determine the tablets' breakdown time. Tablet disintegration equipment was used for the experiment. As a disintegration medium, 900 cc of distilled water was maintained at 37 ± 0.2°C. It was documented how long it took for every pill to dissolve fully.

Wetting time and water absorption ratio: After being individually weighted (Wa), the tablets were carefully placed on top of a folded piece of tissue paper in a Petri dish with a diameter of 5 cm. The plate contained six mL of water. The time it takes for the water to completely cover the top surface of the tablet is known as the wetting time, and it is then measured and noted. The pill was carefully taken out after being moist and weighed again (Wb). The water absorption ratio (R) via the pill was then calculated using the following formula [22].

$$R = \frac{Wb - Wa}{Wb} X100$$

***In-vitro* drug release study:** The optimized solid dispersion (SD), solution (Sol. D), and immediate-release (IC) tablets, as well as the pure drug, were all subjected to dissolve exams using the USP dissolving equipment type 1. A 900 mL hydrochloric acid (HCI) solution with a concentration of 0.1N was used to perform a dissolving study. We maintained a temperature of precisely 37°C±0.5°C and fixed the rotation speed at 50 revolutions per minute (rpm). At regular intervals, fresh dissolving medium was substituted for the samples. A UV spectrophotometer operated at 281 nm was used to filter, dilute, and analyse the samples. The commercially available tablet of both medications was compared to the optimised solid dispersion (SD), solution dispersion (Sol. D), and immediate-release (IC) tablets in terms of their release patterns and rate of dissolution [23].

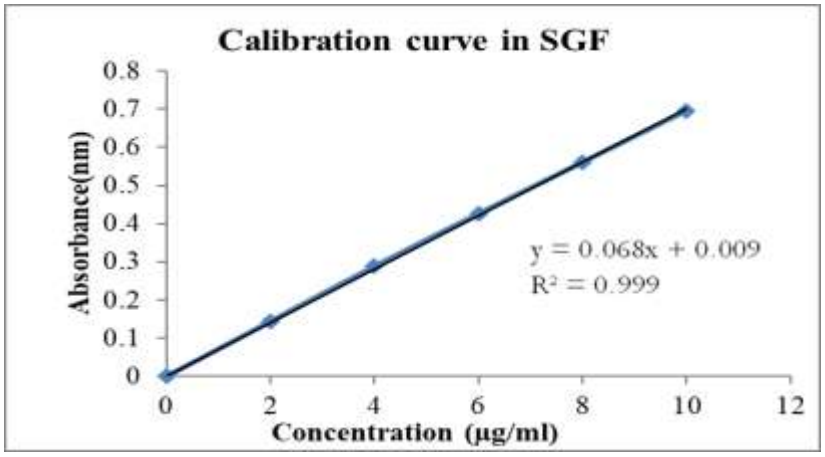
Results & Discussion



Characterization of Drug: This table describes the active pharmaceutical component of the trial. The formulation process takes into consideration the unique chemical and physical features of each medicine [24]. This property of the medicine determines the combination of medicinal components used to construct the dose form. In order to quantify the mass, tapped density, colour and clarity of solutions, pH, organoleptic properties, and loss during drying of pure medications. The findings are summarized in Table 2.

Table 2: Characterization of Trimetazidine

S. No	Characteristics	TMT	
		Specifications	Test Results
1	Nature	Crystalline	Crystalline
2	Color	Yellow color	Yellow color
3	Taste	Bitter	Bitter
4	Melting point	225-228°C	227°C
5	Clarity and color of solution	Clear and colorless	Clear and colorless
6	Loss on drying	Max 0.5%	0.169±0.011
7	Bulk density	---	0.59±0.14
8	Tapped density	----	0.91±0.09
9	Odour	odorless	odorless



Melting point Determination: The melting point of the (TMT) drug is 227°C, falling within the specified range. The test confirmed that the medicine sample was free of impurities. The lack or presence of impurities can cause a substance's melting point to change.

Solubility study: The drug's solubility in water, chloroform, methanol, 0.1NHCl, pH 6.8, and pH 7.4 PBS were tested using the shake flask method. Ten mg of the medication were administered to each solvent. The image below shows how soluble the drug sample is in different solvents.

Saturation solubility studies of TMT: Employing the Higuchi and Connors methods to assess solubility in stages. An aqueous solution of carriers, especially PVP, PEG 4000, and PEG 6000, with a concentration of 0.02 M was mixed with an excess of TMT to create a solution with a concentration ranging from 0.001 to 0.02 M. For a full day, the ingredients were constantly stirred on a rotary shaker. A UV Spectrophotometer was used to filter and analyse more liquid from the supernatant at 231 nm. Phase solubility research can be used to investigate carriers' capacity to dissolve medications in

water. By looking at the phase of solubility curve, it also provides a same stability. TMT has a very high solubility of 10.24 mg/mL in water. The drug's solubility rose linearly with increasing carrier concentration, according to phase solubility tests of the three carriers. This supports the findings of the person who hypothesised that as test polymer concentrations increased, the drug's solubility would increase proportionately [25].The stability constants for each carrier from the phase solubility analysis are shown in Table 4. The greater wettability of the medication may be the cause of the better drug solubility seen in all three carriers. When compared to other polymers, PVP significantly improved TMT's solubility. At 30% w/v PVP, there was a discernible four-fold increase in drug solubility (42.15±0.41 mg/ml), indicating a strong interaction between the two compounds that results in molecular dispersion. The carrier-drug interaction was governed by both hydrogen bonding and electrostatic forces. The Ks values that were achieved were sufficient to generate solid dispersions, which might increase the drug's bioavailability [26].

Table 3: Saturation Solubility profile of the drug

S. No	Carrier concentration (% w/v)	Concentration of TMT (mg/ml)		
		PVP	PEG 4000	PEG 6000
1	0	10.35±0.02	5.36±0.06	6.52±0.01
2	5	16.28±0.09	8.54±0.02	7.54±0.03
3	10	22.41±0.16	10.24±001	10.01±0.01
4	20	29.68±0.28	13.26±0.03	11.42±0.05
5	30	42.15±0.41	18.59±0.05	13.65±0.04

*Each value represents the mean ± standard deviation (n=3).

Formulation of Solid Dispersion (SD)
A solid dispersion of TMT was produced by the kneading method with PEG 6000 and HPMC E5. The composition of TMT solid dispersions is as follows.

EVALUATION OF SOLID DISPERSION SYSTEM (SD)

Percentage Yield: The prepared solid dispersion of TMT has a yield percentage ranging from 92.87±0.06% to 98.04±0.111%. The formulation SD4, which used PEG 6000, produced the greatest yield, whereas the formulation SD5, which used HPMC E5, produced the lowest. The yield data as a percentage for each formulation is shown in the picture and in the table.

Drug content: The solid TMT dispersion's drug content varied between 73.05±0.33% and 96.41±0.44%. PEG 6000 was used to make formulation SD4, which had the greatest drug content, whereas HPMC E5 was used to prepare formulation SD5, which had the lowest drug level. The drug content information for each formulation is included in the table and in the figure [27].

Table 4: Composition Of Different Solid Dispersion Formulations

Formulation	Percentage Yield (%)	Drug Content (%)
TSD1	94.02±0.14	74.31±0.01
TSD2	95.37±0.05	77.28±0.15
TSD3	96.15±0.01	89.42±0.46
TSD4	98.04±0.16	96.41±0.44
TSD5	92.87±0.09	73.05±0.33
TSD6	93.26±0.08	76.48±0.88
TSD7	95.84±0.41	86.31±0.94
TSD8	96.01±0.73	90.75±0.53

Σ n=3

Percentage drug release: In order to measure the proportion of medicine released from the dosage form over time, the dissolving tests were developed to examine the drug's release profile. There is a positive correlation between the

concentration of the polymer and the release profile of any sustained-release product. The dosage that is released from the formulation increases gradually over time. An hour later, the percentage of solid dispersions released ranged from 80.26% to 98.37%. The cumulative percentage of medication administered at different intervals for every formulation is displayed in the table labelled "as." The data previously given makes it evident that the more polymer there was, the faster the medication dissolved. Out of the eight formulations, the solid dispersions prepared using PEG 6000 exhibit the highest dissolution rate [28].

Scanning Electron Microscopy Analysis: The SEM technique was employed to investigate the shape and surface morphology of the optimized IC formulations, providing a qualitative analysis of the structural characteristics of the medicines. The products acquired through various ways of preparation. The scanning electron microscope (SEM) image of the formulations revealed that the drug particles were in an amorphous state. The study demonstrated a transformation in the crystal structure of the medication, resulting in its conversion to an amorphous state within the formulations. The alteration in the crystal structure explains the heightened ability to dissolve [29].

X-ray diffraction study

The optimised TIC formulation pattern and the TMT X-ray diffraction pattern were contrasted. The crystalline structure of pure TMT is shown by the distinct and sharp peaks in its X-ray diffraction pattern. Wide, hazy peaks with decreased intensity were visible in the optimised TIC formulations' X-ray diffraction pattern. The reflection intensities in the formulas diminish. The maximum point of decreased strength signifies the medication's transition into an amorphous state and decrease in crystallinity, which improves drug solubility [30].

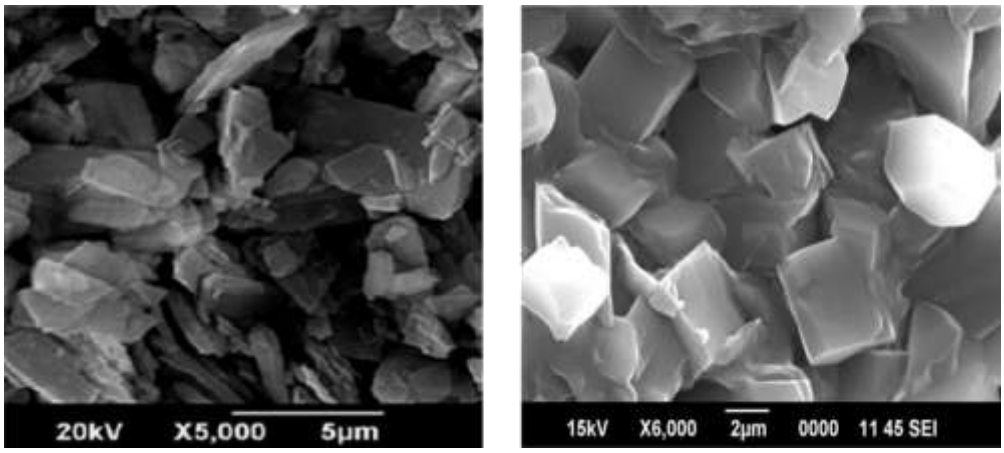


Figure 1: SEM Picture of optimized TIC.

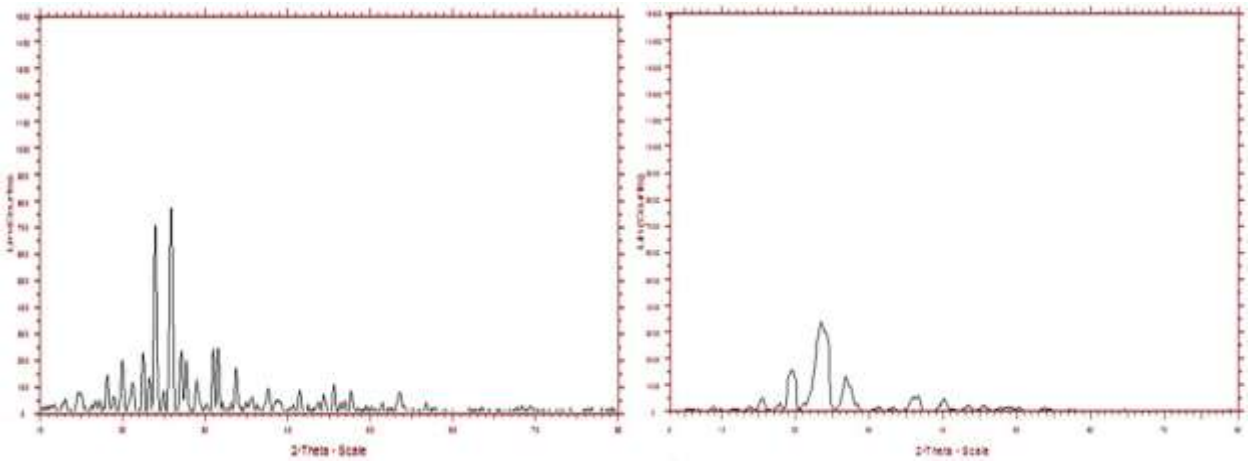


Fig 2: X-ray diffraction of TMT and Optimized TSD

Differential scanning Calorimetry study (DSC): DSC was utilized to analyse the pure medication's and the optimized TIC formulations' thermal behaviour. The melting, boiling, and sublime temperatures are changed or eliminated when optimised TIC formulations are formed. The melting point of the pure drug, 227.36°C, is shown as an endothermic peak in the DSC thermogram of TMT pure pharmaceutical. It implies that the pure crystalline form of the medication TMT was utilised. Unlike the pure medication, the TMT optimised IC formulations' DSC thermogram did not show sudden endothermic peaks. This suggests that inclusion complex structures are present [30].

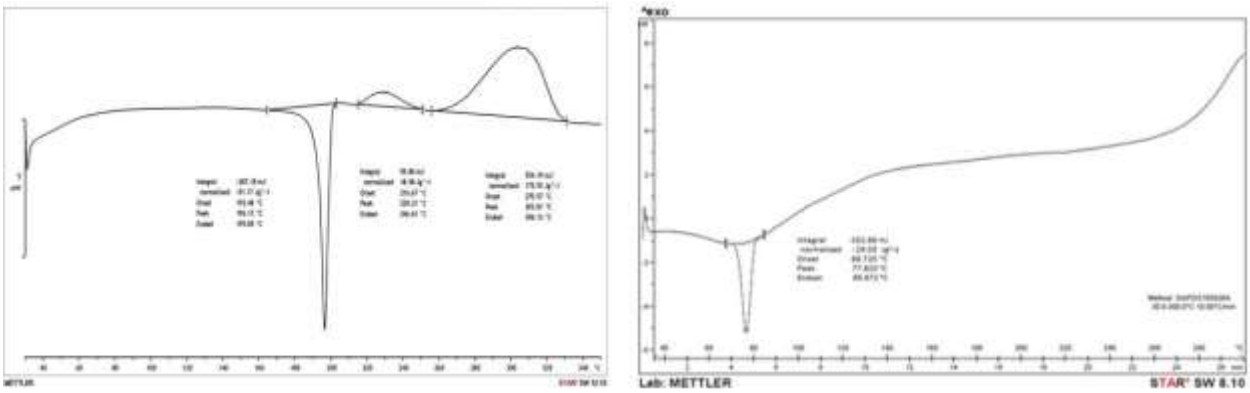


Fig 4: DSC Thermogram of Drug TMT and Optimized solid dispersion

Table 5: Central Composite Design (CCD) matrix with coded and actual values of independent variables (X_1: concentration of super disintegrant, X_2: compression force) and corresponding observed responses—Y_1: Disintegration time (seconds), Y_2: % Cumulative drug release at 30 min, and Y_3: Wetting time (seconds). Results are expressed as mean ± standard deviation (n = 3).

Table 5: Optimization of formulations of fast dissolving tablets of trimetazidine

Std	Run	X1	X2	Y1	Y2	Y3
9	1	3	3.5	27.63±0.28	86.21±0.55	26.51±0.72
11	2	3	3.5	22.01±0.31	87.14±0.91	24.75±0.34
3	3	1	5	23.61±0.56	59.86±0.43	47.02±1.25
12	4	3	3.5	28.49±0.47	91.02±0.87	31.89±1.16
13	5	3	3.5	27.64±0.25	82.36±0.72	27.81±0.15
5	6	0.1715	3.5	75.42±0.31	67.48±0.69	44.09±1.62
10	7	3	3.5	30.95±0.39	83.12±0.21	29.76±0.86
2	8	5	2	72.13±0.34	48.76±0.38	57.14±0.45
4	9	5	5	50.98±0.13	67.98±0.67	38.29±1.72
6	10	5.828	3.5	67.54±0.21	60.24±0.53	54.11±2.66
1	11	1	2	90.16±0.47	80.31±0.12	18.59±0.98
7	12	3	1.3786	86.35±0.34	68.49±0.47	27.36±1.19
8	13	3	5.621	27.41±0.28	71.04±0.38	28.41±1.82

EFFECT OF WETTING TIME

The **Model F-value** of 76.39 implies the model is significant. The calculation of an F-value This massive amount could be due to random chance in 0.01% of instances. A P-value of less than 0.0500 indicates the presence of significant model terms. A2, B2, B, AB, and B are key model terms here. **The Lack of Fit** is not significant in relation to the pure error, as shown by the Lack of Fit F-value of 3.23. There is a 14.35% chance that noise is the reason for a large Lack of Fit F-value. The difference between the **Predicted R2** value of 0.9012 and the **adjusted R2** value of 0.9691 is lower than 0.2. The signal-to-noise ratio is computed using **Adeq. Precision**. It is ideal if the ratio is more than 4. With signal strength of 22.647, you are more than enough.

Wetting Time = +237.81337 --44.59642A -67.69159B ++3.78333AB ++5.20700A2 +6.01244B2

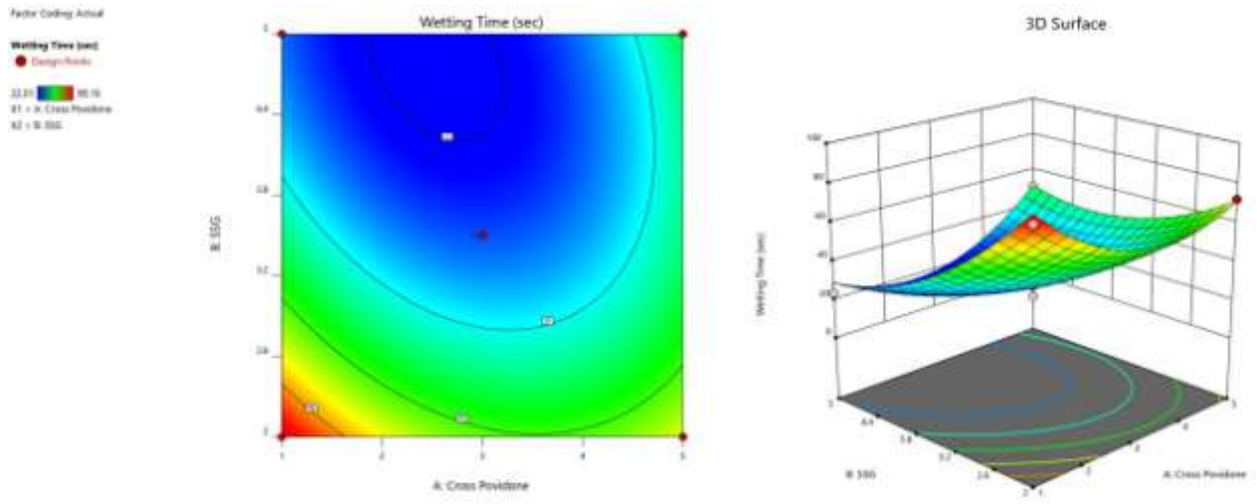


Figure 5: Contour plot (left) and 3D surface plot (right) showing the effect of independent variables—A: Cross Povidone and B: Sodium Starch Glycolate (SSG)—on the wetting time (Y_3) of Trimetazidine fast dissolving tablets.

Effect of drug content:

The **Model F-value** of 30.20 implies the model is significant. Calculating an F-value In a small fraction of cases, noise might be the only factor contributing to this size. A P-value below 0.0500 indicates the presence of meaningful model terms. Here, the letters A, AB, A2, and B2 form an essential set of model words. **A Lack of Fit** F-value of 1.05 suggests that, as compared to pure error, Lack of Fit is hardly noteworthy. A significant Lack of Fit F-value is likely due to noise, with a probability of 46.06%. The difference between the two, 0.9240 for **Adjusted R2** and 0.8222 for **Predicted R2**, is less than 0.2. The signal-to-noise ratio is worked out using **Adeq Precision**. It is ideal if the ratio is greater than 4. It is enough that your signal strength is 14.635.

Drug Content = +85.97 -4.21A +0.2970B +9.92AB -11.70A2 --8.75B2

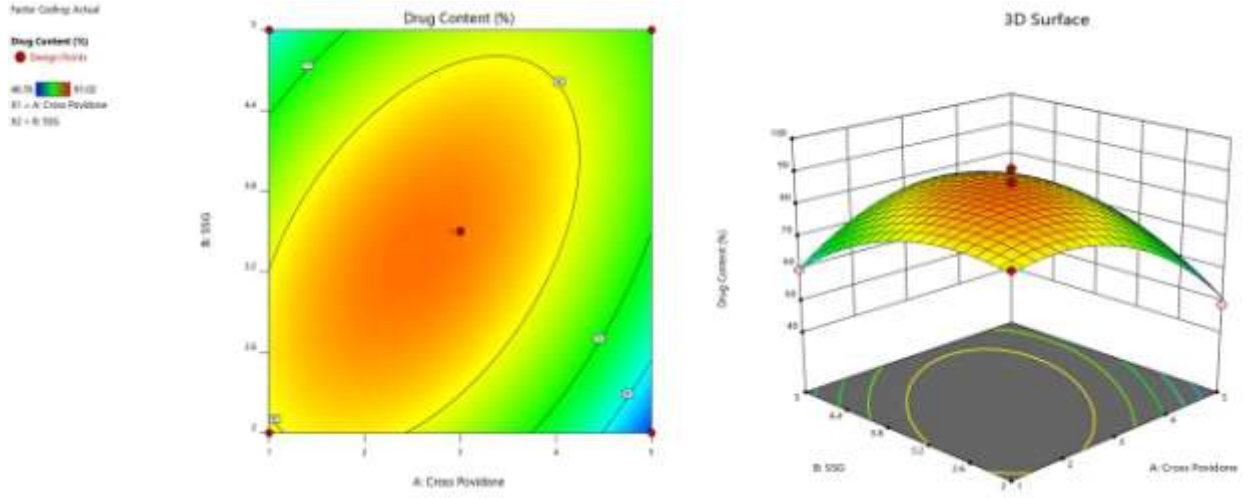


Figure 6: Contour plot (left) and 3D surface plot (right) showing the effect of independent variables—A: Cross Povidone and B: Sodium Starch Glycolate (SSG)—on the wetting time (Y_3) of Trimetazidine fast dissolving tablets.

Effect of disintegration time

The **Model F-value** of 30.48 implies the model is significant. In less than one percent of instances may a value as large as the F-value be due to random chance. When the p-value is less than 0.0500, it indicates that the terms in the equation are meaningful. Important model variables in this situation are A, AB, and A^3. **Lack of Fit** does not deviate considerably from pure error, as shown by the F-value of 1.94. In 26.48 percent of situations, noise is likely to blame for a Lack of Fit F-value

of this size. When there is a little discrepancy. The difference between the two sets of numbers, 0.9247 for **Adjusted R2** and 0.7869 for **Predicted R2**, is very negligible, being lower than 0.2. **Adeq Precision** measures the signal-to-noise ratio. We want a ratio more than 4. A signal-to-noise ratio of 16.567 is considered adequate.
Disintegration Time = +28.14 +5.50A +1.38B -11.82AB +10.926A2 +0.31243B2

Table 6: Evaluation Parameters of Fast Dissolving Tablets

Runs	Thickness	Hardness	Friability	Weight variation	Disintegration Time (sec)	Wetting time in sec	Drug content in %
FDT 1	4.4±0.17	3.25±0.05	0.482	151.12±1.3	24.36±0.43	28.57±1.23	88.53±1.42
FDT 2	4.4±0.15	3.95±0.22	0.628	149.40±1.0	25.41±0.82	28.04±0.95	86.49±0.59
FDT 3	4.4±0.12	3.17±0.13	0.468	150.60±0.7	49.36±0.37	22.53±2.41	57.43±3.42
FDT 4	4.4±0.13	3.5±0.20	0.574	150.40±1.2	24.13±0.85	27.95±0.48	87.51±0.48
FDT 5	4.4±0.12	2.90±0.25	0.556	150.83±3.15	25.03±0.42	28.49±0.52	88.03±0.72
FDT 6	4.4±0.10	3.45±0.14	0.672	146.80±1.89	46.02±0.61	76.53±2.58	65.49±0.34
FDT 7	4.4±0.11	3.42±0.19	0.51	147.23±1.21	24.35±0.85	28.76±1.04	87.42±0.57
FDT 8	4.3±0.11	3.25±0.24	0.50	150.20±1.11	59.82±0.74	75.39±1.29	46.51±1.08
FDT 9	4.2±0.19	3.27±0.04	0.526	150.30±1.22	36.59±0.38	46.98±1.42	65.31±1.27
FDT 10	4.3±0.17	3.37±0.25	0.544	149.90±1.19	56.31±0.84	68.75±0.76	58.62±0.37
FDT 11	4.4±0.19	3.45±0.13	0.488	150.89±1.12	14.23±0.29	93.26±1.47	78.53±0.75
FDT 12	4.4±0.18	3.4±0.6	0.492	148.15±1.18	25.64±0.42	88.74±0.85	66.59±0.94
FDT13	4.3±0.12	3.5±0.5	0.511	151.21±0.88	30.29±0.48	38.75±0.42	69.53±0.85

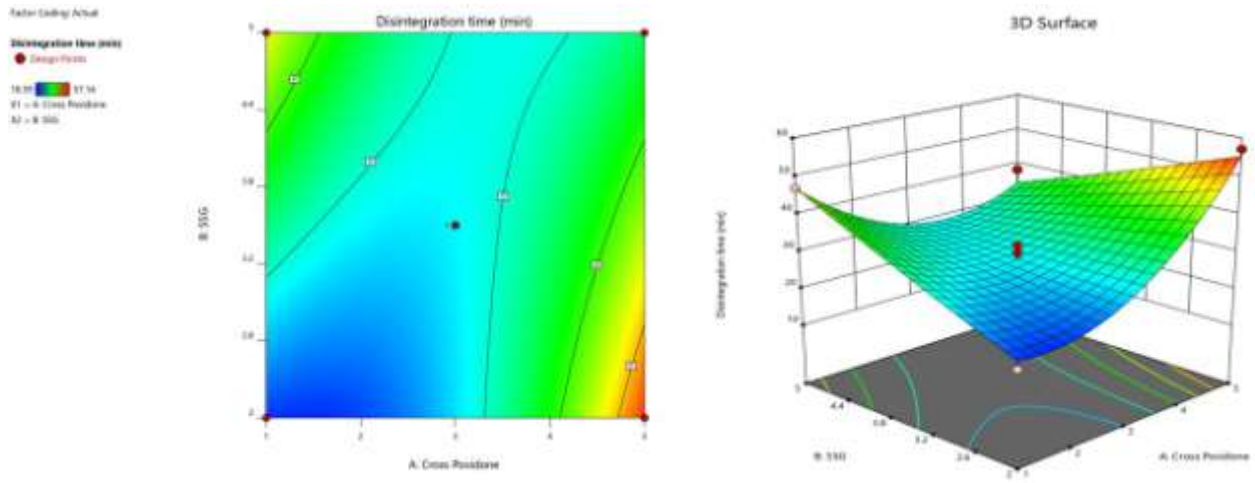
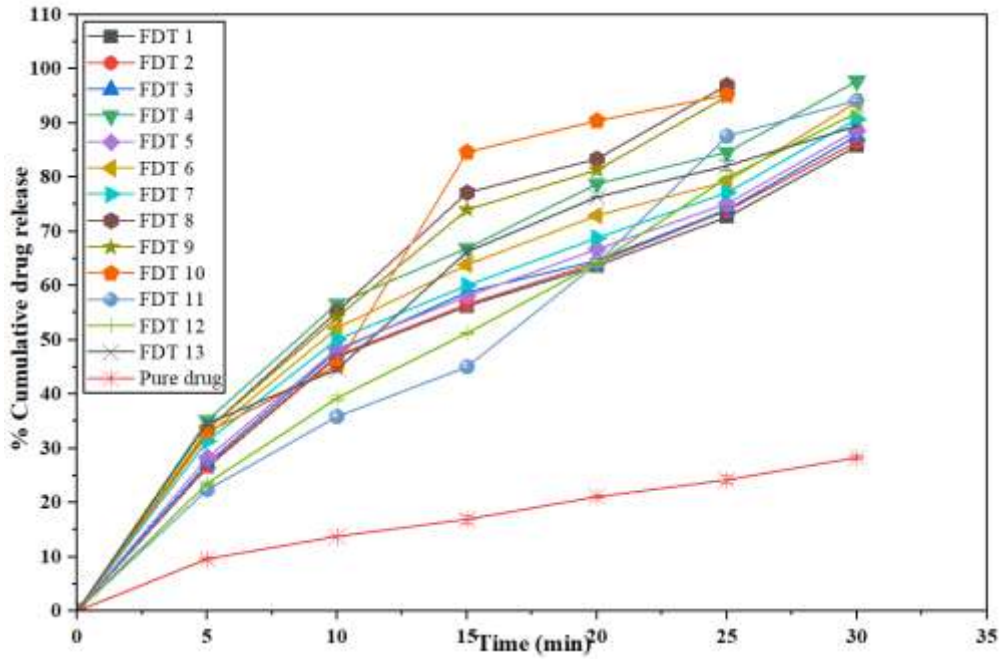


Figure 7: Contour plot (left) and 3D surface plot (right) showing the effect of independent variables—A: Cross Povidone and B: Sodium Starch Glycolate (SSG)—on the wetting time (Y_3) of Trimetazidine fast dissolving tablets.

***In Vitro* Drug Release Profile of Fast Dissolving Tablets:** All FDT formulations (FDT 1–13) exhibited significantly higher cumulative drug release compared to the pure drug. This confirms that the fast-dissolving tablets improve drug solubility and dissolution rate. FDT 10 showed the highest drug release (~100%) by 30 minutes, followed closely by FDT 8 and FDT 6, indicating optimal disintegration and dissolution properties. These formulations likely used efficient combinations of super disintegrants or optimized excipient ratios. The red curve representing the pure drug demonstrates poor solubility, with only ~25% release at 30 minutes [31]. This validates the need for formulating fast-dissolving systems to improve bioavailability. Most formulations display a steady increase indrugrelease over time, suggesting consistent disintegration and dissolution behavior [32].



All values are expressed as mean ±SD. n=3

Figure: In vitro drug release profile of various Trimetazidine Fast Dissolving Tablet (FDT) formulations (FDT 1–13) compared with the pure drug over a 30-minute period. All FDT formulations demonstrated significantly higher cumulative drug release than pure drug, indicating enhanced dissolution. Among them, FDT 10 showed the highest release (~100%), followed by FDT 8 and FDT 6, suggesting optimal formulation characteristics. The pure drug exhibited poor release

(<30%), highlighting the effectiveness of the fast-dissolving tablet approach in improving drug solubility and bioavailability. Data are presented as a mean % cumulative drug release (n = 3) [33].

CONCLUSION

This research proved that Trimetazidine Fast Dissolving Tablets (FDTs) were developed and evaluated in vitro using a solid dispersion strategy and a direct compression technique. Out of all the polymers that were evaluated, PEG 6000 had the most impact on Trimetazidine's solubility and dissolution rate. The formulation TSD4 had the highest drug content ($96.41 \pm 0.44\%$) and drug release (98.37%). Additionally, the formulation parameters, such as the concentration of super disintegrants (crospovidone and SSG) and compression force, were optimally fine-tuned using factorial design and response surface methodology (RSM). Faster disintegration, less wetting, more drug content, and nearly 100% drug release within 30 minutes were some of the enhanced in vitro performances displayed by the optimizedformulation (FDT 10). The optimized solid dispersion was found to be amorphous and to have improved dissolving behaviour, according to the SEM, DSC, and XRD investigations. This lends credence to the idea that Trimetazidine's bioavailability is enhanced in the FDT system. A potential oral delivery strategy for improving patient compliance and therapeutic efficacy, notably in controlling angina pectoris, is offered by fast-solving tablets of Trimetazidine, which were produced using solid dispersion and optimized via factorial design, according to the study's overall conclusions. Scaling up, in vivo investigations, and possible therapeutic use can be strongly supported by these findings.

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