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A novel analytical method for Dasatinib Tablet by liquid chromatography in the presence of Triton X-100 and biorelevant media in dissolution medium

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ABSTRACT: The purpose of this study is to develop and validate a rapid and simple HPLC method for determining the dissolution of Dasatinib in tablet form. The Dasatinib was separated from the dissolution medium containing Triton X-100 and also from biorelevant dissolution media having a complex matrix using high-performance liquid chromatography (HPLC-Shimadzu Prominence 20A) with a reverse-phase C18 column (particle size: 5µm; dimension: 4.6 mm X 250 mm). The column temperature was maintained at 30°C. The mobile phase consisted of a mixture of ammonium acetate buffer pH 5.0, acetonitrile, and water. The flow rate was set to 1.0 mL/min, and detection was performed at a wavelength of 230 nm. The method was validated for specificity, linearity and range, accuracy, precision, and robustness in accordance with ICH requirements. The retention time of Dasatinib was determined to be 4.1 minutes. Concentration range of the study was 7 µg/ml to 168 µg/ml, and the calibration was linear (r^2= 1.000). The developed method allows for easy detection of the percent drug release in Dasatinib tablets in pH 4.0 acetate buffer containing 1.0% Triton X-100 medium, which is the dissolution medium specified by the Food and Drug Administration and in biorelevant dissolution media (FaSSIF, FeSSIF, FaSSGF) showing in vitro-in vivo correlation (IVIC). The RP-HPLC technique used is stable, simple, accurate, and completely validated for the release of Dasatinib from tablet dosage forms.

KEYWORDS: Dasatinib; dissolution method; drug release %; RP-HPLC; tablet; validation

1. INTRODUCTION

Dasatinib (DST) is a tyrosine kinase inhibitor [1-3] with the chemical name N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl) piperazin-1-yl]-2-methylpyrimidin-4-yl] amino]-1,3-thiazole-5-carboxamide (Figure 1). It is a white to off-white powder that is insoluble in water and slightly soluble in ethanol and methanol. DST is used for the treatment of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) [4].

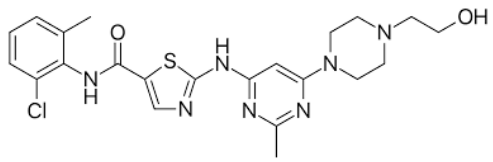

Figure 1. Chemical structure of DST

Due to DST belonging to BCS class II, characterized by high permeability and low solubility, the dissolution process is considered a crucial quality factor for the tablet formulation.[1] Drugs classified as BCS class IIa and IIb exhibit solubility that is dependent on pH and distinctive dissolution profiles within the physiological pH range [5]. The solubility in aqueous solutions significantly

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diminishes with increasing pH levels. Specifically, at pH 2.6, the solubility is 18.4 mg/mL, decreasing to 0.08 mg/mL at pH 4.5, and dropping below 1 µg/mL at pH 7.0. These changes align with its basic pKa values of 6.8 and 3.1 and a weakly acidic pKa of approximately 10.9. This indicates that minor adjustments in the pH of the dissolution media could result in substantial variations in the dissolution profile, especially as sink conditions are approached [6].

In the literature, previous experiences with DST dissolution showed that SLS was considered unsuitable as a surfactant. Several other commonly used nonanionic surfactants were assessed, including pluronic acid, cetyltrimethyl-ammonium bromide, and Triton X-100. Ultimately, Triton X-100 was chosen due to its convenience and widespread availability on a global scale [2, 6].

Given the recent approval of DST by the US FDA, there have been limited analytical methods reported for its quantification in both pure active pharmaceutical ingredient form (API) and biological samples [7–10]. However, there is currently a lack of a dedicated dissolution method designed to separate DST and Triton X-100 in all in-vitro dissolution media and also biorelevant dissolution media having an inherently complex matrix i.e. FaSSIF, FeSSIF and FaSSGF. In fact, developed assay methods sometimes may not work for dissolution analyses. This is because the contents in dissolution media may be incompatible especially with the mobile phase or column, leading to overlapping of peaks from the media with the main peak we intend to analyze.

The occurrence of this overlapping situation is indeed more prevalent in complex matrix media. For example, the use of a surfactant in the dissolution media, different salts, or mediums known as biorelevant media, which mimic in vivo dissolution conditions, can lead to this situation. Therefore, developing an effective analytical method is crucial. When examining articles in the literature, we generally see the development of an analytical method that operates in FDA-approved dissolution medium.

Moreover, compendial dissolving media frequently do not provide IVIVCs for class 2 medications because relevant physiological parameters are not taken into account. Biorelevant dissolution media are more effective in simulating the body environment, making them more useful for understanding in vitro-in vivo correlations. Therefore, working with these media is of great importance in bioequivalence studies [11].

The aim of this research is to establish and confirm a fast and straightforward HPLC technique for assessing the dissolution of DST in tablet form. The separation of DST from the dissolution medium, which includes Triton X-100 and biorelevant dissolution media (FaSSIF, FeSSIF and FaSSGF), was accomplished through high-performance liquid chromatography.

2. RESULTS AND DISCUSSION

2.1. Method development of DST

The developed method aimed to determine the drug release of DST in tablet formulations without interference from Triton X-100 in the dissolution medium. To achieve effective separation, we tested several mobile phases with different compositions. We obtained optimum separation with a mixture of Mobile Phase A and Mobile Phase B (10:90 v:v). Mobile Phase A is a mixture of ammonnium acetate buffer pH 5.0: acetonitrile (40:60 v:v) and Mobile Phase B is a mixture of asetonitrile : water (90:10 v:v). The stationary phase used for peak separation was a C18 column. The resulting chromatographic peak exhibited good symmetry, minimal tailing, and satisfactory resolution between DST and Triton X-100 is given in Figure 2.

2.2. Method validation

The HPLC instrument met the analysis criteria for system suitability tests for the DST chromatogram, as shown in Table 1.

2.2.1. Specificity

The specificity chromatograms showed no peaks due to the solvent, mobile phase, or placebo during the retention time of DST. Additionally, there was no interference between the solvent peaks from the dissolution medium pH 4.0 acetate 1.0% Triton X-100, biorelevant media (FaSSIF, FeSSIF and FaSSGF) and the active substance in the standard and sample solution chromatograms. It was

demonstrated that the large peak from Triton X-100 did not overlap with DST or any other solvent peaks (see Figure 3 and Figure 4). The method's selectivity was confirmed.

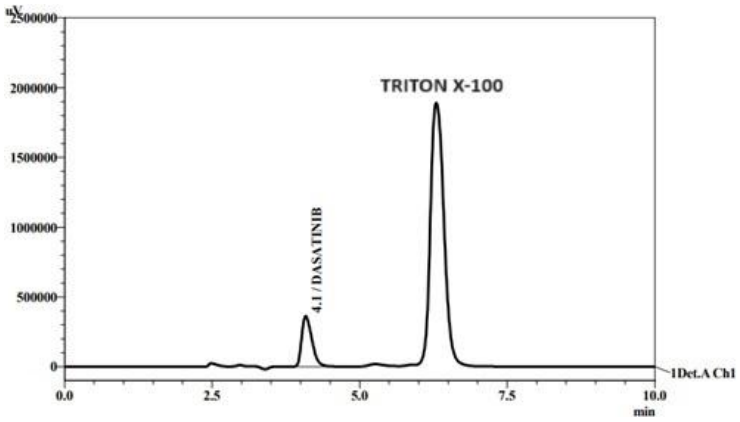

Figure 2. Chromatogram of DST working standard showing t_R 4.1 min.

Table 1. A summary of system suitability test parameters for DST.

Parameter	HPLC Results
Retention time (t_R)	4.1±0.01
No. of theoretical plate (N)	2501
Tailing factor (A_s)	1.50
Range	7 - 168 µg/mL
Linearity (Regression equation)	y = 31309861.772x - 16070.652
%Y Intercept	-0.37
Correlation coefficient	r^2 = 1.000
Accuracy at 80% level[a] (mean± SD)	99.49±1.81
Accuracy at 100% level[a] (mean± SD)	99.99±1.43
Accuracy at 120% level[a] (mean± SD)	99.61±1.54
Intermediate precision[b] (mean± SD and RSD%)	87.69±0.96 and 1.10
Intermediate precision[c] (mean± SD and RSD%)	92.67±1.96 and 2.12
Repeatability[b] (mean± SD and RSD%)	92.49±1.21 and 1.31
Repeatability[c] (mean± SD and RSD%)	96.24±3.42 and 3.55

[a] Replicates of three determinations.
[b] Replicates of six determinations of DST 140 mg Test Product.
[c] Replicates of six determinations of Sprycel 140 mg Film Tablet
Standard deviation (SD) and Relative standard deviation (RSD)

2.2.2. Linearity and range

Linearity was examined by injecting eight different concentrations of pure DST ranging from 7 to 168 µg/mL. The peak absorbance was plotted against the concentration to determine the slope, Y-intercept, and correlation coefficient of each DST concentration. (Figure 5) The data generated from the linearity studies showed a statistically significant correlation between peak absorbance and concentration. (Table 2) The DST method was found to be linear within the concentration range of 7 to 168 µg/mL, with regression coefficients of 1.000.

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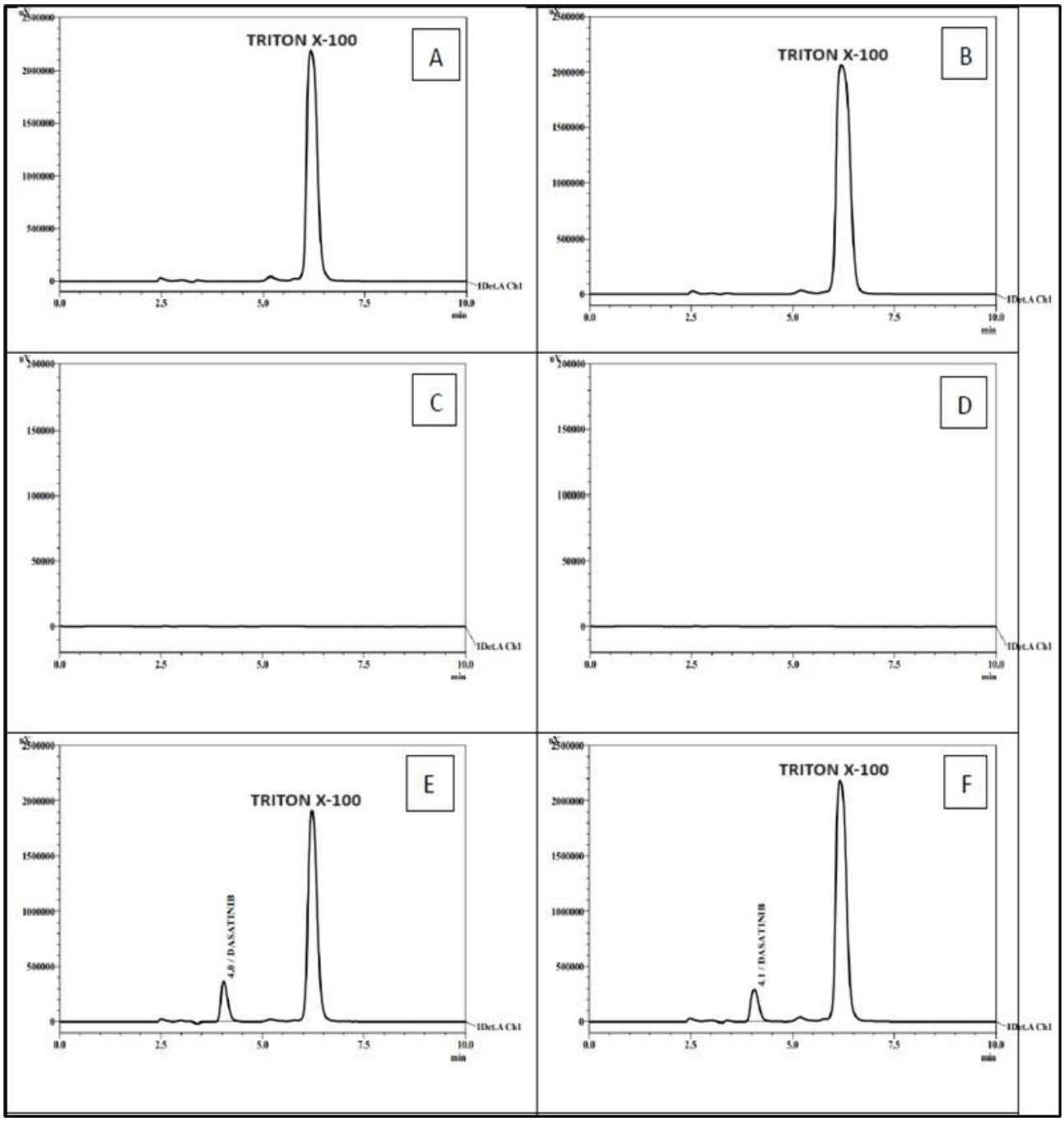

Figure 3. Chromatogram of blank (pH 4.0 acetate buffer in 1.0% Triton X-100) (A), placebo (B), mobile phase (C), blank without Triton X-100 (only pH 4.0 acetate buffer) (D), working standard (E) and sample at 45th minute showing t_R 4.1 min (F).

2.2.3. Accuracy

The accuracy of the analytical procedure was determined by comparing the true value to the experimental value. To ascertain accuracy, three concentrations (112, 140, and 168 µg/mL) were chosen from various ranges of the DST standard curves. DST recovery was examined in triplicate for drug sample concentrations at 80%, 100%, and 120%. Recovery experiments were used to examine the effects of excipients, which are frequently used in pharmaceutical drug formulations. The sample demonstrated a good level of quantitative skill as evidenced by the recovery of DST. Table 3 displays the accuracy results.

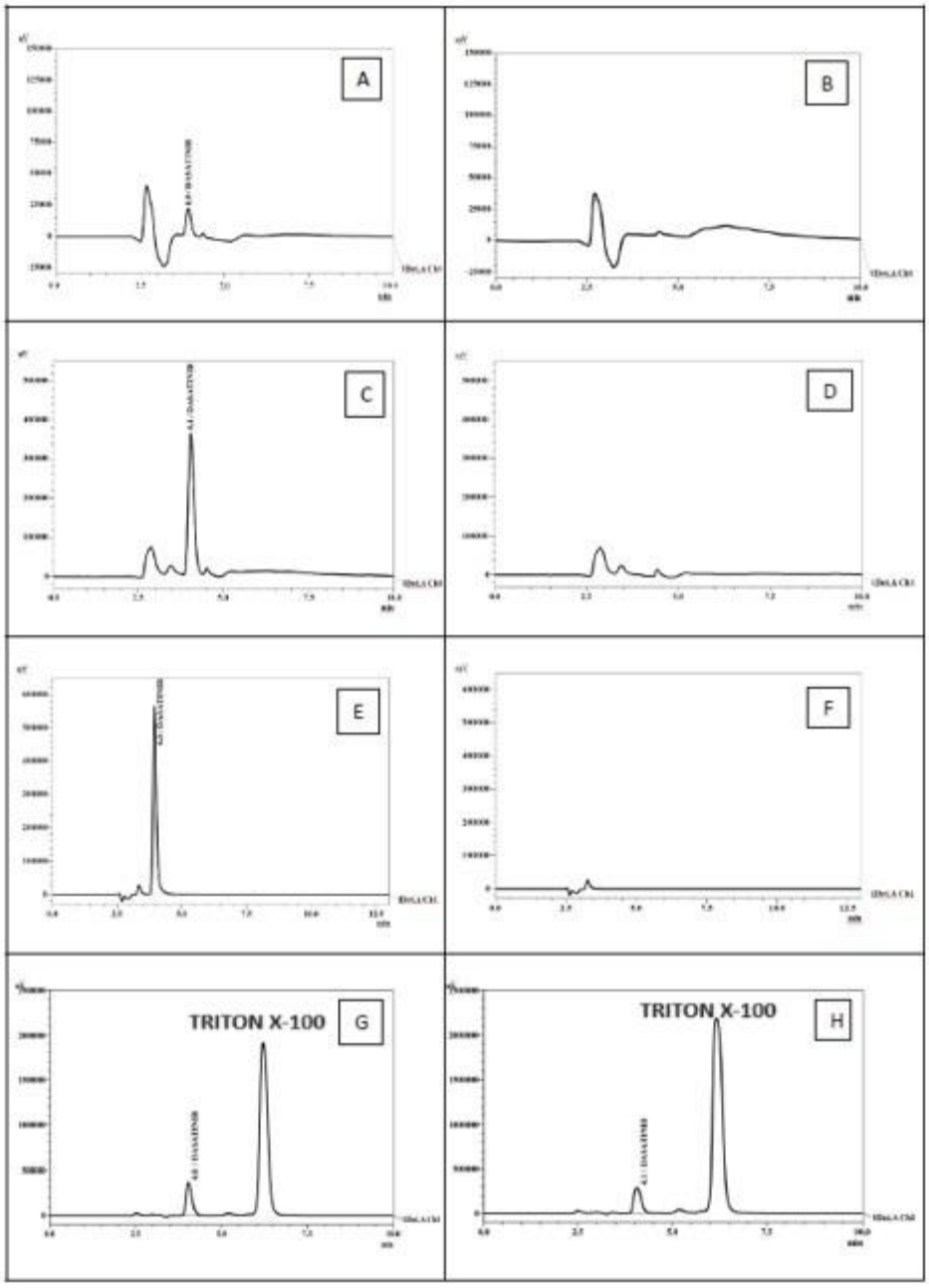

Figure 4. Chromatogram of FaSSIF medium (A), FaSSIF blank (B), FeSSIF medium (C), FeSSIF blank (D), FaSSGF medium (E), FaSSGF blank (F), working standard (G) and sample at 45th minute showing tR 4.1 min (H).

2.2.4. Precision

Following ICH regulations, we evaluated the precision of the developed HPLC method by conducting a study on intermediate precision and calculating the RSD% from six replicates of DST samples obtained from the dissolution study. To investigate the DST for intermediate precision analysis, we also examined DST samples on a different day using a different HPLC instrument. The precision of the method was provided.

Table 2. Results of linearity

Level (%)	Concentration (µg/ml)	Peak Ares (AU)
5%	7.05	214978
10%	14.10	430011
20%	28.20	853590
40%	56.40	1744308
60%	84.60	2640049
80%	112.80	3505597
100%	141.00	4400582
120%	169.20	5286225
	Correlation coefficient (r)	**1.000**
	Regression coefficient (r^2)	**1.000**
	Slope	**31309861.772**
	Y-Intercept	**-16070.652**
	Y-Intercept 100%	**-0.37**
	Residual sum of squares	**514874058**

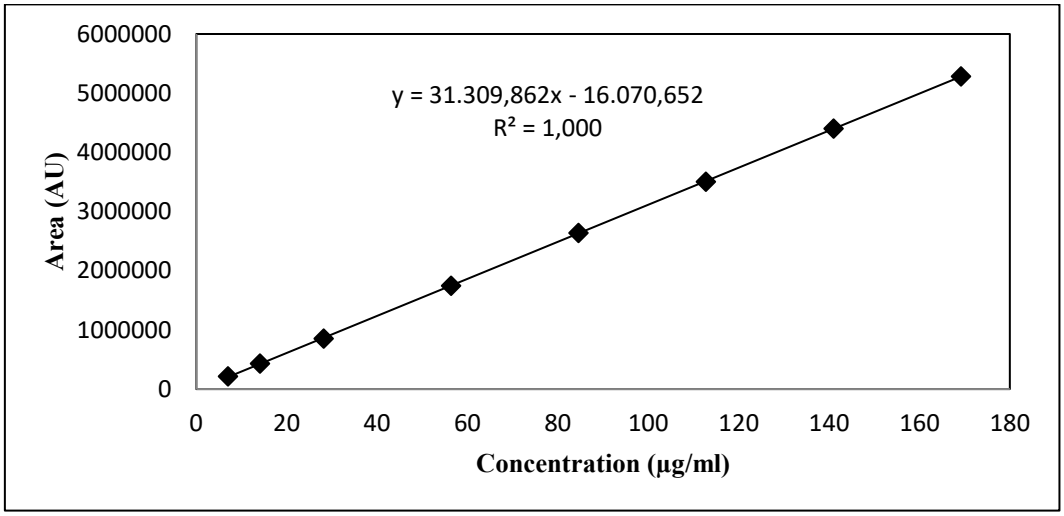

Figure 5. Calibration curve for DST with area of peak and concentration of standard solution

Table 3. Results of the determination of the accuracy of the method

Sample No	DST Recovery (%)
%80-1	98.18
%80-2	98.72
%80-3	101.56
%100-1	99.58
%100-2	101.58
%100-3	98.80
%120-1	98.29
%120-2	101.30
%120-3	99.25
SD	1.41
RSD %	1.41
Confidence Interval %	99.70±1.13

2.2.5. Robustness

The study of the method's robustness involved altering the chromatographic parameters, specifically the flow rate by ±0.1 mL/min and paddle rate by ±5 rpm for the dissolution system. Both standard and sample solutions were analyzed to demonstrate the method's reliability against these changes. The retention time of the active substance observed peak area, and RSD% were reported and compared with the precision results in accordance with acceptable specifications. The robustness results are displayed in Table 4.

Table 4. Evaluation data for robustness study of DST

Robustness parameters	t_R (minute)	Peak area*	% Drug Release ± SD	RSD%
Flow rate				
Flow rate (0.9 mL/min)	4.5	4534299	92.90±1.23	1.33
Flow rate (1.1 mL/min)	3.7	3726609	93.38±1.18	1.27
Pedal rotate speed				
55 rpm	4.1	3885807	88.44±1.83	2.07
65 rpm	4.1	4045006	92.06±0.99	1.08

*Results of six replicates, t_R Retention time, SD Standard deviation, RSD Relative standard deviation

2.2.6. Stability of the Solutions

The stability of both standard and sample solutions was established over a 48-hour period at room temperature (RT). The results are presented in the Table 5 below. In particular, it was shown by the solution stability results that the Triton X-100 peak did not shift over time in the the chromatograms. (Figure 6)

Table 5. Results of solution stability

Time	Conditions	Drug Released $\%_{Sample}$	Difference%	Working Standard %	Difference %
Initial	Room Temperature	92.0	NA	100.0	NA
12 Hours		92.4	0.4	100.0	0.0
24 Hours		92.2	0.2	100.1	0.1
48 Hours		92.1	0.1	99.3	0.7

3. CONCLUSION

A new analytical method developed and validated in the present study were found to be simple, sensitive, accurate, and precise. The results indicate that this method is suitable for dissolution studies and routine quality control analysis of DST present in 140 mg Film Tablet. Additionally, the linear range of this validation study includes related dosages of 20 mg, 50 mg, 70 mg, and 100 mg DST Tablets.

The effectiveness of the new method in bio-relevant media, which faithfully reflect in vivo conditions, was demonstrated. Our approach differs from existing methods in that it provides accurate findings in analytically challenging FaSSIF/FeSSIF/FaSSGF environments and in vitro dissolution media containing Triton X-100 over a wide pH range.

All parameters have been validated according to ICH guidelines Q2 (R1). Finally, the method is deemed specific, precise, robust, linear, and accurate within the range of 7 µg/ml to 168 µg/ml specification limit. It can be used for routine quality control analysis and stability studies of DST formulations.

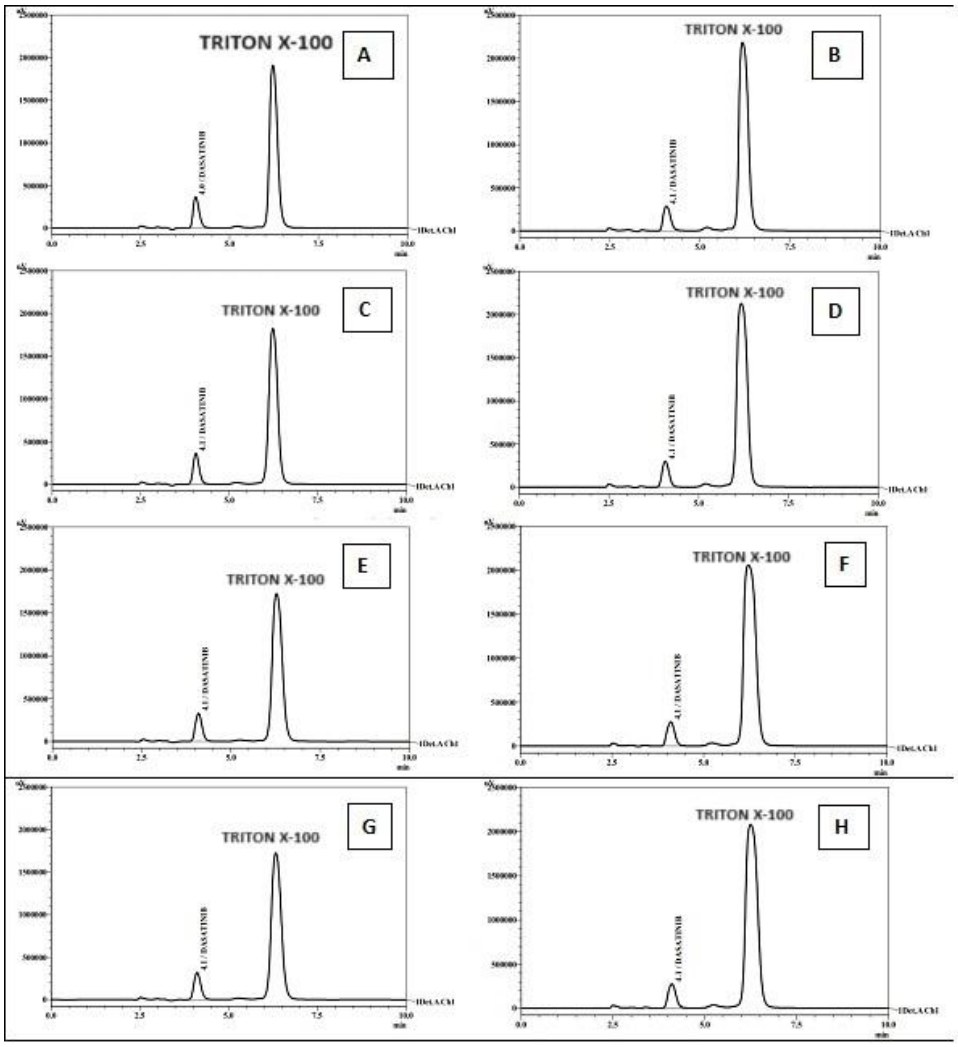

Figure 6. Chromatograms of solution stability; working standard t=0 (A), sample solution t=0 (B), working standard t=12th hour (C), sample solution t=12th hour (D), working standard t=24th hour (E), sample solution t=24th hour (F), working standard t=48th hour (G), sample solution t=48th hour (H).

4. MATERIALS AND METHODS

4.1. Chemicals and reagents

Dasatinib monohydrate pure drug substance was kindly provided by MSN Pharmaceuticals Limited API, India. Validation parameters were conducted using DST working standard purchased from Sigma-Aldrich (Batch Number: 0000272735). All solvents used in the analysis were of HPLC grade, including Elga Labwater Purelab Classic for water, J.T Baker HPLC Gradient Grade for methanol, and J.T Baker HPLC Far UV/Gradient Grade for acetonitrile. Analytical Grade reagents such ammonium acetate (Sigma Aldrich-Emsure/ACS, Reag. Ph Eur, Germany), potassium dihydrogen phosphate (Sigma Aldrich-Emsure/ISO, Germany), hydrogen peroxide 30% (Sigma Aldrich-Emprove, Ph Eur, BP, USP,Germany,), triethylamine (Sigma Aldrich for synthesis, Belgium), hydrochloric acid 37% (Isolab Chemicals, Germany), sodium hydroxide (Fluka Ph Eur, BP, NF, E524, pellets, 98-100.5%), glacial acetic acid 100% (Sigma Aldrich, Emprove, Ph Eur, BP, JP, USP, E 260, Germany) and o-phosphoric acid 85% (Sigma Aldrich Emsure, ACS, ISO, Reag. Ph Eur, Switzerland), Triton X-100 (Scharlau, EssentQ, Spain), 3F Powder (Biorelevant, Free Flowing Powder, UK), sodium chloride (Sigma Aldrich Emsure, ACS, ISO, Reag. Ph Eur, Denmark), sodium dihydrogen phosphate monohydrate (Sigma Aldrich Emsure, ACS, ISO, Reag. Ph Eur, Germany) were used also throughout the analysis. The DST tablets 'Sprycel 140 mg Tablets' were purchased as the original drug for

comparison with the test tablets. The original drug product, Sprycel, was manufactured by Swords Laboratories Unlimited Company T/A Bristol-Myers Squibb Pharmaceutical Operations. Each tablet contains 140 mg of DST. The test tablets, referred to as 'DST 140mg Test Product' in this article, are white to off-white coloured, round, biconvex, unnotched, film-coated tablets containing 140 mg of DST. The HPLC Shimadzu Prominence, equipped with a variable detector (SPD20A) and a pump (LC20AT), was used for all studies. The solutions were degassed using the Prominence DGU-20A5 degasser.

4.2. Chromatographic Conditions

A stainless-steel GL Science Inertsil ODS 3V column, measuring 4.6 x 250 mm and filled with octadecyl silane stationary phase with ligands bound to the silica surface, was used. The column temperature was set to 30°C. Standard and sample preparation was carried out using an Advantage Lab (AL-0412) ultrasonicator. The mobile phase consisted of a mixture of mobile phase A, which contained 0.05 M ammonium acetate buffer at pH 5.0, and an acetonitrile mixture (40:60 v/v), and mobile phase B, which contained an acetonitrile:water mixture (90:10). The final ratio of mobile phase was 10:90 (A:B v/v). Prior to use in the study, the mobile phase was filtered through a 0.45 µm RC membrane filter and degassed using an ultrasonic sonicator for 10 minutes. The mobile phase flow rate was 1.0 mL/min, with an injection volume of 10 µL and a wavelength of 230 nm. 0.18 M potassium dihydrogen phosphate was used as diluent throughout the study and the pH of the solution was maintained at 2.5 by adjusting with o-phosphoric acid.

4.3. Dissolution Conditions

The DISTEK Evolution 6300 dissolution apparatus was used for all dissolution experiments, following the Food and Drug Administration Dissolution Methods Database. The dissolution medium was prepared as per FDA guidelines using pH 4.0 acetate buffer with 1% Triton X-100 (Scharlau, EssentQ, Spain) with a volume of 1000 ml and a temperature of 37°C. The USP dissolution apparatus II (paddle) was set to 60 rpm for 45 minutes. 3 ml of the sample were collected from each of the six dissolution vessels and filtered through a PTFE filter. Moreover, dissolution analysis with biorelevant media (FaSSIF, FeSSIF, FaSSGF) were also performed.

4.3.1. Preparation of Dissolution Medium pH 4.0 with 1.0% Triton X-100

To prepare the solution, dissolve 19.13 g of sodium acetate trihydrate in 6040 ml of water. Then, add 300 ml of 0.2 N acetic acid solution and 64 ml of Triton X-100. Adjust the pH to 4.0 ± 0.5.

4.3.2. Preparation of Dissolution Medium FaSSIF

To prepare the solution, dissolve 2.688 g of NaOH pellets, 25.306 g of NaH_2PO_4 Monohydrate, 39.590 g of NaCl in 5760 ml of purified water. Adjust the pH to 6.5 with either 1 N NaOH or 1 N HCl. Make up to volume 6400 ml with purified water at room temperature. Add 14.336 g of 3F powder to this solution and stir until the powder is completely dissolved. The solution is ready to use after 2 hours until it will become slightly opalescent.

4.3.3. Preparation of Dissolution Medium FeSSIF

To prepare the solution, dissolve 25.856 g of NaOH pellets, 55.360 g of Glacial Acetic Acid, 75.994 g of NaCl in 5760 ml of purified water. Adjust the pH to 5.0 with either 1 N NaOH or 1 N HCl. Make up to volume 6400 ml with purified water at room temperature. Add 71.680 g of 3F powder to this solution and stir until the powder is completely dissolved.

4.3.4. Preparation of Dissolution Medium FaSSGF

To prepare the solution, dissolve 12.794 g of NaCl in 5760 ml of purified water. Adjust the pH to 1.6 with HCl. Make up to volume 6400 ml with purified water at room temperature. Add 0.382 g of 3F powder to this solution and stir until the powder is completely dissolved.

4.3.5. Preparation of 0.05 M ammonium acetate buffer solution

To prepare the solution, dissolve 3.750 g of ammonium acetate in 1000 ml of water. Then, add 1 ml of triethylamine and adjust the pH to 5 with acetic acid. Finally, filter the solution through a 45 µm RC filter.

4.3.6. Preparation of Standard solution

The standard stock solution was prepared by placing 28 mg of DST standard into a 100 mL volumetric flask and adding 50 mL of diluent. The mixture was sonicated for 15 minutes in an ultrasonic bath. Once the solution reached room temperature, it was diluted to volume to achieve a concentration of 280 µg/mL. A 10 ml flask was used to dilute 5 ml of the stock solution with the dissolution medium to the required volume. The resulting solution was mixed well and used to test all DST validation parameters at the required concentrations. The final concentration of the standard solution was 140 µg/mL.

4.3.7. Preparation of Sample solution

Each individual dissolution vessel was filled with 1000 ml of dissolution medium. Once the temperature reached 37 ± 0.5°C, one tablet containing 140 mg of DST was added to each vessel (six tablets in total). The paddle was rotated at a speed of 60 rpm. After 45 minutes, an aliquot was withdrawn from each vessel and filtered individually through a 0.45 µm PTFE filter before being transferred to an HLC vial (DST-140mg =0.14 mg/mL).

4.4. Method Validation

The method was validated according to ICH requirements. The validated parameters included specificity, linearity and range, accuracy, precision, and robustness.

4.4.1. Specificity

A specificity (selectivity) test was conducted to determine the method's capacity for measuring the active substance intended to be measured in the sample under study. For the selectivity test, mobile phase, blank, placebo, standard, and sample solutions were injected into the HPLC system, and the resolution of the peaks from the nearest eluting peak was measured. The acceptance criteria were as follows: there should be no peak due to blank, mobile phase, or placebo in the retention time of DST in the standard and sample solution chromatograms. It should be demonstrated that DST does not overlap with other peaks in the chromatograms of the standard and sample solutions. In other words, the standard and sample chromatograms should be similar.

4.4.2. Linearity and range

The linearity of an analytical procedure refers to its ability to demonstrate test results that are directly proportional to the concentration of the analyte in samples over a specified range. To test linearity, various concentrations of DST solutions were prepared from standard stock solutions and diluted with diluent. The concentration range of 7 µg/mL to 168 µg/mL was identified, and eight separate concentrations (7, 14, 28, 56, 84, 112, 140 and 168 µg/mL) were selected. To evaluate linearity, we performed least square regression analysis on the peak area, resulting in a calibration equation with slope, Y-intercepts, and correlation coefficient (r^2).

4.4.3. Accuracy

The accuracy of an analytical method is determined by the closeness between the expected and experimental values. It is calculated by the percent recovery of the analyte. To confirm the accuracy of the method for quantifying DST, raw material solutions were prepared by adding 80%, 100%, and 120% concentrations to a constant amount of placebo. A total of nine samples were prepared, with three for each level. Triplicate samples of three different concentrations of DST were mixed with a pure drug placebo containing 112 µg/mL, 140 µg/mL, and 168 µg/mL DST (80%, 100%, and 120% of label claim). The recovery was then calculated using the peak area.

4.4.4. Precision

The precision of the developed method was evaluated for both intra-day and inter-day precision, in accordance with ICH recommendations. To achieve this, a dissolution study was

conducted on six dosage units, and the percentage of drug release, average percentage of drug release, and percentage relative standard deviation (RSD) of the samples were calculated. To ensure precision, the RSD percentage of the DST peak absorbance was measured. To determine the intermediate precision, the experiment was repeated on a different day using a different HPLC system and conducted by a different analyst. The % relative standard deviation (RSD) value was calculated based on the DST absorbance obtained. The % RSD for the dissolution of six test preparations should not exceed 5.0.

4.4.5. Robustness

Robustness refers to the reliability of an analytical method even when performed under slightly varied conditions. To determine the robustness of the method, the flow rate was deliberately changed by ±0.1 mL/min and the dissolution paddle rate by ±5 rpm. The method was then used to test two samples and two standards of DST (0.14 g/mL) under all the aforementioned conditions. Under all altered circumstances, we compared all system suitability characteristics and conditional modifications.

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