Development and Validation of RP-HPLC Method Along with Forced Degradation Study for Estimation of Sorafenib in Bulk Drug and Pharmaceutical Dosage Form

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Abstract

The present study focuses on the development and validation of a simple, precise, accurate, and robust reverse-phase high-performance liquid chromatography (RP-HPLC) method for the quantitative estimation of **Sorafenib** in bulk drug and pharmaceutical dosage form, along with its forced degradation behavior under various stress conditions. Method development was carried out using a Phenomenex C18 column (250 mm × 4.6 mm, 5 µm), with a mobile phase consisting of **Acetonitrile and 0.05% orthophosphoric acid (75:25 v/v)** in isocratic mode at a flow rate of **1.0 mL/min**. The detection was performed at **265 nm**, and Sorafenib showed a retention time of approximately **4.58 minutes**. The method was validated as per ICH Q2(R1) guidelines.

System suitability parameters such as theoretical plates (>15000), asymmetry (<1.2), and % RSD (<0.1%) confirmed the suitability of the method. The assay of the marketed tablet formulation showed **99.53%** drug content, indicating compliance with pharmacopeial specifications. Forced degradation studies demonstrated that Sorafenib is stable under thermal, photolytic, and oxidative conditions but susceptible to acidic and alkaline hydrolysis. The method showed excellent linearity over the concentration range of **80–120 µg/mL** with a correlation coefficient (R^2) of **0.9999**. The **LOD and LOQ** were found to be **0.74 µg/mL** and **2.23 µg/mL**, respectively. Accuracy was confirmed through recovery studies with results in the range of **98.95%–100.68%**, and precision studies showed % RSD well within acceptable limits. Robustness testing demonstrated the method's reliability under minor deliberate changes in chromatographic conditions.

In conclusion, the developed RP-HPLC method is validated, stability-indicating, and suitable for routine analysis of Sorafenib in bulk and dosage forms.

Key Words: Sorafenib, RP-HPLC, Method Validation, Forced Degradation, Linearity, System Suitability Etc.

1. Introduction

Sorafenib tosylate is an oral multikinase inhibitor that targets both the serine/threonine and receptor tyrosine kinases involved in tumor progression and angiogenesis. It is widely used in the treatment of advanced hepatocellular carcinoma, renal cell carcinoma, and differentiated thyroid carcinoma refractory to radioactive iodine treatment[1]. Sorafenib functions by inhibiting several intracellular and cell surface kinases, including VEGFR-2, PDGFR-β, c-KIT, and RAF kinases[2]. Due to its critical therapeutic role in oncology, the accurate quantification of Sorafenib in pharmaceutical dosage forms is essential for quality control and regulatory compliance.

Analytical method development and validation are integral components of pharmaceutical analysis, ensuring that the drug substance and products are evaluated with precision, accuracy, and reliability. Among the various techniques available, Reverse Phase High-Performance Liquid Chromatography (RP-HPLC) has emerged as the most preferred tool due to its robustness, reproducibility, high sensitivity, and specificity[3]. It is especially valuable for stability-indicating assay methods which are crucial for determining drug stability under various stress conditions.

Forced degradation studies, as recommended by the International Council for Harmonisation (ICH), provide valuable insights into the chemical behavior of a drug under acidic, basic, oxidative, photolytic, and thermal stress[4]. These studies help establish the degradation pathways and intrinsic stability of the drug, thereby ensuring the development of a suitable stability-indicating method[5]. Furthermore, ICH guideline Q2(R1) outlines the parameters necessary for analytical method validation, including linearity, accuracy, precision, specificity, limit of detection (LOD), limit of quantitation (LOQ), and robustness[6].

Although some methods have been previously reported for Sorafenib estimation using LC-MS and HPLC, many are either cost-intensive or not validated as per ICH norms[7]. Therefore, the aim of the present study is to develop a simple, precise, accurate, and validated RP-HPLC method for the quantification of Sorafenib in bulk drug and pharmaceutical dosage form. This method also incorporates forced degradation studies to establish its stability-indicating potential.

2. Materials and Methods [8-20]

2.1 Materials

API: Sorafenib Tosylate

- **Solvents and Reagents**: Methanol, Acetonitrile, 0.05% Orthophosphoric Acid, Water (HPLC grade)
- **Marketed Sample**: Soranib 200 mg tablet

2.2 Preliminary Characterization

2.2.1 Physical Properties

- Sorafenib Tosylate: Light yellow powder with characteristic odor.
- Factor for conversion: 0.730 (MW Sorafenib / MW Sorafenib Tosylate)

2.2.2 Solubility

- Soluble in methanol and water with sonication at 3 mg/mL concentration.

2.3 UV Spectroscopy

- **Solvent**: Methanol
- **Wavelength scan**: 200–400 nm
- **λmax identified**: 265 nm

2.4 Method Development via RP-HPLC

- **Column**: Phenomenex C18 (250 × 4.6 mm, 5 µm)
- **Mobile phase trials**: Methanol:Water, Acetonitrile:Water, and combinations with 0.05% OPA
- **Optimized condition (Trial 6)**:

Chromatographic Conditions:

- Detector: U.V. Detector
- Column: Phenomenex C18
- Column Dimension: 250 mm X 4.6 mm i.d., 5µm

- Column Oven temperature: 40°C
- Injection Volume: 20µl
- Wavelength: 238 nm
- Mobile phase: Acetonitrile: 0.05% OPA in water (75:25)
- Flow Rate: 1.0 ml/min
- Run time: 10 Minutes

- **Preparation of System suitability test (Sorafenib Tosylate standard solution):**
- Weighed accurately 27.40 mg of Sorafenib Tosylate (Equivalent to 20 mg of Sorafenib) and transferred it in a clean and dried 20 ml of volumetric flask, added 15 ml of methanol, sonicated to dissolve it completely, made the volume up to the mark with methanol. Further diluted 1ml to 10 ml with mobile phase. (100 PPM of Sorafenib)
- System suitability is a Pharmacopoeial requirement and is used to verify, whether the chromatographic system is adequate for analysis to be done. The tests were performed by collecting data from five replicate injection of standard drug solution and the results are recorded.

2.5 System Suitability

- **Standard solution**: 100 PPM
- Criteria:
  - %RSD $\leq$ 2.0
  - Tailing Factor $\leq$ 2.0
  - Theoretical Plates $\geq$ 2000

2.6 Sample Analysis

- **Formulation**: Soranib 200 mg tablets
- Sample preparation involved methanol extraction, filtration, and dilution with mobile phase.
- % Assay calculated using validated formula.

2.7 Forced Degradation Studies

Conditions Applied

- **Physical**: Thermal (105°C, 48 hrs), Photolytic (sunlight, 72 hrs)
- **Chemical**:
  - Acid (5 N HCl, 8 & 4 hrs)
  - Base (5 N NaOH, 8 & 3 hrs)
  - Oxidative (30% H_2O_2, 8 & 24 hrs)

Objective: 5–20% degradation range

- Samples analyzed and % degradation calculated.

3. Validation as per ICH Guidelines

3.1 Specificity

- No interference from placebo or excipients.
- Blank and placebo injections confirmed the method's specificity.

3.2 Linearity

- Concentration range: 80–120 µg/mL
- Correlation coefficient: >0.998
- %RSD: <2%

3.3 Accuracy (% Recovery)

- Recovery within 98–102% at all levels (80%, 100%, 120%)
- %RSD: <2%

3.4 Precision

Repeatability

- Six replicates analyzed
- % Assay: 90–110%
- %RSD: <2%

Intermediate Precision

- Performed on different day
- %RSD: <2% across 12 samples

3.5 Limit of Detection and Quantification

- LOD and LOQ calculated from calibration curve:
  - LOD = 3.3 σ / S
  - LOQ = 10 σ / S

3.6 Robustness

- Parameters varied:
  - Flow rate ±0.1 mL/min
  - Temperature ±2°C
  - Wavelength ±3 nm
- System suitability maintained across variations.

3.7 Solution Stability

- Standard and test solutions stable for 24 hours under lab conditions.

3.8 Filtration Study

- Filter compatibility studied with PVDF and Nylon filters.
- No significant loss observed post-filtration.

4. RESULTS AND DISCUSSION

4.1 Preliminary Characterization and Identification of Drug

4.1.1 Color, Odour, and Appearance

The physical examination of Sorafenib tosylate revealed that it is a **white, odourless, amorphous powder**. These results are in line with the reported physical characteristics, confirming the identity and physical form of the drug.

4.1.2 Solubility Study

Solubility testing demonstrated that Sorafenib was **insoluble in water** but showed **good solubility in methanol**, which was thus selected as the diluent for preparing stock solutions.

4.2 UV Spectral Analysis

4.2.1 Selection of Solvent

Methanol was selected based on its compatibility and ability to dissolve Sorafenib completely.

4.2.2 Selection of Analytical Wavelength

1) Blank Methanol:

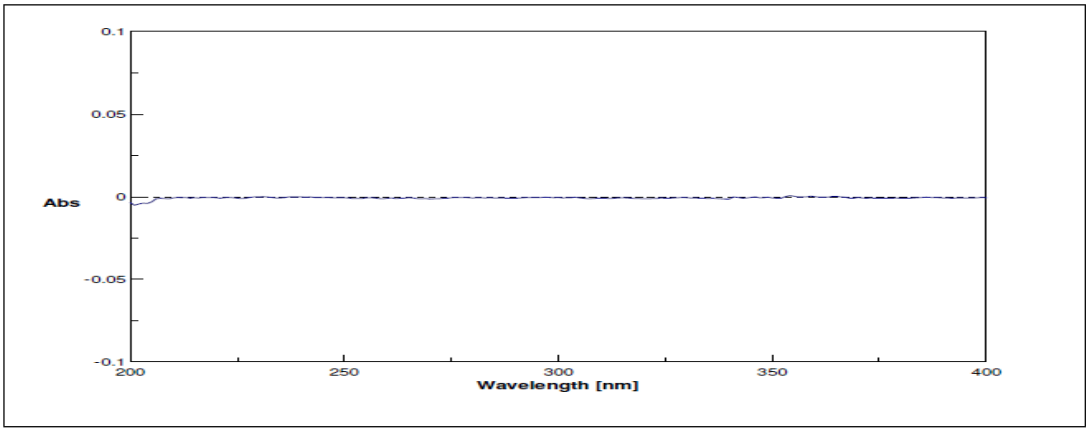


Figure. No.1: UV spectrum of Methanol as a blank

2) Sorafenib STD solution: (10 PPM)

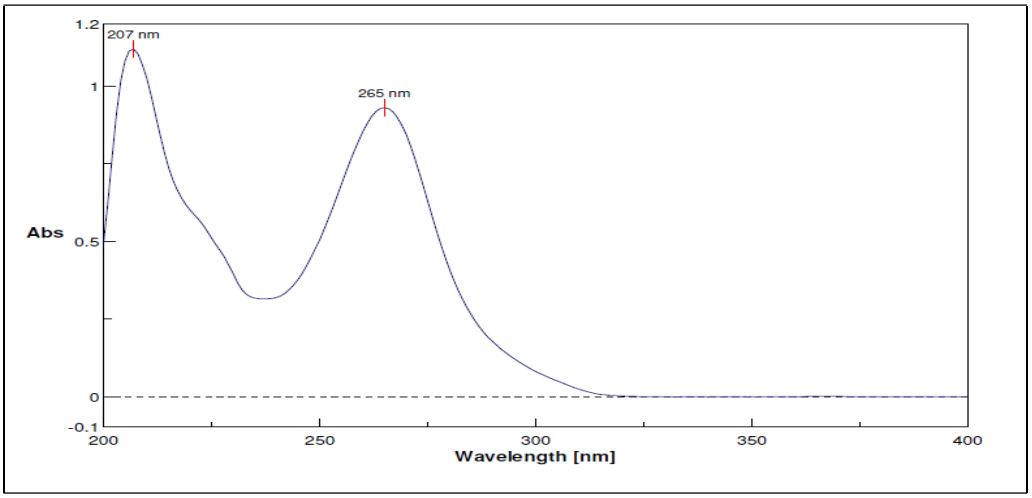


Figure. No. 2: UV spectrum of Sorafenib

The UV spectrum of Sorafenib revealed two absorption maxima at 207 nm and 265 nm. The 265 nm wavelength was chosen for analytical purposes, avoiding 207 nm due to its proximity to the solvent cut-off region.

4.3 Method Development by RP-HPLC

4.3.1 Optimization of Chromatographic Conditions

- **Column**: Phenomenex C18 (250 mm × 4.6 mm, 5 µm)
- **Mobile Phase**: Acetonitrile: 0.05% OPA in water (75:25 v/v)
- **Flow Rate**: 1.0 mL/min
- **Detection Wavelength**: 265 nm
- **Injection Volume**: 20 µL
- **Temperature**: 40°C
- **Run Time**: 10 minutes
- **Chromatogram:**

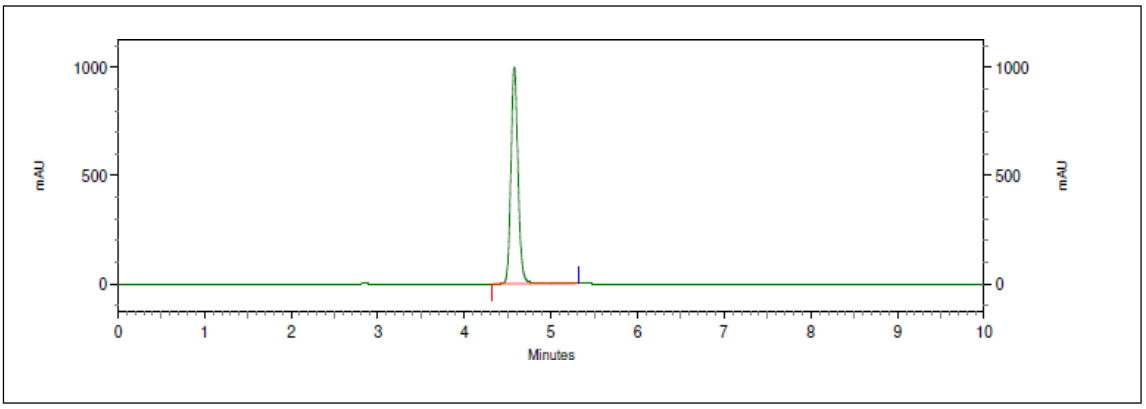


Figure. No. 3: Typical chromatogram of Trial 6

Six trials were conducted. Initial trials either showed no elution or poor peak characteristics. Trial 6 offered the best performance with a retention time of 4.58 minutes, asymmetry of 1.13, and theoretical plates of 15057. Therefore, conditions from Trial 6 were finalized (Table 1).

4.4 System Suitability Test

All five replicate injections of the standard solution passed the system suitability criteria:

- % RSD of area: **0.05%** (Limit: NMT 2.0%)
- Theoretical plates: **>15000** (Limit: NLT 2000)
- Asymmetry: **1.13–1.14** (Limit: <2.0)

These results confirmed the system's suitability for routine analysis.

Table No. 1: Results for System Suitability Test of Sorafenib

Sr No.	Standard solution	Area	Asymmetry	Theoretical plates
1	Standard_1	96013254	1.13	15085
2	Standard_2	96024587	1.13	15078
3	Standard_3	96011204	1.13	15068
4	Standard_4	96124857	1.14	15071
5	Standard_5	96056857	1.14	15082
Mean		96046152	1.13	15077
STD Dev.		47638.651		
% RSD		0.05		

Data interpretation: It was observed from the data tabulated above; the method complies with system suitability parameters. Hence, it can be concluded that the chromatographic methods adequate for intended analysis.

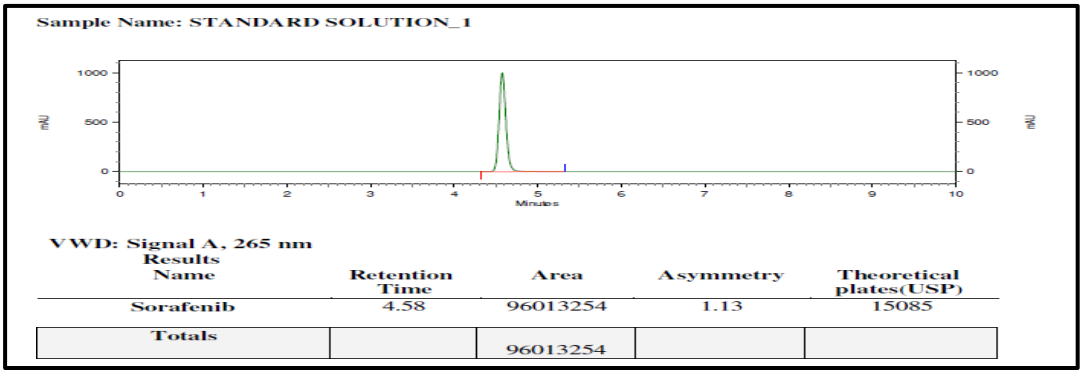


Figure No. 4: Typical chromatogram Standard solution 1 of system suitability solution

4.4.1 Analysis of Marketed Test samples (Assay)

a) Soranib 200 mg Tablet:

Weight of 20 tablets = 10594.0 mg

Average weight of tablet = 10594.0/ 20 = 529.7 mg

Table No. 2: Assay results of Soranib 20 mg tablet

Sample	Area	% Assay	Mean Assay
Sample 1	95542567	99.62	99.53
Sample 2	95512886	99.44	

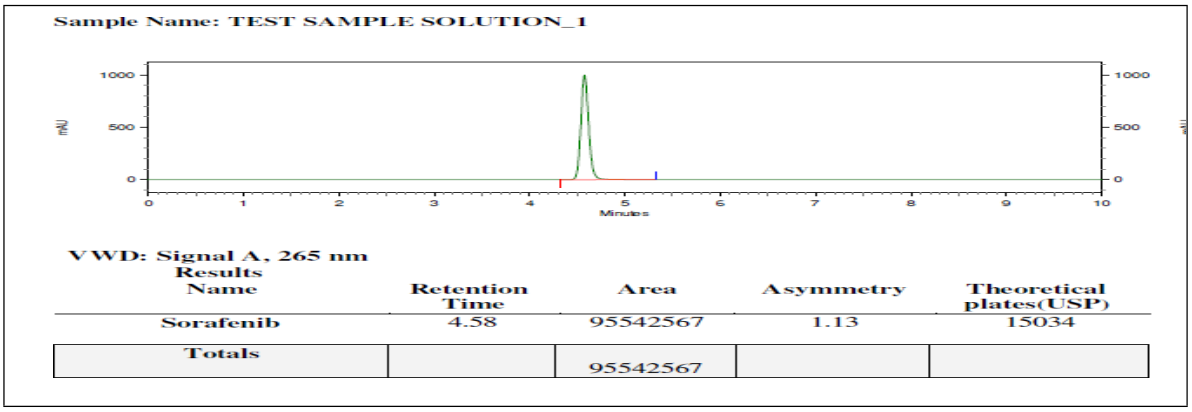


Figure No. 5: Typical chromatogram Test Sample solution

Acceptance criteria:

1) % Assay found should be in the range of 90-110%.

Data interpretation:

The assay of the marketed tablet (Soranib 200 mg) was conducted, and the **mean assay was 99.53%**, which is within the acceptable range of **90–110%**.

4.5 Forced Degradation Study

Forced degradation was carried out under physical and chemical conditions:

Condition	Exposure	% Degradation
Control	-	0.00%
Thermal	105°C for 48 hours	Nil
Photolytic	Sunlight for 72 hours	Nil
Acid (Trial 1)	5N HCl, 8 hrs	32.88%
Acid (Trial 2)	5N HCl, 4 hrs	17.17%
Base (Trial 1)	5N NaOH, 8 hrs	39.68%
Base (Trial 2)	5N NaOH, 3 hrs	15.16%
Peroxide	30% H_2O_2, up to 24 hrs	Nil

Interpretation: Significant degradation was observed in acid and base hydrolysis. No degradation was found in thermal, photolytic, or peroxide conditions, indicating **acid-base lability** and **oxidative and photostability** of Sorafenib.

4.6 Method Validation

4.6.1 Filtration Study

Both 0.45 µ PVDF and Nylon filters met the acceptance criteria (NMT 2.0% absolute difference). PVDF showed minimal interference and was preferred.

4.6.2 Solution Stability

Standard and test solutions were stable at room conditions for **up to 24 hours**, with % absolute differences well below 2.0%.

4.6.3 Specificity

No interference was observed at Sorafenib's retention time from blank or placebo solutions, confirming specificity.

4.6.4 Linearity and Range

Table No. 3: Linearity Data for Sorafenib

Level	Conc (µg/mL)	Area	Mean	% RSD
80%	80.00	76759536 76742512 76785419	76762489	0.028
90%	90.00	86143497 86102591 86245863	86163984	0.086
100%	100.00	96012584 96025843 96042158	96026862	0.015
110%	110.00	105143888 105025965 105065894	105078582	0.057
120%	120.00	115169941 115130259 115093256	115131152	0.033

Table No. 4: Linearity summary of Sorafenib

Sr no.	Parameter	Result value	Acceptance criteria
1	Beer's linearity range	80.00-120.00µg/mL	NA
2	Correlation coefficient (R^2)	0.99990	NLT 0.98
3	Intercept	180689.80	To be report
4	Slope	956519.24	To be report
5	% RSD for area at each level	NA	NMT 2.0

4.6.6 Accuracy (Recovery Study)

1) ACCURACY (RECOVERY):

The accuracy of an analytical method is the closeness of test results obtained by that method to the true value. The accuracy of an analytical method is determined by applying the method to analyzed samples to which known amounts of analyte have been added.

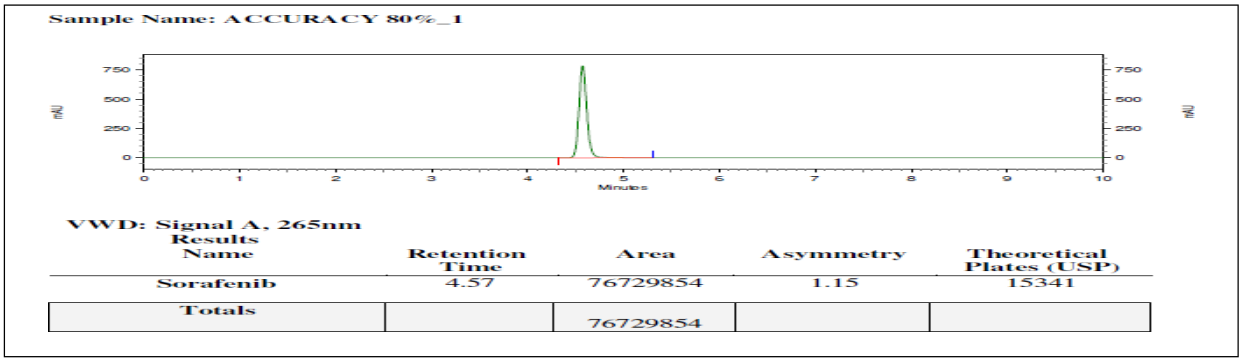
Table No. 5: Result and statistical data of Accuracy of Sorafenib

Level (%)	Area	Recovered conc (µg/mL)	Added conc (µg/mL)	% Recovery	Mean Recovery	% RSD
80	76729854	79.89	79.86	100.04	99.61	0.371
	76512487	79.66	80.15	99.39		
	76328976	79.47	79.94	99.41		
100	96215874	100.18	100.01	100.17	99.78	0.721
	96410257	100.38	100.16	100.22		
	95325988	99.25	100.30	98.95		
120	115236840	119.98	120.09	99.91	100.28	0.385
	115410235	120.16	119.87	100.24		
	115841258	120.61	119.79	100.68		

Overall Recovery: 99.89 %

% RSD for Overall Recovery: 0.539

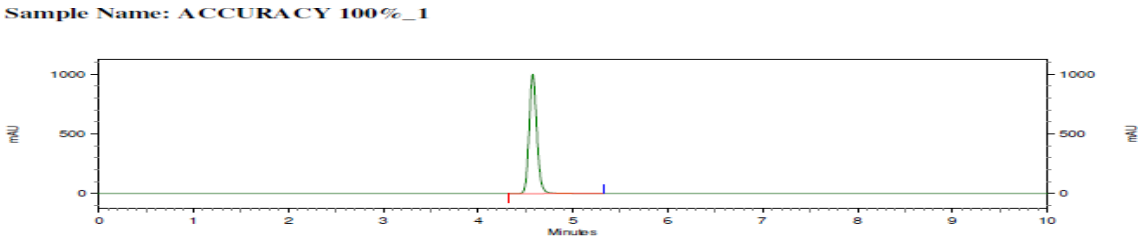
Chromatograms:



VWD: Signal A, 265nm
Results

Name	Retention Time	Area	Asymmetry	Theoretical Plates (USP)
Sorafenib	4.57	76729854	1.15	15341
Totals		76729854		

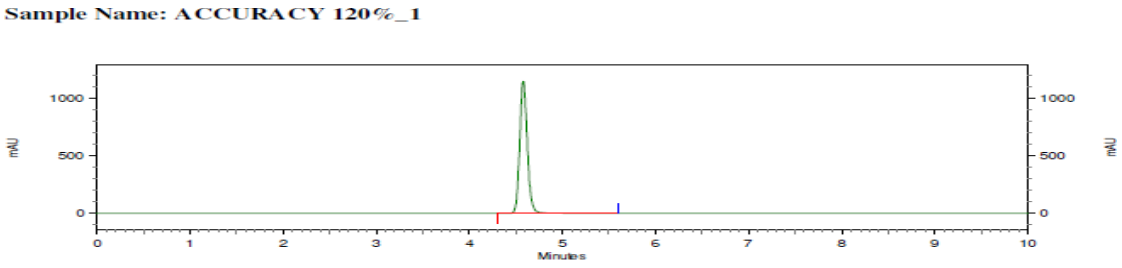
Figure No.6: Typical chromatogram of Accuracy 80%



VWD: Signal A, 265 nm
Results

Name	Retention Time	Area	Asymmetry	Theoretical plates(USP)
Sorafenib	4.58	96215874	1.14	15105
Totals		96215874		

Fig. No. 7: Typical chromatogram of Accuracy 100%



VWD: Signal A, 265 nm
Results

Name	Retention Time	Area	Asymmetry	Theoretical Plates (USP)
Sorafenib	4.58	115236840	1.14	14912
Totals		115236840		

Figure No.8: Typical chromatogram of Accuracy 120%

Data interpretation: Recovery of analytical procedure was found well within acceptance criteria at all 3 levels. % Recovery not gets hampered by changed in analyte concentration.

2) PRECISION

Precision of an analytical method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings of a homogenous sample. Precision of an analytical method is usually expressed as standard deviation or relative standard deviation. Precision was performed on Test sample.

Table No. 6: Result of Intra- day and Inter- Day Precision for Sorafenib

	Sample	**Test Sample (mg)**	**Area**	**% Assay**
Repeatability	Sample 1	264.5	95320417	99.39
	Sample 2	264.7	95841286	99.85
	Sample 3	264.2	95012485	99.18
	Sample 4	265.1	94328749	98.13
	Sample 5	264.8	94687284	98.61
	Sample 6	264.4	95210329	99.31
	Mean			**99.08**
	STD DEV			**0.6124**
	% RSD			**0.618**
Intermediate precision (Inter-Day)	Sample 1	264.1	95541328	99.77
	Sample 2	264.5	95321467	99.39
	Sample 3	265.2	94857586	98.64
	Sample 4	265.4	94725789	98.43
	Sample 5	264.8	94820146	98.75
	Sample 6	264.7	95125418	99.11
	Mean			**99.02**

	STD DEV	**0.5045**
	% RSD	**0.510**
Repeatability Plus Inter-day	**Mean**	**99.047**
	STD DEV	**0.5360**
	% RSD	**0.541**

Chromatograms:

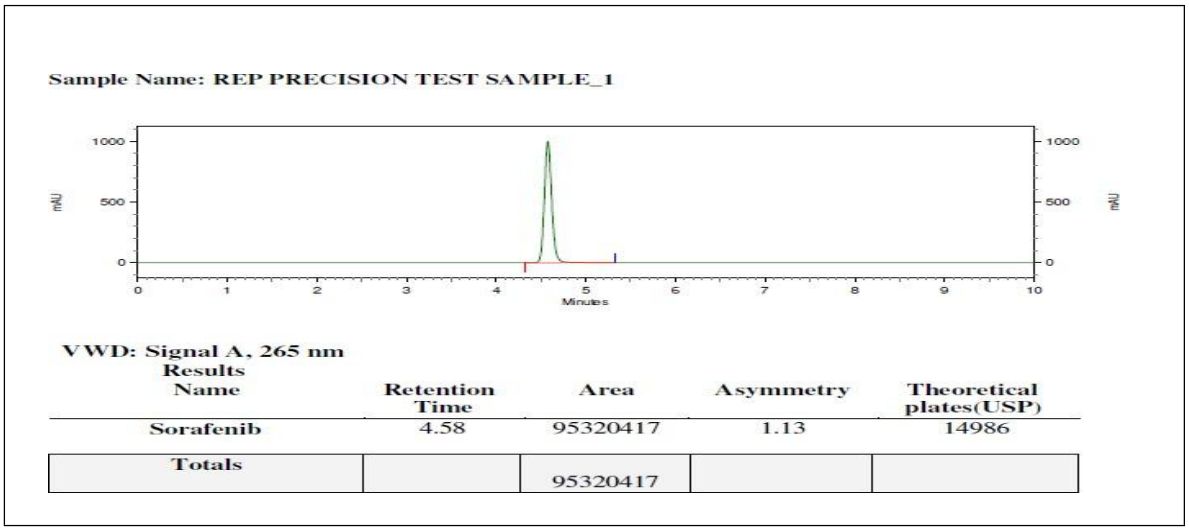


Figure No.9: Typical chromatogram of Repeatability precision (Sample 1)

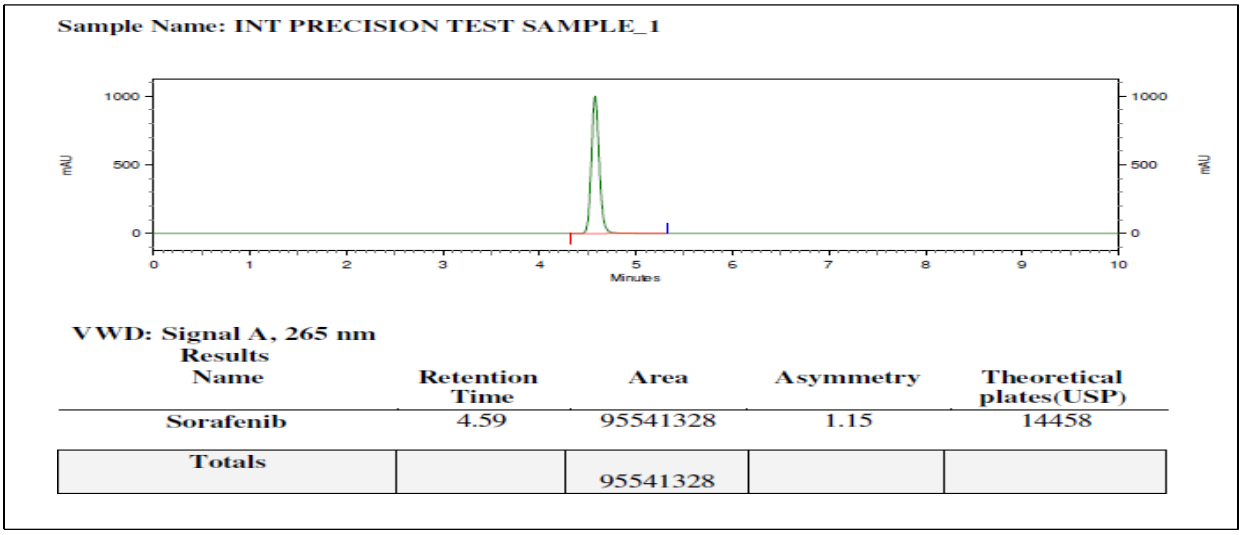


Figure No.10: Typical chromatogram of Inter-day precision (Sample 1)

Acceptance criteria:

% Assay: % Assay value for each sample (Individual sample) and mean assay value for precision (6 sample), mean assay value intermediate precision (6 sample), and mean assay value for precision plus intermediate precision sample (12 samples): 90-110%

% RSD: % RSD for precision study samples (6 sample), Intermediate precision study samples (6 samples) and precision plus intermediate precision sample (12 samples): NMT 2.0

Data interpretation: % Assay and% RSD was found well within acceptance limit and hence method is precise (Reproducible).

3) ROBUSTNESS:

The robustness of an analytical method is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

Following changes made under Robustness:

- Change in Wavelength
- Change in flow rate
- Change in column oven temperature

Table No. 7: Result of Robustness study of Sorafenib

Change in Parameter	R.T.	Standard area	Asymmetry	Theoretical plates
Wavelength by +3 NM (265 NM)	4.57	89937969	1.16	15018
Wavelength by -3 NM (262 NM)	4.57	88750782	1.15	15015
Flow rate by +10% (1.1mL/min)	4.15	83567370	1.15	14266
Flow rate by -10% (0.9mL/min)	5.08	100893288	1.16	16133
Column oven temp by +2ºC (42 ºC)	4.56	96125847	1.12	15175
Column oven temp by -2ºC (38 ºC)	4.59	95846285	1.15	14728

Chromatograms:

A. Change in Wavelength by +3 NM:

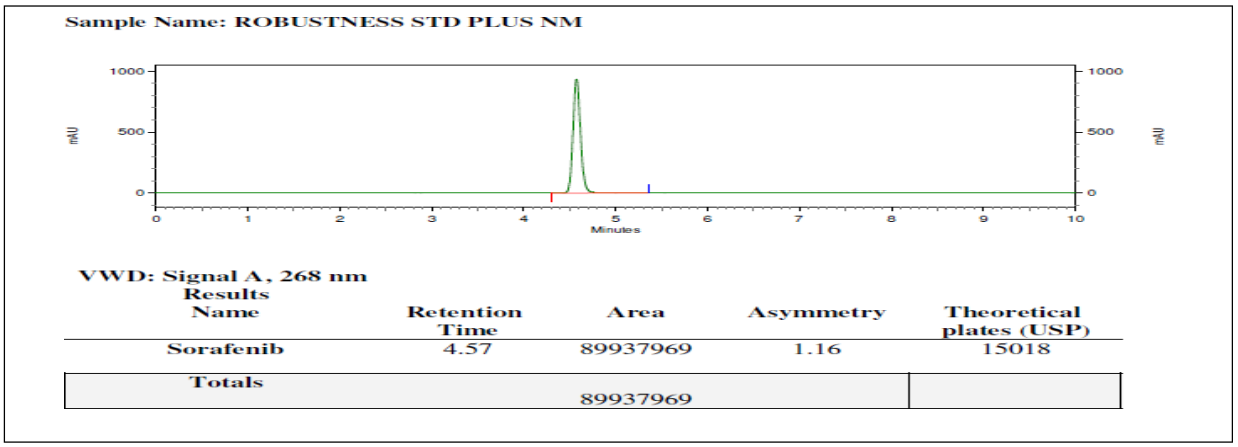


Figure No.11: Typical chromatogram of Standard +3 NM

B. Change in Wavelength by -3 NM:

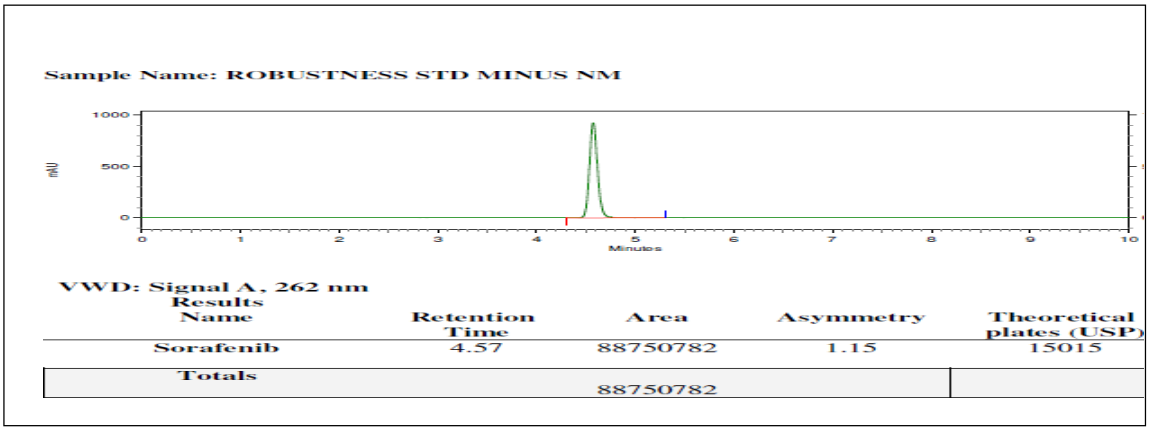


Figure No.12: Typical chromatogram of Standard -3 NM

C. Change in Flow rate by + 10% (1.1 mL/min)

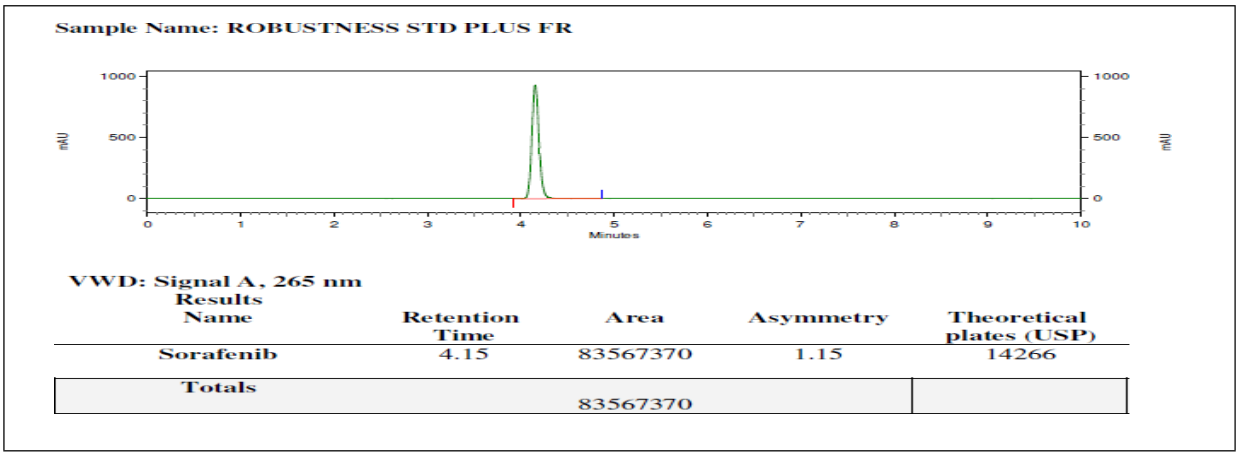
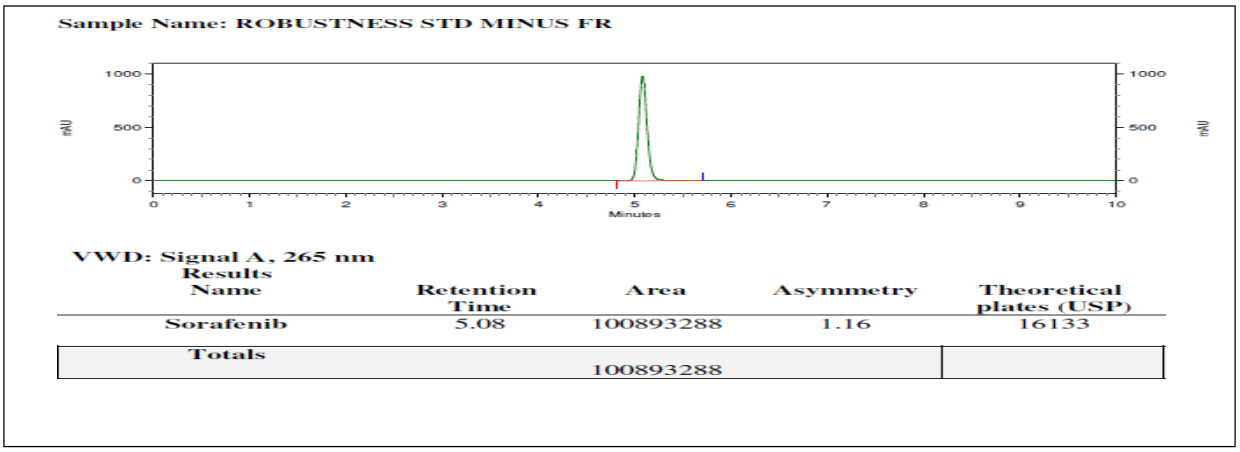


Figure No.13: Typical chromatogram of Standard +10% F.R.

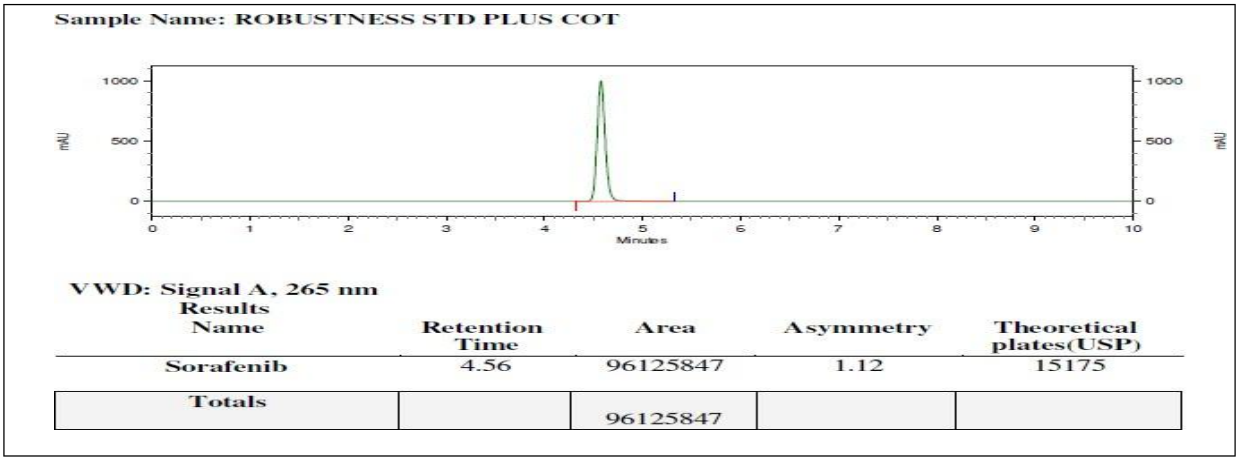
D. Change in Flow rate by - 10% (0.9 mL/min)



Name	Retention Time	Area	Asymmetry	Theoretical plates (USP)
Sorafenib	5.08	100893288	1.16	16133
Totals		100893288		

Figure No.14: Typical chromatogram of Standard -10% F.R.

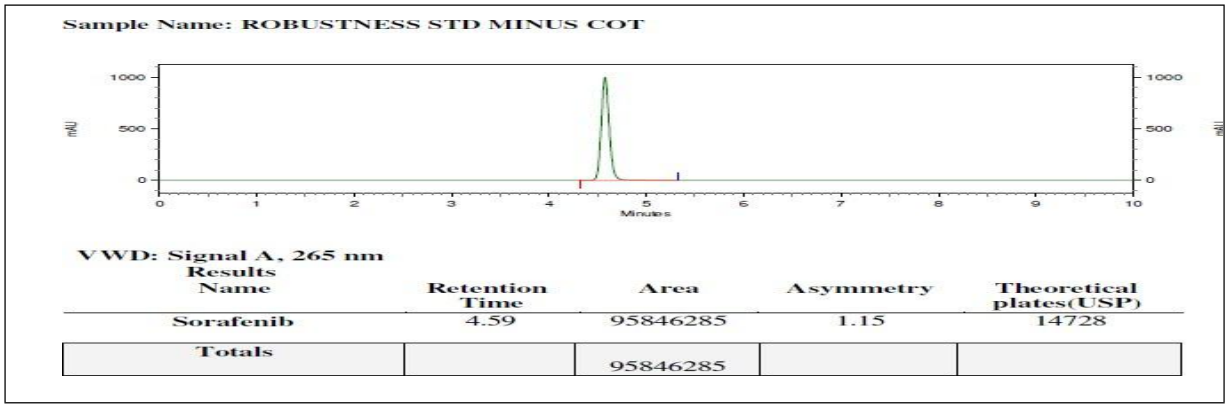
E. Change in Column Oven temperature by +2°C:



Name	Retention Time	Area	Asymmetry	Theoretical plates(USP)
Sorafenib	4.56	96125847	1.12	15175
Totals		96125847		

Figure No. 15: Typical chromatogram of Standard +2°C C.O.T.

F. Change in Column Oven temperature by -2°C:



Name	Retention Time	Area	Asymmetry	Theoretical plates(USP)
Sorafenib	4.59	95846285	1.15	14728
Totals		95846285		

Figure .No.16: Typical chromatogram of Standard -2ºC C.O.T.

Data interpretation: From the above results, it was concluded that the system suitability test result was found well within the limits and analytical method was robust.

5. SUMMARY AND CONCLUSION

Summary:

The present study focused on the development and validation of a robust, specific, and stability-indicating reverse-phase high-performance liquid chromatography (RP-HPLC) method for the estimation of Sorafenib in bulk and pharmaceutical dosage form, along with a comprehensive forced degradation study.

The method development began with the selection of methanol as a suitable solvent for Sorafenib based on solubility studies. The optimized chromatographic conditions involved the use of a Phenomenex C18 column (250 mm × 4.6 mm, 5 µm), an isocratic mobile phase of Acetonitrile and 0.05% orthophosphoric acid in water (75:25 v/v), at a flow rate of 1.0 mL/min, with UV detection at 265 nm.

Through a series of method trials, the sixth trial provided optimum retention time, peak shape, asymmetry, and theoretical plate count, making it suitable for further validation. System suitability tests confirmed acceptable peak symmetry (Asymmetry factor ~1.13), high efficiency (N > 15000), and minimal variability (%RSD < 0.05%).

The method was validated as per ICH Q2(R1) guidelines covering all parameters:

- **Linearity:** Excellent linearity was observed in the range of 80–120 µg/mL with R^2 = 0.9999.
- **Accuracy:** Recovery results were within 98–102%, with mean recovery of 99.89% and %RSD < 2%.
- **Precision:** Both intra-day and inter-day precision showed %RSD well below 2%, confirming reproducibility.
- **LOD and LOQ:** Found to be 0.74 µg/mL and 2.23 µg/mL respectively.
- **Robustness:** The method was resilient to small deliberate variations in flow rate, wavelength, and column temperature.
- **Specificity:** No interference from blank or placebo was observed, confirming the method's specificity.

A forced degradation study was conducted under thermal, photolytic, acidic, basic, and oxidative conditions. Sorafenib was stable under thermal, photolytic, and peroxide

conditions, but showed significant degradation under acidic and basic conditions, indicating the method's ability to differentiate the drug from its degradation products.

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