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APPLICATION OF QbD APPROACH FOR ROBUST ANALYTICAL METHOD DEVELOPMENT OF SUNITINIB MALATE BY UHPLC

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Sunitinib, QbD, Method development, UHPLC, ICH guidelines,

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ABSTRACT: Objective: Sunitinib malate is an oral, potent multi-targeted TKI that displays antitumor and anti-angiogenic actions. The core focus of the present research work is to establish an innovative QbD-based analytical method for the estimation of Sunitinib malate in solid dosage form by ultra-high performance liquid chromatography (UHPLC). **Materials and Methods:** The change in independent variables, wavelength, flow rate and Acetonitrile concentration with response to retention time, area and tailing factor were studied using Box-Behnken design. Chromatographic separation was accomplished by using XBridge shield RP18 (50mm x 3mm, 2.5µm) column, flow rate was adjusted to 0.7mL/min. at a temperature of 25ºC. The detection was carried out at 388nm with a run time of 5 min. **Results and Discussion:** The retention time of Sunitinib malate was found to be 2.391 min. The method is robust, accurate and precise, as depicted by the statistical data of analysis. The correlation coefficient was found to be 0.999. The solution was found to be stable for 24 hours at 25^0C. Hence the current research work was found to be economical and rapid and can be used for routine laboratory analysis for quality control.

INTRODUCTION: Sunitinib malate is chemically N-[2-(diethylamino) ethyl] – 5 - [(Z) - (5 – fluoro - 1, 2dihydro- 2-oxo-3H-indol-3-ylidine) methyl]-2, 4-dimethyl-1H pyrrole-3-carboxamidean. It is an oral, potent, multi-targeted TKI that displays antitumor and antiangiogenic actions [1]. It has been reported to inhibit VEGFR-1, VEGFR-2, VEGFR-3, KIT (stem-cell factor [SCF] receptor), PDGFR-a, and PDGFR-b in both cellular and biochemical evaluations.

QUICK RESPONSE CODE

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All these receptors are involved in the angiogenesis of well-differentiated primitive neuro ectodermal tumors (PNETs). *In-vitro*, sunitinib malate was described to persuade apoptosis of endothelial cells of the human umbilical vein. Furthermore, it prohibits FMS-like tyrosine kinase 3, the neurotrophic factor receptor of the glial cell line, and the colony-stimulating factor-1 (CSF-1R) receptor.

Mechanism of sunitinib malate action in endothelial cells expressing the receptors of vascular endothelial growth factor (VEGFs) was reported to be the binding of VEGFs to VEGFR results in the dimerization of VEGFR and activation of VEGFR intracellular kinase domain, which requires the presence of ATP and penetration of sunitinib malate into the cell

cytoplasm and its competition with ATP for the VEGFR ATP binding pocket. In the presence of sunitinib malate, activated VEGFR can no longer activate its intercellular kinase domain, further inhibiting downstream cell signalling [2, 3].

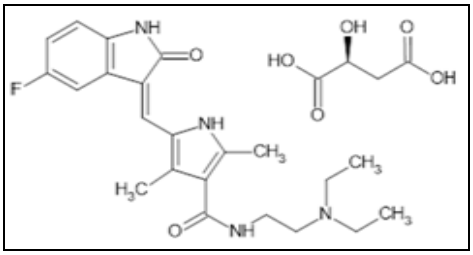


FIG. 1: STRUCTURE OF SUNITINIB MALATE

The main goal of the design of experiments is to ensure the quality of the finished products. QbD ensures combination of both the process and the product knowledge obtained during development which can deliver its planned performance consistently. Development measurements are based on the analytical target profile (ATP) and critical quality attribute (CQA) to assess the performance characteristics. The QbD approach overcomes the disadvantages of traditional development methods, such as time delay in studying one parameter variation one time, the number of runs required and further optimization. The study is performed based upon Box-Behnken design. The design consists of set of points lying at the midpoint of each edge and the replicated center point of the multi-dimensional cube. In order to evaluate the robustness of the strategy, the Box-Behnken Design (BBD), which requires fewer runs than a central composite design in cases of three or four variables, was used in the experimental design and statistical analysis of the data, which was acquired using Design-Expert software (version 12.0.3.1). The literature survey revealed various analytical techniques like UV spectrophotometry, HPTLC, HPLC and LC - MS/MS [4-21] were reported. No QbD-based UHPLC method for Sunitinib malate was developed and validated. An attempt was made to develop a simple, rapid, accurate, economical, and QbD-based technique for the dosage form of Sunitinib malate capsules.

MATERIALS AND METHODS: A simple, rapid, economical, QbD based method development was developed and validated as per ICH guidelines for Sunitinib malate capsule dosage form using UHPLC method.

Chromatographic Conditions: A UHPLC-developed chromatographic separation is achieved using the XBridge Shield RP18 column (50mm× 3 mm×2.5µm) column operating at a 0.7 mL/min. flow rate. The volume of injection was changed to 10µl at a temperature of 25 ° C with a run time of 5 min. Detection was carried out at 388 nm using the UV detector. Mobile phase separation was achieved by taking Ammonium acetate buffer: Acetonitrile (55:45v/v). The dimethyl sulfoxide was used to solubilize sunitinib.

Quantitative Estimation:

Preparation of Buffer Solution: 0.7mM Ammonium acetate buffer was prepared by dissolving 0.7791 g of Ammonium acetate in 1000 mL water. The solution was filtered through0.45µ nylon filter.

Preparation of Mobile Phase: Mobile phase is prepared by adding buffer and acetonitrile in the ratio of 55:45. The solution was mixed and degassed.

Preparation of Standard Stock Solution: 25mg of Sunitinib malate transferred in to 20Ml volumetric flask and added 10mL of Dimethyl sulfoxide (DMSO) dissolved and makeup with mobile phase (1250 µg/mL).

Standard Preparation Solution: Pipette out 2 ml of standard stock preparation into volumetric flask and makeup with mobile phase (125µg/mL) and mix well.

Preparation of Sample Solutions: 20 capsules were accurately weighed and average weight was calculated. Approximately139.18 mg (25 mg of Sunitinib malate) capsule powder was weighed and transferred into 20 mL volumetric flask.

About 10 mL of DMSO was added and sonicated. Use the mobile phase to make up the volume and mix well. 2 mL was pipetted from the above solution and the volume was made up by the mobile phase. The solution has been filtered with a 0.45 micron nylon syringe filter in the vial.

QbD Technique: The optimized chromatographic technique was developed by applying QbD based Box- Behnken design. Three independent factors were taken. The impact of change in these

independent factors (wavelength, flow rate and ACN concentration) were compared with the response to dependent factors (retention time, area and tailing factor) were studied.

The Design-Expert software (version 12.0.3.1) was utilized for the experimental design and statistical analysis of data. The Box-Behnken Design (BBD) was chosen due to its efficiency in requiring fewer runs compared to a central composite design, especially in scenarios involving three or four variables, ensuring a thorough evaluation of the method's robustness.

The variables Wavelength (A), flow rate (B), and Acetonitrile concentration (C) were treated as independent factors, while Retention time (RT) (R1, min), Area (R2), and Tailing factor (R3) were designated as response variables. A 2-factor, 3-level Box-Behnken Design (BBD) was established, encompassing 15 experimental runs. The significance of the design was assessed through statistical parameters, including the ANOVA method and Good fit evaluation. Method parameter optimization was carried out using the response surface method, and the results of experimental runs were incorporated back into the software. The coding factor and 3D surface responses were considered and analyzed in the process.

Further the developed method was validated according to ICH guidelines for specificity, system suitability, linearity, precision, accuracy and robustness.

Method Validation:

Specificity: Specificity is the ability to check unequivocally of the analyte in the presence of components which be impurities, degradeant and matrix. 10µl of blank solution was injected into chromatograph and checked.

Accuracy: It is the state of being correct. The closeness of agreement between the true values which is accepted the value found. Based on the comparison to reference standard method.

Accuracy of Sunitinib malate was achieved by injecting three replicate injections at the concentration of 50%, 100% and 150% respectively. The percentage Recovery for each level should be between 98.00 to 102.00%

Precision: Precision of an analytical method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple sampling of a homogenous sample. Precision of analytical method is usually expressed as the standard deviation and relative standard deviation. The precision of the instrument was determined by assaying the samples six of times and relative standard deviation was calculated. Inject 10µl of the blank solution and the standard solution five times and calculate the %RSD for the area of six replicate injections.

The RSD for the area of six injections results should not be more than 2%.

Ruggedness: Ruggedness is also called as intermediate precision. The method performed on different day by using different make column and different analyst.

The standard solutions were injected for five times and measured the area for all 5 injections in UHPLC.

Robustness: The robustness of the method was analysed by changing experimental, chromatographic condition. Altering in flow rate (0.7±1mL/min), changes in column oven temperature (40±5°C), Changes mobile phase buffer pH (3.5±0.2), changes in mobile phase composition and changes in wavelength allowable limits from actual chromatographic conditions.

Linearity: Linearity is the ability of the method to obtain test results that are directly proportional to the analyte concentration within a given range. The linearity of the method was performed by preparing the concentration range of 62.5-187.5µg/mL for Sunitinib malate, from standard stock solution. Calibration curves were constructed by plotting concentration versus area of sunitinib malate. Correlation coefficient should be not less than 0.999.

RESULTS AND DISCUSSION: The horizon of the present work is to develop a new QbD based optimization of the chromatographic condition using RP-UHPLC method and to validate the method using ICH guidelines. The mobile phase comprising of mixture of ammonium acetate buffer: Acetonitrile (55:45, v/v) was chosen as an

ideal mobile phase, since it gave a good resolution and peak shapes with perfect optimization. The detection was carried out at 388 nm. The flow rate was optimized at 0.7ml/min. X Bridge Shield RP-18 (50mm x 3mm, 2.5µm) column was used for the analysis. A mixture of dimethyl sulfoxide and mobile phase was used as diluent. The retention time of Sunitinib malate was found to be 2.391 min. respectively with a run time of 5 min. theoretical plate for Sunitinib malate were 7971.38 respectively. Chromatogram is given in **Fig. 2.**

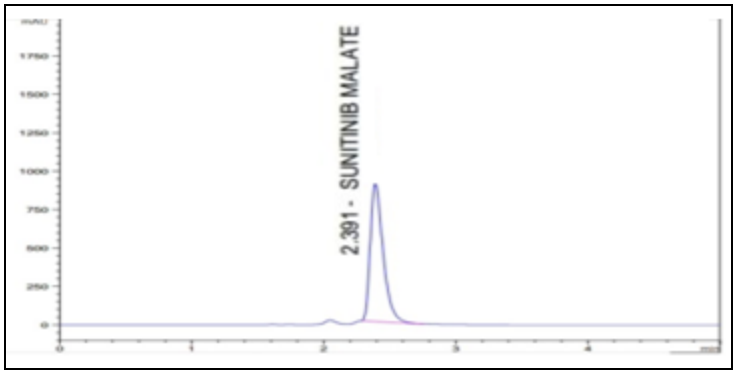


FIG. 2: CHROMATOGRAM OF SUNITINIB MALATE

QbD Approach: Three independent factors (wavelength, flow rate and ACN concentration) were taken based on the observation during the trials and from various optimization studies. The experiment was carried out based on the qualitative responses of the co- factors (retention time, area and tailing factor) and observed responses were noted and summarized in **Table 1.**

TABLE 1: EXPERIMENTAL DESIGN FOR INDEPENDENT VARIABLES AND CO-VARIANTS, EXPERIMENTAL AND PREDICTED VALUES

S. no.	Wavelength (A)	Flow rate (B)	ACN(C)	Rt(R_1)	Area(R_2)	Tailing factor (R_3)	Desirability
1	**388**	**0.7**	**45**	**2.391**	**6093**	**1.486**	**1.000**
2	388	1	30	2.109	6123	1.297	1.000
3	420	0.4	45	3.297	5893	1.623	1.000
4	388	0.8	45	2.393	6093	1.486	1.000
5	420	0.7	30	2.602	5723	1.456	1.000
6	389	0.7	45	2.396	6093	1.486	1.000
7	388	0.4	30	3.412	6234	1.617	1.000
8	420	0.7	60	2.005	5784	1.477	1.000
9	356	0.7	60	2.007	5234	1.469	1.000
10	388	0.4	60	3.122	6342	1.614	1.000
11	388	1	60	1.253	5934	1.287	1.000
12	356	0.4	45	3.402	4999	1.609	1.000
13	356	1	45	1.954	5096	1.291	1.000
14	420	1	45	1.957	5892	1.287	1.000
15	356	0.7	30	2.611	5523	1.478	1.000

Among various models' quadratic model was selected. The procedure was evaluated for the effect of individual factors and their covariant responses **Table 2** (ANOVA Analysis).

TABLE 2: STATISTICAL PARAMETERS BY ANOVA ANALYSIS FOR THE RESPONSE

Parameter	SS (Sum of Squares)	Df	MS (Mean Square)	F -value	P-value	Model F value	Model P value
Retention time (R_1)	0.2461	3	0.0820	7.57	0.0263	55.77	0.0002
Area (R_2)	1.429	3	4.762	14.80	0.0064	7.80	0.0179
Tailing factor (R_3)	0.2065	3	0.0688	3.76	0.0939	94.03	0.0001

The high F-values implies that the models are significant and there is only a 0.01% chance that F-values could occur due to noise. p-values (0.0002, 0.0179, 0.0001) less than 0.0500 indicate model terms are significant. If the value is greater than 0.0500 that indicates the model terms are not

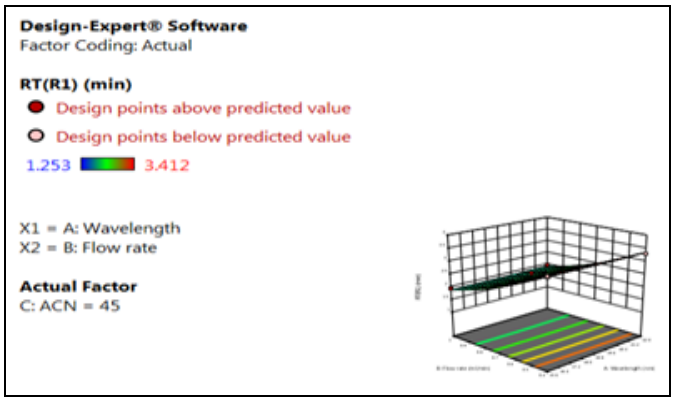
significant. The suggested quadratic equation for all the individual responses in terms of coded factors are shown as follows:

Retention time = +2.47 - 0.0144A - 0.7386B – 0.2934C + 0.0270AB + 0.0017AC-0.1415BC + $0.0083A^2$ + $0.1803B^2$ -$0.1702C^2$

Area = +6096.14 + 304.95A– 52.20B- 38.63C-24.50AB+87.50AC– 74.25BC – $609.31A^2$ – $16.61B^2$–+$78.94C^2$

Tailing factor = +1.47 - 0.0004A - 0.1596B-0.0001C +0.0005AB -0.0032AC-0.0005BC - $0.0086A^2$ - $0.0009B^2$ – $0.0001C^2$+0.0000ABC – 0.0000 A^2 B – 0.0000 A^2 C – 0.0000 AB^2 + $0.0000AC^2$ + $0.0000B^2C$ + $0.0000BC^2$ +$0.0000A^3$ +$0.0000B^3$+$0.0000C^3$

The variables R_1, R_2, and R_3 and quadratic terms with positive sign indicates synergistic effect and the negative sign indicates antagonistic effect in polynomial equation. The independent variables provide varying factor from low to high. When two variables interact their responses were recorded as AB, AC, BC. It is observed that when there is interaction between A and B independent variables R_1 and R_3 have synergistic effect where as R_2 shows antagonistic effect. When there is interaction between A and C independent variables R_1 and R_2 have synergistic effect where as R_3 shows antagonistic effect. All the dependent variables have antagonistic effect when there is interaction between B and C independent variables. These effects were further embellished by using 3D surface response and their contour plots given by the software explains the interactive relationship of two factors on the response by keeping the third factor constant. The 3D surface plots of the interaction effect were shown in **Fig. 3, 4.**



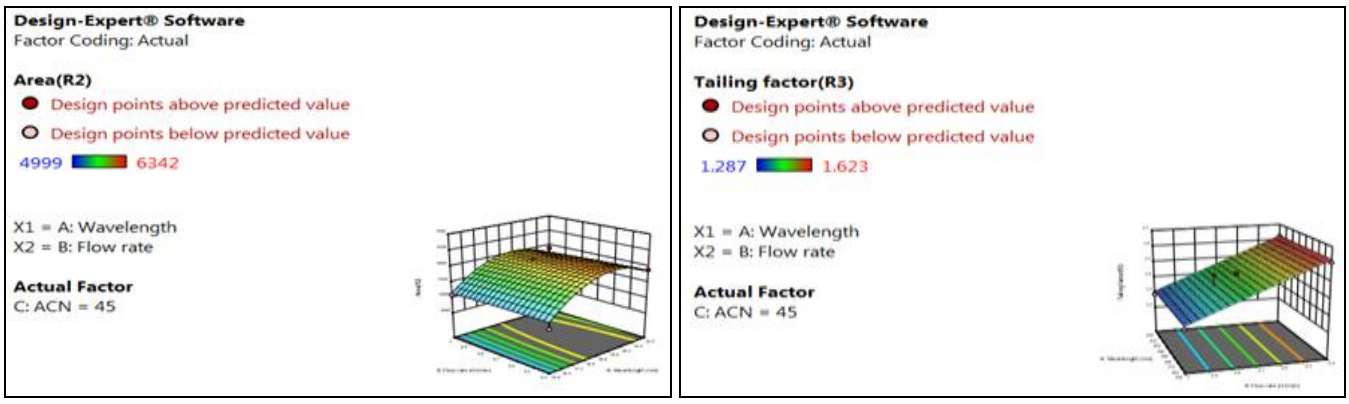


FIG. 3: 3D- RESPONSE OF RETENTION TIME (RT) (R1), AREA (R3), TAILING FACTOR (R3)

The optimized method was determined by setting the maximum and minimum values for the independent variables and entering their response variables as summarized in the **Table 3.** The numerical optimization suggests the desired method solution.

The desired method parameters were found to be wavelength at 388 nm and flow rate at 0.7 mL/min. with ACN concentration of 45% at desirability of 1.000. The graphical optimization of desirability was shown in the **Fig. 4** (desirability)

TABLE 3: INDEPENDENT VARIABLES AND THEIR CORRESPONDING LEVELS

Variable	Symbol	-α	-1	0	+1	+α
Wavelength	A	356	376	388	400	420
Flow rate	B	0.4	0.6	0.7	0.8	1
ACN	C	30	40	45	50	60

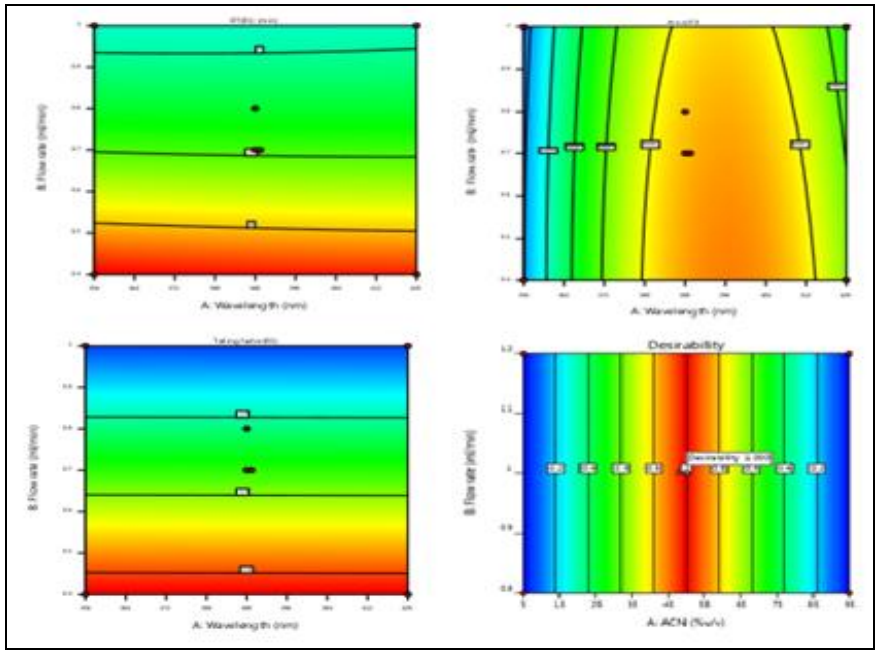


FIG. 4: DESIRABILITY CHART

The adjusted and predicted R-squared concludes that the applied statistical model effectively predicts the response. The 3D surface shows that R^2, P-value, F-value are within the limits which shows that the method is significant. Hence, the obtained optimized method by Box-Behnken design and optimized chromatographic conditions which was further validated as per ICH guidelines.

Validation Parameters:

System Suitability: System suitability parameters like tailing factor, retention time, theoretical plates per unit, resolution factor are determined by injecting 5 replicates of Sunitinib malate. %RSD was found to be less than 2% indicating good performance of the system.

Specificity: Specifity studies shows that there is no interfering peak at retention time of the analyte peak. Calibration curve shows that the method is linear and greater correlation exists between concentration and peak area.

The %RSD is 0.74, Rt was 2.391 min, Peak area was 6023.448. The developed method was vadilated and the results obtained were found to be within the limits.

Linearity*:* Chromatograms were acquired when standard solutions with linearity in the concentration range of 62.5-187.5µg/mL were injected. Linearity of concentration and peak area was plotted. R^2 was found to be 0.9991. From the calibration graph regression parameters were calculated and linearity graph was shown in **Fig. 5.**

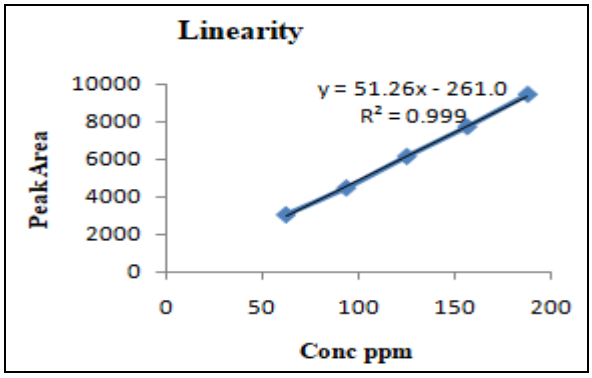


FIG. 5: LINEARITY OF SUNITINIB

Accuracy: The accuracy was analysed at 50-150%. The chromatograms were recorded and %RSD was found to be within the limits. The accuracy data was tabulated in **Table 4.** The accuracy of Sunitinib was found to be 99.16 to 99.65% respectively which is within the acceptance limit as per ICH guidelines

TABLE 4: ACCURACY RESULTS

Recovery Level	Sample	Mean Peak Area	% Recovery	Mean Recovery (%)	%RSD
50%	1	3028.192	99.78	99.65	0.13
	2	3050.525	99.65		
	3	3078.419	99.52		
100%	1	6206.661	99.65	99.47	0.22
	2	6185.477	99.23		
	3	6213.884	99.54		
150%	1	9358.491	99.65	99.16	0.22
	2	9364.791	99.54		
	3	9419.931	99.23		

NOTE: Three samples at three different concentration were analysed; SD: Standard Deviation, n=3

Precision: The precision of the analytical method was determined by assaying sufficient number of samples and relative standard deviation was calculated.

The results obtained were tabulated in **Table 5.** The %RSD of Sunitinib was found to be 0.33.

TABLE 5: PRECISION RESULTS

S. no.	Peak Retention Time (min.)	Peak area counts
1.	2.391	6075.336
2.	2.391	6044.421
3.	2.391	6064.390
4.	2.392	6080.911
5.	2.392	6040.565
6.	2.391	6037.234
MEAN	2.391	6057.143
STD DEV	0.0005	18.87
%RSD	0.02	0.33

%RSD: Relative Standard deviation, [n=6]

Ruggedness: The standard solutions were injected for five times and measured the area for all five injections in UHPLC. Results obtained were tabulated in **Table 6.**

TABLE 6: RUGGEDNESS

S. no.	Peak Retention Time (min.)	Peak area counts
Injection1	2.391	6016.362
Injection2	2.391	6022.849
Injection3	2.392	6039.673
Injection4	2.392	6068.921
Injection5	2.391	6034.285
MEAN	2.3914	6036.418
STD DEV	0.0005	20.3589
%RSD	0.0229	0.33

SD: Standard deviation, n=5

Robustness: Robustness was performed by changing experimental, chromatographic conditions. The results were tabulated in **Table 7.**

TABLE 7: ROBUSTNESS RESULTS FOR SUNITINIB MALATE

Drug name	Parameter	Chromatographic condition	
	Flow rate change	RT (min.)	Area Counts
Sunitinib Malate	0.6mL/min	2.485	6156.326
	0.7mL/min	2.391	6085.354
	0.8mL/min	2.289	6056.239
	Wavelength change±2%	RT (min.)	Area Counts
	386nm	2.392	6181.546
	388nm	2.391	6074.523
	390nm	2.391	6065.236

SD: Standard deviation, n=6

Assay: Test result is showing that the test method is precise. The percentage assay of Sunitinib malate is found to be 100.14%. Results are within the limits. The results are summarized in the **Table 8.**

TABLE 8: ASSAY

Label claim	Average weight	Area Counts	Percentage assay
25mg	139.18 mg	6051.247	100.14

All the parameters were validated and the validation reports were summarised in **Table 9.**

TABLE 9: VALIDATION PARAMETERS

S. no.	Parameters	Acceptance Criteria	Results
1	System suitability	Theoretical plate	7971.38

		Tailing Factor	1.2
2	Specificity	No interference was observed between placebo and blank with principal peak	Blank-Nil, Placebo-Nil Standard-2.39, Sample-2.392
3	Accuracy	98-102%	99.53%
4	Precision	RSDNMT 2%	0.33%
5	Linearity	Correlation coefficient NLT 0.999	0.999
6	Solution stability	RSD NMT 2%	Stable for 24 hours
7	Assay	90-110%	100.14%
8	Robustness	RSDNMT 2%	Complies

CONCLUSION: The optimized method was suitable, linear, precise accurate and robust for the estimation of sunitinib malate in capsule dosage form. The developed method is rapid, extremely small flow rate with relatively short run time.

All these factors enable rapid quantification and estimation of the sunitinib malate in capsule pharmaceutical formulation without any excipient interference. It can therefore be concluded that the developed method is more economical and practical. It can be applied for the analysis of the sunitinib malate in research and quality control laboratories.

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CONFLICT OF INTEREST: The authors have no conflicts of interest in this work.

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