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METHOD DEVELOPMENT AND VALIDATION OF DABRAFENIB IN BULK FORM AND MARKETED FORMULATION BY USING RP-HPLC

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Abstract:

A new Analytical simple, rapid, precise, accurate and reproducible RP-HPLC method for estimation of Dabrafenib in bulk form and marketed Pharmaceutical dosage forms. Separation of Dabrafenib was successfully achieved on a Develosil ODS HG-5 RP C18, 5µm, 15cmx4.6mm i.d. column in an isocratic mode of separation utilizing Methanol : Phosphate buffer (0.02M, pH-3.6) in the ratio of 45:55% v/v at a flow rate of 1.0 mL/min and the detection was carried out at 255nm. The method was validated according to ICH guidelines for linearity, sensitivity, accuracy, precision, specificity and robustness. The response was found to be linear in the drug concentration range of 12-28mcg/mL for Dabrafenib. The correlation coefficient was found to be 0.9995 for Dabrafenib. The LOD and LOQ for Dabrafenib were found to be 5.004µg/mL and 15.164µg/mL respectively. The proposed method was found to be good percentage recovery for Dabrafenib, which indicates that the proposed method is highly accurate. The specificity of the method shows good correlation between retention times of standard solution with the sample solution. Therefore, the proposed method specifically determines the analyte in the sample without interference from excipients of pharmaceutical dosage forms.

Keywords: *Dabrafenib, RP-HPLC, Accuracy, Precision, Robustness, ICH Guidelines.*

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INTRODUCTION:

Dabrafenib is a kinase inhibitor used to treat patients with specific types of melanoma, non-small cell lung cancer, and thyroid cancer. Dabrafenib mesylate (Tafinlar) is a reversible ATP-competitive kinase inhibitor and targets the MAPK pathway [1]. It was approved on May 29, 2013, for the treatment of melanoma with V600E or V6000K mutation. It was also used for metastatic non-small cell lung cancer with the same mutation. In May 2018, Tafinlar (Dabrafenib), in combination with Mekinist (Trametinib), was approved to treat anaplastic thyroid cancer caused by an abnormal BRAF V600E gene. Dabrafenib (brand name Tafinlar) is a targeted kinase inhibitor prescribed to treat cancers with specific BRAF gene mutations (primarily V600E and V600K) [2]. It works by blocking abnormal proteins that signal cancer cells to grow and spread. The IUPAC Name of Dabrafenib is N-[3-[5-(2-amino pyrimidin-4-yl)-2-tert-butyl-1, 3-thiazol-4-yl]-2-fluoro phenyl]-2, 6-difluoro benzene sulfonamide [3]. The Chemical Structure of Dabrafenib is shown in figure-1.

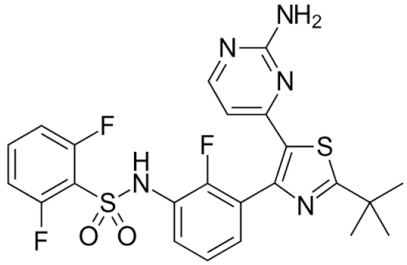


Fig-1: Chemical Structure of Dabrafenib

Literature survey revealed a few methods reported for determination of Dabrafenib in bulk drug as well as marketed pharmaceutical preparation [25-30].

In this research, a new sensitive and rapid HPLC method was developed for the determination of Dabrafenib in pharmaceutical dosage forms, and this method was validated according to ICH and FDA guidelines [25, 30].

MATERIALS AND METHODS:

Instruments Used:

Table-1: List of Instrument Used

S. No.	Instruments/Equipments/Apparatus
1.	**HPLC** with Empower2 Software with Isocratic with UV-Visible Detector (Waters).
2.	**T60-LAB INDIA** UV – Vis spectrophotometer
3.	Electronic Balance **(SHIMADZU ATY224)**
4.	Ultra Sonicator **(Wensar wuc-2L)**
5.	Thermal Oven
6.	Develosil ODS HG-5 RP C18, 5µm, 15cmx4.6mm i.d.
7.	P^H Analyzer **(ELICO)**
8.	Vacuum filtration kit **(BOROSIL)**

Chemicals / Reagents Used:

Table-2: List of Chemicals Used

		Specifications	

S.No.	Name	Purity	Grade	Manufacturer/Supplier
1.	Doubled distilled water	99.9%	HPLC	Sd fine-Chem ltd; Mumbai
2.	HPLC Grade Water	99.9%	HPLC	Sd fine-Chem ltd; Mumbai
3.	Methanol	99.9%	HPLC	Loba Chem; Mumbai.
4.	Hydrochloric Acid	99.9	A.R.	Sd fine-Chem ltd; Mumbai
5.	Acetonitrile	99.9%	HPLC	Loba Chem; Mumbai.
6.	Sodium Hydroxide	99.9	A.R.	Sd fine-Chem ltd; Mumbai
7.	Ethanol	99.9	A.R.	Sd fine-Chem ltd; Mumbai
8.	Octanol	99.9	A.R.	Sd fine-Chem ltd; Mumbai

Method Development:

Selection of Wavelength:

The detection wavelength was selected by dissolving the drug in mobile phase to get a concentration of 10µg/ml for individual and mixed standards. The resulting solution was scanned in U.V range from 200-400nm. The UV spectrum of Dabrafenib was obtained and the Dabrafenib showed absorbance's maxima at 255nm [4]. The UV spectra of drug are follows:

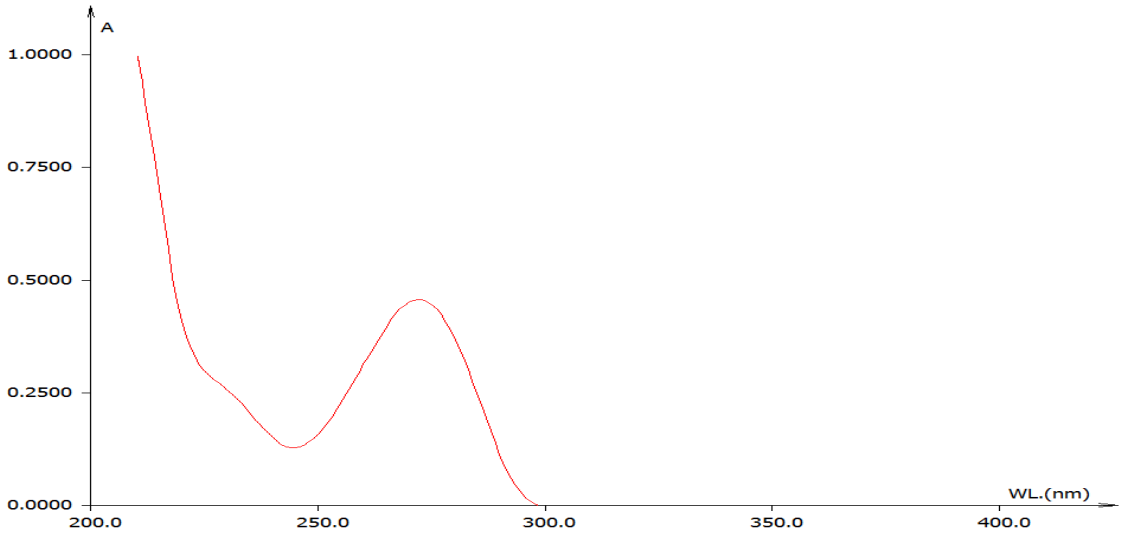


Fig-2: UV Spectrum of Dabrafenib (255nm)

Observation: While scanning the Dabrafenib solution we observed the maxima at 255nm. The UV spectrum has been recorded on T60-LAB INDIA make UV – Vis spectrophotometer model UV-2450.

Table-3: Trials for the Method Development and Results

S.No.	Column Used	Mobile Phase	Flow Rate	Wave length	Observation	Result
1	Symmetry C_{18}, 5µm, 25cmx4.6mm i.d.	ACN : Water = 70 : 30	0.8 ml/min	255nm	Early elution of peak	Method rejected
2	Waters C_{18}, 5µm, 25cmx4.6mm i.d.	Methanol: ACN = 40 :60	1.0 ml/min	255nm	Tailing Peaks	Method rejected
3	Waters C_{18}, 5µm, 25cmx4.6mm i.d.	ACN: Phosphate buffer (0.02M) = 70:30	1.0 ml/min	255nm	Low resolution peak	Method rejected
4	Develosil ODS HG-5	Methanol : Phosphate	1.0	255nm	Many	Method

	RP C_{18}, 5µm,15cmx4.6mm i.d.	buffer (0.01M) = 50:50 (pH-3.8)	ml/ min		Peaks	rejected
5	Develosil ODS HG-5 RP C_{18}, 5µm, 15cmx4.6mm i.d.	Methanol : Phosphate buffer (0.02M) = 65:35 (pH-2.6)	1.0 ml/min	255nm	Many Peaks	Method rejected
6	Develosil ODS HG-5 RP C_{18}, 5µm, 15cmx4.6mm i.d.	Methanol : Phosphate buffer (0.02M) = 45:55 (pH-3.6)	1.0 ml/min	255nm	Good Peaks	Method Accepted

Preparation of Standard Solution:
10 mg of Dabrafenib working standard was accurately weighed and transferred into a 10 ml clean dry volumetric flask. Add about 7 ml of diluents and sonicate to dissolve it completely and volume was made up to the mark with the same solvent which gave stock solution of 1000 ppm.
Further pipette 1 ml of the above stock solution into a 10 ml volumetric flask was diluted up to the mark with diluents (100 ppm solution).
Further 1 ml of prepared 100 ppm solution was pipetted into a 10 ml volumetric flask and was diluted up to the mark with diluents which gave 10 ppm Dabrafenib working standard solution. The solution was mixed well and filtered through 0.45µm filter [5].

Preparation of Sample Solution:
Twenty tablets were taken and the average weight was calculated as per the method prescribed in I.P. The weighed tablets were finally powdered and triturated well. A quantity of powder of Dabrafenib equivalent to 10mg were transferred to clean and dry 10 ml volumetric flask and 7 ml of HPLC grade methanol was added and the resulting solution was sonicated for 15 minutes. Make up the volume up to 10 ml with same solvent. Then 1 ml of the above solution was diluted to 10 ml with HPLC grade methanol. One ml (0.1 ml) of the prepared stock solution diluted to 10 ml and was filtered through membrane filter (0.45µm) and finally sonicated to degas [6].

Preparation of 0.02M Potassium dihydrogen orthophosphate Solution:
About 2.72172grams of Potassium dihydrogen orthophosphate was weighed and transferred into a 1000ml beaker, dissolved and diluted to 1000ml with HPLC Grade water. The pH was adjusted to 3.60 with diluted orthophosphoric acid.

Preparation of Mobile Phase:
550ml of Phosphate buffer (0.02M) pH 3.60 and 450ml of HPLC Grade Methanol were mixed well and degassed in ultrasonic water bath for 15 minutes. The solution was filtered through 0.45 µm filter under vacuum filtration [7].

RESULTS AND DISCUSSION:

Development of Analytical Method:
Optimized Chromatographic Method:

Table-4: Optimized Chromatographic Conditions

Mobile phase	Methanol : Phosphate buffer (0.02M, pH-3.6) = 45:55
Column	Develosil ODS HG-5 RP C_{18}, 5µm, 15cmx4.6mm i.d.
Column Temperature	Ambient
Detection Wavelength	255 nm
Flow rate	1.0 ml/ min.
Run time	07 min.
Temperature of Auto sampler	Ambient
Diluent	Mobile Phase
Injection Volume	20µl
Type of Elution	Isocratic

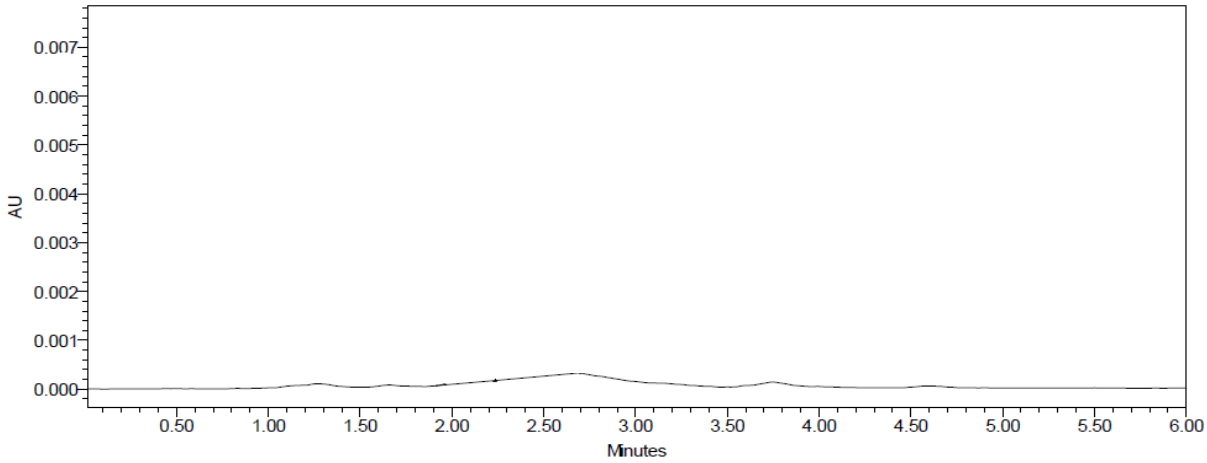


Fig-3: Chromatogram of Blank Solution

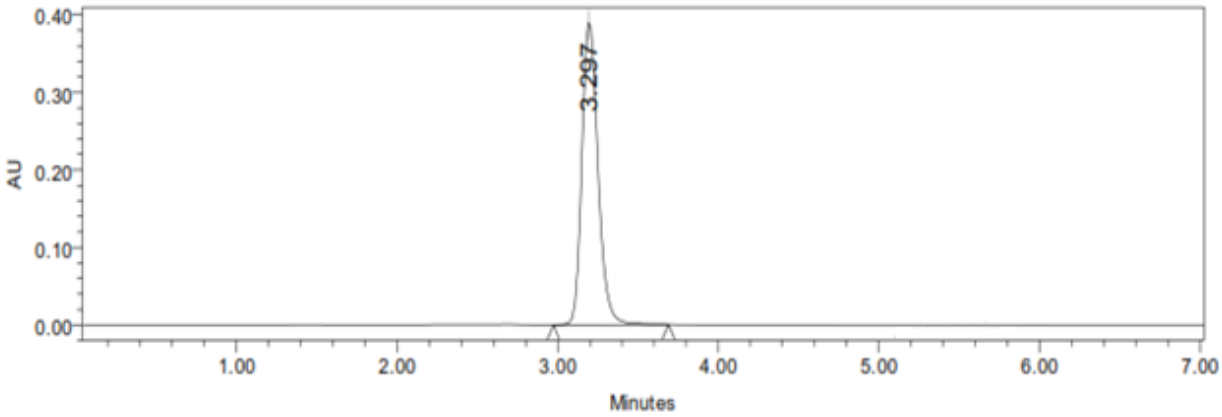


Fig-4: Chromatogram of Dabrafenib in Optimized Chromatographic Condition

Observation: The selected and optimized mobile phase was Phosphate Buffer: Methanol = 55:45 (pH-3.6) and conditions optimized were flow rate (1.0 ml/minute), wavelength (255nm), Run time was 07 mins. Here the peaks were separated and showed better resolution, theoretical plate count and symmetry [8]. The proposed chromatographic conditions were found appropriate for the quantitative determination of the Dabrafenib.

Method Validation

The method was validated as per ICH and FDA guidelines, and the validation parameters included specificity, linearity, range, accuracy, precision, sensitivity (LOQ and LOD), and robustness [9-12, 25, 30].

System Suitability: System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analyzed constitute an integral system that can be evaluated as such. Following system suitability test parameters were established [13]. The data are shown in Table-5 & 6.

Table-5: Data of System Suitability Test

S.No.	Injection No.	RT	Area	USP Plate Count	USP Tailing
1	Injection 1	3.253	284568	7368	1.26
2	Injection 2	3.254	285684	7295	1.25
3	Injection 3	3.215	283659	7346	1.27
4	Injection 4	3.297	284754	7394	1.29
5	Injection 5	3.253	283695	7425	1.25
6	Injection 6	3.213	284578	7385	1.27

Mean			**284489.7**	**7368.833**	**1.265**
S.D			**752.5617**		
%RSD			**0.26453**		

Table-6: System Suitability Results for Dabrafenib (Flow rate)

S.No.	Parameter	Limit	Result
1	Asymmetry	T ≤ 2	Dabrafenib = 0.12
2	Theoretical plate	N > 2000	Dabrafenib = 7258
3	Tailing Factor	(Tf) < 2	Dabrafenib = 1.25

Linearity: To evaluate the linearity, serial dilution of analyte were prepared from the stock solution was diluted with mobile phase to get a series of concentration ranging from 0-28µg/ml for Dabrafenib. The prepared solutions were filtered through Whatman filter paper (No.41). From these solutions, 20µl injections of each concentration were injected into the HPLC system and chromatographed under the optimized conditions. Calibration curve was constructed by plotting the mean peak area (Y-axis) against the concentration (X-axis) [14-17].

Plotting of Calibration Graphs: The resultant areas of linearity peaks are plotted against Concentration.

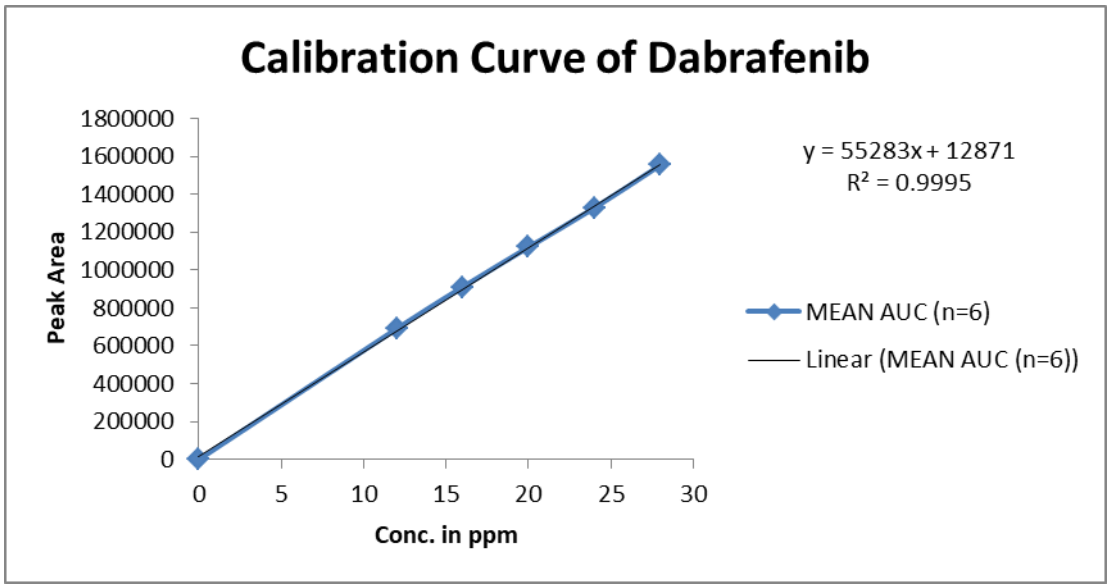


Fig-5: Standard Curve for Dabrafenib

Observation: Linearity range was found to be 0-28µg/ml for Dabrafenib. The correlation coefficient was found to be 0.9995, the slope was found to be 55283 and intercept was found to be 12871 for Dabrafenib.

Table-7: Linearity Readings for Dabrafenib

CONC.(µg/ml)	MEAN AUC (n=6)
0	0

12	690316
16	910621
20	1121057
24	1328903
28	1554666

Accuracy:

Recovery Study: To determine the accuracy of the proposed method, recovery studies were carried out by adding different amounts (80%, 100%, and 120%) of pure drug of Dabrafenib were taken and 3 replications of each has been injected to HPLC system. From that percentage recovery values were calculated from the linearity equation y = 55283x + 12871 [18-20]. The results were shown in table-8.

Table-8: Accuracy Results of Dabrafenib

Sample ID	Concentration (µg/ml)			%Recovery of Pure drug	Statistical Analysis
	Conc. Found	Conc. Recovered	Peak Area		
S_1 : 80 %	8	8.064107	458679	99.867	Mean= 100.4113% S.D. = 0.473694346 % R.S.D.= 0.471753
S_2 : 80 %	8	7.843532	446485	100.637	
S_3 : 80 %	8	8.19449	465887	100.73	
S_4 : 100 %	10	9.892661	559767	99.41	Mean= 100.6646667% S.D. = 1.166369295 R.S.D.= 1.158667
S_5 : 100 %	10	9.978655	564521	100.868	
S_6 : 100 %	10	10.19623	576549	101.716	
S_7 : 120 %	12	11.85907	668476	99.878	Mean= 100.4637% S.D. = 0.51154309 % R.S.D. = 0.509181
S_8 : 120 %	12	12.16785	685546	100.69	
S_9 : 120 %	12	12.18644	686574	100.823	

Observation: The mean recoveries were found to be 100.411, 100.664 and 100.463% for Dabrafenib. The limit for mean % recovery is 98-102% and as both the values are within the limit, hence it can be said that the proposed method was accurate [21].

i) Repeatability

Precision: The precision of each method was ascertained separately from the peak areas obtained by actual determination of six replicates of a fixed amount of drug Dabrafenib [22-25]. The percent relative standard deviations were calculated for Dabrafenib are presented in the Table-9.

Table-9: Repeatability Results of Dabrafenib

HPLC Injection Replicates	AUC for Dabrafenib
Replicate – 1	285479
Replicate – 2	284571
Replicate – 3	286954
Replicate – 4	283261
Replicate – 5	285964
Replicate – 6	284259
Average	**285081.3**
Standard Deviation	**1318.666**
% RSD	**0.462558**

Observation: The repeatability study which was conducted on the solution having the concentration of about 20µg/ml for Dabrafenib (n =6) showed a RSD of 0.462558% for Dabrafenib. It was concluded that the analytical technique showed good repeatability.

ii) Intermediate Precision / Ruggedness [26]

Table-10: Ruggedness Results for Dabrafenib

Conc. of Dabrafenib (API) (µg/ml)	Observed Conc. of Dabrafenib (µg/ml) by the proposed method			
	Intra-Day		Inter-Day	
	Mean (n=3)	% RSD	Mean (n=3)	% RSD
8	8.21	0.76	8.23	0.46
10	10.37	0.33	10.36	0.57
12	12.56	0.23	12.56	0.75

Observation: Intraday and interday studies show that the mean RSD (%) was found to be within acceptance limit (≤2%), so it was concluded that there was no significant difference for the assay, which was tested within day and between days. Hence, method at selected wavelength was found to be precise.

Robustness: Robustness is defined as the capacity of that method to be unaffected by even small deliberate changes that occur in the method parameters. The evaluation of robustness of a method is done by varying the chromatographic parameters such as pH, temperature, flow rate, mobile phase proportions change, ionic strength etc., and determining any possible effect on the results obtained by that method [27].

Table-11: Result of Method Robustness Test for Dabrafenib

Change in Parameter	% RSD
Flow (0.8 ml/min)	0.554
Flow (1.2 ml/min)	0.867
More Organic	0.886
Less Organic	0.817
Wavelength of Detection (257 nm)	0.813
Wavelength of detection (253 nm)	0.794

Observation: Influence of small changes in chromatographic conditions such as change in flow rate (± 0.1ml/min), Temperature (±2^{0}C), Wavelength of detection (±2nm) & organic phase (±5%) studied to determine the robustness of the method are also in favour of (Table-11, % RSD < 2%) the developed RP-HPLC method for the analysis of Dabrafenib (API).

LOD: The limit of detection (LOD) is the lowest concentration of analyte in a sample which can be detected, but not quantitated. LOD is a limit test that specifies whether an analyte is above or below a certain value. Signal-to-noise ratio of three-to-one is used to determine LOD [28].

L.O.D. = 3.3 (SD/S).

Where, SD = Standard deviation of the response

S = Slope of the calibration curve

Observation: The LOD was found to be 5.004µg/ml for Dabrafenib.

LOQ: The Limit of Quantitation (LOQ) is defined as the lowest concentration of an analyte in a sample that can be determined with acceptable precision and accuracy under the stated operational conditions of the method. Signal-to-noise ratio of ten-to-one is used to determine LOQ [29].

L.O.Q. = 10 (SD/S)

Where, SD = Standard deviation of the response

S = Slope of the calibration curve

Observation: The LOQ was found to be 15.164µg/ml for Dabrafenib.

Assay: – Assay refers to chromatography based purity assay where a compound of unknown activity or purity is compared to a reference standard with precisely determined bioactivity or purity [30].

$$\text{Assay} = \frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P}{100} \times \text{Average weight} = \text{mg/tab}$$

Where:

AT = Test Preparation Peak Area

AS = Standard preparation Peak Area

WS = Working standard weight taken in mg

WT = Sample weight taken in mg

DS = Standard solution dilution

DT = Sample solution dilution

P = Working standard percentage purity

The assay was performed as explained in the previous chapter. The results which are obtained are following:

Table-12: Recovery Data for Estimation Dabrafenib in Lafinlar Capsules

Brand Name of Dabrafenib	Labelled amount of Drug (mg)	Mean (± SD) amount (mg) found by the proposed method (n=6)	Assay % (± SD)
Lafinlar Capsules (Novartis)	50mg	49.393 (± 0.568)	99.698 (± 0.476)

Observation: The amount of drug in Lafinlar Capsules was found to be 49.393 (± 0.568) mg/tab for Dabrafenib & % Purity was 99.698 (± 0.476) %.

SUMMARY AND CONCLUSION:

To develop a precise, linear, specific & suitable stability indicating RP-HPLC method for analysis of Dabrafenib, different chromatographic conditions were applied & the results observed are presented in previous chapters. Isocratic elution is simple, requires only one pump & flat baseline separation for easy and reproducible results. So, it was preferred for the current study over gradient elution. In case of RP-HPLC various columns are available, but here Develosil ODS HG-5 RP C_{18}, 5µm, 15cmx4.6mm i.d. column was preferred because using this column peak shape, resolution and absorbance were good. Detection wavelength was selected after scanning the standard solution of drug over 200 to 400nm. From the U.V spectrum of Dabrafenib it is evident that most of the HPLC work can be accomplished in the wavelength range of 255 nm conveniently. Further, a flow rate of 1 ml/min & an injection volume of 20µl were found to be the best analysis. The result shows the developed method is yet another suitable method for assay which can help in the analysis of Dabrafenib in different formulations.

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