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Stability Indicating RP-HPLC Method for the Analysis of Dacomitinib and its Related Impurities in Bulk and Oral Solid Dosage Formulations

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Dacomitinib is an epidermal growth factor receptor inhibitor prescribed for the treatment of metastatic non small-cell lung carcinoma. There are no reported significant official of HPLC methods that resolve the impurities and degradation products generated during stability studies. Therefore, an isocratic RP-HPLC-UV method was developed for the determination of Dacomitinib in the presence of its related impurities and degradation products. The separation of Dacomitinib, impurity 1 and 2 was achieved on Agilent ZORBAX Eclipse (250×4.6 mm; 5 µ id) column as stationary phase, 0.1M sodium perchlorate at pH 5.6, acetonitrile as mobile phase in the ratio of 20:80 (V/V) at a flow rate of 1.0 mL/min in isocratic condition as mobile phase and UV detection was carried at 253 nm. In the optimised conditions, well resolved and retained peaks were observed at a retention time of 5.8 min, 4.0 min and 7.7 min for Dacomitinib, impurity 1 and 2 respectively. In the developed method, a very sensitive detection limit of 0.06 and 0.025 µg/mL was observed for impunity 1 and 2 respectively. The calibration was observed to be within the

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concentration range of 20 – 200 µg/mL for Dacomitinib and 0.2 – 2 µg/mL for impurity 1 and 2. The proposed method was used to investigate the effective separation of impurities along with degradation compounds formed under different degradative conditions and confirms that the method is stability indicating. Hence it can be concluded that the method was found to be simple, sensitive, specific, accurate, linear, precise, rugged, robust, and useful for estimation and characterizing the stability of Dacomitinib, impurity 1 and 2.

Keywords: Dacomitinib; impurity analysis; HPLC estimation; stress degradation study.

1. INTRODUCTION

Dacomitinib is an irreversible inhibitor of epidermal growth factor receptor and used for the treatment of metastatic non small-cell lung carcinoma (NSCLC) [1]. Dacomitinib inhibits the proliferation and induce induction of apoptosis in human epidermal growth factor receptor (EGFR) expressing tumor cells by binding EGFR irreversibly and specifically [2]. Dacomitinib was found to be advanced than the similar activity drugs such as afatinib, gefitinib or erlotinibin the treatment of metastatic NSCLC with EGFR mutations L858R or del19 [3]. Dacomitinib also found to be more advanced than afatinib, cisplatin and carboplatin for the patients with different EGFR mutations. Sourness in mouth, loss of weight, decreased appetite, swelling or infection around the nails, and dry skin are the side effects with the use of Dacomitinib [4,5].

Impurities are the unwanted chemical compounds may be formed during the synthesis or may be derived from starting material, intermediates, reagents, solvents, catalysts and remains as standard drug or drug product. The quantity of various impurities in the drug/drug product will determines the ultimate safety of the drug product [6]. As the literature on the available methods for the analysis of Dacomitinib confirms that there is no analytical method reported for the analysis of Dacomitinib in bulk and formulations. In literature, two LCMS [7,8] methods and one UPLC [9] method reported for the analysis of Dacomitinib in biological samples and pharmacokinetic studies. Hence the present work was aimed to develop an analytical HPLC method for the estimation of Dacomitinib and its impurities in pharmaceutical formulations. Based on the availability, impurity 1 and 2 were selected for the study and the molecular structure of Dacomitinib. Impurities 1 and 2 in the study was given in Fig. 1.

2. MATERIALS AND METHODS

2.1 Reagents

The working standard of drug Dacomitinib (98.82% purity) and its Impurities (1 and 2) studied were obtained from Pfizer Ltd., Basheer Bagh, Hyderabad, Telangana, India. Methanol (HPLC Grade) and Acetonitrile (HPLC grade) were purchased from Merck chemicals, Mumbai. Ultra-Pure (Milli-Q®) Water was used during the study. All the other chemicals used during the study for analytical reagent grade and were purchased from Merck Chemicals, Mumbai.

2.2 Instrumentation

Analysis of Dacomitinib and its impurities was carried with Agilent 1100 series (USA) instrument equipped with G1311 A Quaternary pump, Thermostatic auto sampler (G 1329A) having sample injection capacity of 0.1 – 1500 µL and UV detector (G 1314 A) with programmable wavelength module for detecting the column eluents. Chromatograms were integrated with Agilent chem. station LC software.

2.3 Preparation of Solutions

2.3.1 Dacomitinib and impurity solutions

Standard stock solution of 1 mg/mL (100 µg/mL) was prepared by weighing 50 mg of standard drug and its impurities and dissolved it in 50 mL methanol separately. The standard dilutions required in method development and validation study was prepared from the prepared 100 µg/mL standard stock solution of Dacomitinib and its impurities separately. The mixed standard solution containing Dacomitinib, Impurity 1& 2 was prepared by mixing the known and selected concentrations of drug and its impurities separately during the analysis.

2.3.2 Formulation solution

The marketed formulation tablets of Dacomitinib with brand Vizimpro® (30 mg) were powdered using sterile mortar and pestle. An amount of the powder equivalent to 10 mg of Dacomitinib was weighed and was dissolved in 10 mL of methanol. After that the content of Dacomitinib was filtered (0.45 µ membrane filter) and diluted to standard concentration then was used for the assay.

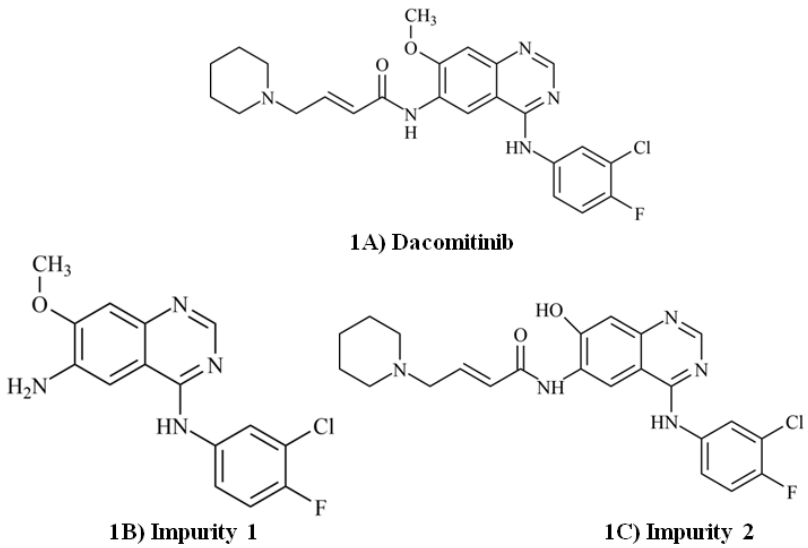


Fig. 1. Chemical structure of Dacomitinib and its impurities in this study

2.3.3 Method development

The suitable UV detector wavelength for the detection of Dacomitinib and its impurities was determined using UV spectrophotometer. The standard solution containing 10 µg/mL of Dacomitinib and its impurities was scanned in the UV spectrophotometer in the range of 400-200 nm. The iso-absorption spectra obtained from the wavelength scanning spectra of Dacomitinib and its impurities confirms the suitable wavelength for the detection of Dacomitinib and its impurities.

The suitable method conditions for the analysis of Dacomitinib and its impurities were confirmed by analysing the standard solution in different analytical conditions by changing the parameters. The method parameters like mobile phase composition, pH, flow rate and nature of stationary phase were optimised by changing one parameter and keeping other parameters intact. The condition that produced the best results for the separation and analysis of Dacomitinib and its impurities were further validated.

2.4 Method Validation

The method was validated as per available literature [10,11,12] and ICH [13] guidelines.

2.5 System Suitability

The spiked levels of standard solution were analysed in triplicate following the developed method. The resultant chromatograms were used for the evaluation of system suitability parameters such as number of theoretical plates, asymmetric factor (tail factor) and relative retention time (RRT).

2.6 Range of Analysis

The standard solution impurities 1 and 2 were individually analysed for the identification of limit of detection (LOD) and limit of quantification (LOQ). The signal (s) to noise (n) ratio (s/n) method was used for the determination of LOD and LOQ. The calibration curve was constructed from LOQ range and considered as 1% impurity in the standard solution. The calibration was prepared such that 1% of the both the impurities are in the standard. The prepare calibration curve solutions were analysed in the method and the range of the method was determined using least square analysis.

2.7 Precision and Ruggedness

Standard solution of Dacomitinib containing 1% solution of both the impurities were analysed six times in the same day for intraday precision, six times in two different days for interday precision and six times by change in two different analysts in ruggedness. The peak area response of the resultant chromatograms was summarised and the % relative standard deviation (RSD) of the peak area response was calculated for standard Dacomitinib and its two impurities studied. The % RSD of < 2 was considered as the method is precise.

2.7.1 Robustness

The influence of small change in the developed conditions for the separation and determination of Dacomitinib and its impurities was determined in robustness study. Mobile phase composition, pH and detector wavelength were changed, and the standard solution was analysed with change in each condition separately. The % change in the peak area response was calculated and the % change of <2 was considered as acceptable as per guidelines.

2.7.2 Recovery

The spiked recovery at 50%, 100 % and 150 % spiked levels of target (100 %) concentration was analysed in triplicates. The % recovery was calculated for Dacomitinib and its impurities in each individual analysis and % recovery was calculated in each spiked level for Dacomitinib and its impurities. The % recovery of 98-102 for individual analysis and % RSD of less than 2 in each spiked level was considered as acceptable.

2.7.3 Force degradation studies

50 mg of standard drug Dacomitinib was exposed to acidic (50 ml of 0.1 N HCl), base (50 mL of 0.1 N NaOH) and peroxide (50 ml of 3 % hydrogen peroxide) conditions for 24 h. Then it was neutralised and diluted to standard concentration. In thermal and photolytic degradation studies, the standard drug kept in hot air oven at 60 °C and under UV light at 254 nm respectively for 24 h and then it was diluted to standard concentration. All the stress exposed samples of Dacomitinib were analysed in the developed method. The chromatograms were observed for the effectiveness of the developed method for the separation of known impurities along with unknown stress degradation products. The peak area of the stress exposed samples was compared with un-stress standards and the % degradation of Dacomitinib in each degradation study was calculated.

2.8 Formulation Analysis

The formulation solution of Dacomitinib with brand Vizimpro (30 mg) was analysed in the developed method. The % assay was calculated by comparing the formulation results with that of the calibration curve results.

3. RESULTS AND DISCUSSIONS

In the development of a simple HPLC method for the separation and identification of Dacomitinib and its impurities, different method conditions were studied, and the summary of the method development trails performed, and results observed were given in Table 1. The blank and the standard chromatograms observed in the optimised conditions were given in Fig. 2.

The LOD of impurity 1 and 2 was found to be 0.06 and 0.025 µg/mL whereas the LOQ was found to be 0.2 and 0.09 µg/mL respectively. In the two impurities studies, the lOQ of impurity 1 was found to be high i.e 0.2 µg/mL and this was considered as lower limit in the calibration range. The standard dilutions were made such that the concentration of impurities was found to be 1 % in the standard. Hence the calibration was observed to be within the concentration range of 20 – 200 µg/mL for Dacomitinib and 0.2 – 2 µg/mL for impurity 1 and 2. The regression equation was found to be y = 7192.x - 17754 (R^2 = 0.999), y = 49970x - 965.4 (R^2 = 0.999) and y = 67294x - 1596 (R^2 = 0.999) for Dacomitinib, impurity 1 and 2 respectively. Linearity results were given in Table 2.

The repeatability, reproducibility, and system suitability of the method was determined at spiked levels. The results of the RRT, number of theoretical plates, tail factors and resolution for standard and both impurities studied was found to be within the acceptable limit (Table 3) hence the method was found to be suitable and acceptable.

Standard solution at a concentration of 100 µg/mL of Dacomitinib with 1 % concentration of both the impurities (1 µg/mL) was studied for precision and ruggedness study. The peak area % RSD was found to be 0.21, 0.35 and 0.26 in intraday precision, 0.99, 0.40 and 0.68 in interday precision and 0.67, 0.34 and 0.74 in ruggedness respectively for Dacomitinib, impurity 1and 2 respectively. This confirms that the method is rugged and precise.

In robustness study, the % change in the peak area of Dacomitinib and its impurities in all the changed conditions was found to be within the acceptable limits of less than 2. The system suitability conditions were also evaluated in all the changed conditions and found to be within the acceptable limit and there is no considerable change in the system suitability parameters when compared with optimised conditions (Table 4). This confirms that there is no considerable change in the separation and quantification of Dacomitinib and impurities when small changes occurred in the method and hence the method is robust.

Table 1. Method development conditions tried during optimization process

S No	Mobile Phase composition	Result	Conclusion
1	MP: pH 5.2phosphate buffer, methanol 80:20(V/V); SP: Shodex C18-4D (250×4.6 mm; 5 µ id) column; WL: 253 nm; FR: 1.0 mL/min	No clear separation of standard Dacomitinib and impurities 1 & 2.	Method Rejected
2	MP: pH 6.2 Acetate buffer, methanol 25:75(V/V); SP: Shodex C18-4D (250×4.6 mm; 5 µ id) column; WL: 253 nm; FR: 1.0 mL/min	No clear separation of standard Dacomitinib and impurities 1 & 2. Merged peaks were observed.	Method Rejected
3	MP: pH 3.5 20 mM ammonium formate buffer, acetonitrile80:20(V/V); SP: Alltima CN (250×4.6 mm; 5 µ id) column; WL: 253 nm; FR: 1.0 mL/min	Compounds were separated but the resolution between the peaks was found to be very less. The peak response of compounds was found to be very less.	Method Rejected
4	MP: 0.2M sodium perchlorate at pH 6.1, methanol 80:20(V/V); SP: Agilent ZORBAX Eclipse (250×4.6 mm; 5 µ id) column; WL: 253 nm; FR: 1.0 mL/min	Compounds are separated but are not in the acceptable limit and the peak response was found to be very less.	Method Rejected
5	MP: 0.1M sodium perchlorate at pH 5.6, acetonitrile 20:80 (V/V); SP: Agilent ZORBAX Eclipse (250×4.6 mm; 5 µ id) column; WL: 253 nm; FR: 1.0 mL/min	Three compounds were separated but the resolution between the impurity 2 and standard was found to be not acceptable	Method Rejected
6	MP: 0.2M sodium perchlorate at pH 6.1, acetonitrile 80:20 (V/V); SP: Agilent ZORBAX Eclipse (250×4.6 mm; 5 µ id) column; WL: 253 nm; FR: 1.0 mL/min	Compounds are separated but peak split was observed for standard and impurity 1. Broad peaks were observed with high tailing factors.	Method Rejected
7	MP: 0.1M sodium perchlorate at pH 5.1, acetonitrile 20:80(V/V); SP: Agilent ZORBAX Eclipse (250×4.6 mm; 5 µ id) column; WL: 253 nm; FR: 1.0 mL/min	Overlapping of the chromatographic peaks with bad peak resolution and broad peaks was observed.	Method Rejected
8	MP: 0.1M sodium perchlorate at pH 5.1, acetonitrile 65:35(V/V); SP: Agilent ZORBAX Eclipse (250×4.6 mm; 5 µ id) column; WL: 253 nm; FR: 1.0 mL/min	Symmetric peaks with acceptable peak shape and acceptable system suitability was observed.	Method Accepted

Table 2. Linearity results

S. No	Dacomitinib		Impurity 1		Impurity 2	
	Concentration in µg/ml	Peak Area	Concentration in µg/ml	Peak Area	Concentration in µg/ml	Peak Area
1	20	138217.6	0.2	9648.7	0.2	12958.2
2	40	275774.8	0.4	19496.8	0.4	25833.3
3	60	411307.3	0.6	28849.5	0.6	38139.1
4	80	534556.9	0.8	37481.2	0.8	50224.8
5	100	702840.8	1.0	48579.5	1.0	65193.7
6	120	831470.9	1.2	59042.3	1.2	79234.8
7	140	997112.8	1.4	69958.1	1.4	94093.6
8	160	1135956.2	1.6	78992.3	1.6	106086.7
9	180	1297780.1	1.8	89004.5	1.8	119889.1
10	200	1409677.4	2.0	98966.4	2.0	132615.9

Table 3. System suitability results

Compound	Spiked level studied	Retention Time (min)	RRT	Theo plate	Tail Factor	Resolution
Dacomitinib	50 %	5.900±0.029		8759	1.14	8.15
	100 %	5.911±0.025		8695	1.10	8.11
	150 %	5.911±0.025		8714	1.13	8.14
Impurity 1	50 %	4.028±0.025	0.683±0.003	5095	1.04	---
	100 %	4.042±0.008	0.684±0.004	5132	1.06	---
	150 %	4.039±0.010	0.683±0.005	4968	1.03	---
Impurity 2	50 %	7.694±0.019	1.304±0.003	9844	0.94	6.81
	100 %	7.700±0.017	1.303±0.003	9863	0.93	6.85
	150 %	7.706±0.019	1.304±0.003	9802	0.91	6.82

 # Values given in table is the average ± standard deviation of three replicate experiments

Table 4. Robustness results

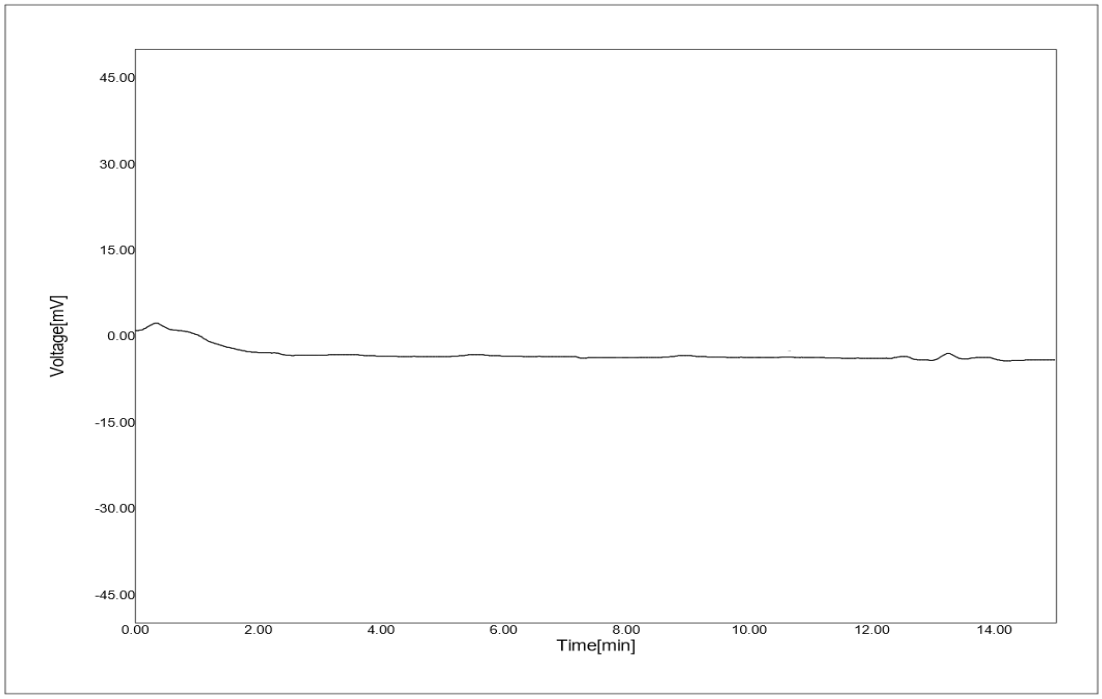
S No	Compound	Change	Peak Area	% Change	Plate count	Tail factor	Resolution
1	Dacomitinib	MP 1	696268.1	0.94	8595	1.13	8.05
2		MP 2	695967.7	0.98	8476	1.13	8.01
3		pH 1	697127.1	0.81	8403	1.12	8.06
4		pH 2	698604.5	0.60	8546	1.11	8.05
5		WL 1	700094.9	0.39	8499	1.15	8.07
6		WL 2	705914.8	0.44	8543	1.12	8.02
7	Impurity 1	MP 1	47997.7	1.20	4935	1.08	---
8		MP 2	48019.3	1.15	4998	1.07	---
9		pH 1	47920.5	1.36	4972	1.09	---
10		pH 2	48051.5	1.09	4868	1.08	---
11		WL 1	48176.3	0.83	4811	1.09	---
12		WL 2	48503.6	0.16	4920	1.08	---
13	Impurity 2	MP 1	64893.8	0.46	9568	0.96	6.77
14		MP 2	65294.5	0.15	9625	0.95	6.71
15		pH 1	64917.6	0.42	9588	0.90	6.75
16		pH 2	65065.2	0.20	9510	0.91	6.79
17		WL 1	64879.7	0.48	9611	0.92	6.72
18		WL 2	64917.8	0.42	9636	0.95	6.75

MP (mobile phase) 1: 0.1M sodium perchlorate at pH 5.1, acetonitrile 60:40; MP 2: 0.1M sodium perchlorate at pH 5.1, acetonitrile 70:30; WL (wavelength) 1: 238 nm; WL 2: 248 nm; pH 1: 5.0; pH 2: 5.2

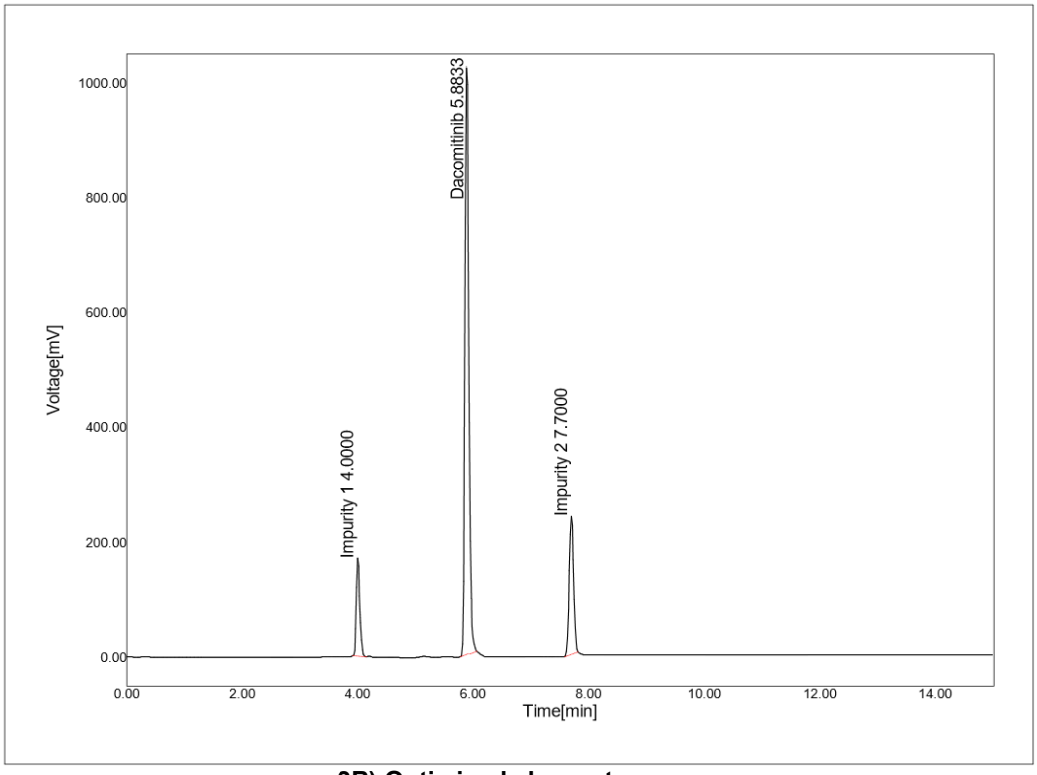
Table 5. Recovery results

S. No.	Compound	Recovery Level	Concentration in µg/ml			Amount found Mean ± SD	% recovered Mean ± SD	% RSD of Recovery
			Target	Spiked	Final			
1	Dacomitinib	50 %	40	20	60	59.837±0.063	99.728±0.105	0.11
2		100 %	40	40	80	79.841±0.105	99.801±0.131	0.13
3		150 %	40	60	100	99.428±0.378	99.428±0.378	0.38
4	Impurity 1	50 %	0.4	0.2	0.6	0.594±0.003	99.000±0.441	0.45
5		100 %	0.4	0.4	0.8	0.793±0.002	99.083±0.260	0.26
6		150 %	0.4	0.6	1.0	0.986±0.002	98.633±0.231	0.23
7	Impurity 2	50 %	0.4	0.2	0.6	0.595±0.003	99.222±0.419	0.42
8		100 %	0.4	0.4	0.8	0.789±0.002	98.667±0.289	0.29
9		150 %	0.4	0.6	1.0	0.985±0.003	98.500±0.300	0.30

**Values given in table are the average ± standard deviation for three replicate experiments*



2A) Black chromatogram



2B) Optimised chromatogram

Fig. 2. System suitability chromatograms of Dacomitinib, impurity 1 & 2 in the developed method

In the spiked recovery study, target concentration was considered as 40 µg/mL for Dacomitinib, 0.4 µg/mL for impurity 1 & 2 and formulation spiking was carried at 50%, 100% and 150 % spiked levels. The % recovery in each analysis for Dacomitinib and its impurities was found to be with in the acceptable limits and the % RSD in each spiked level was found to be less than 2 which is in the acceptable limit for Dacomitinib and its impurities studied, and results proved the accuracy of the method.

In the stress degradation studies, a very high % degradation of 9.68 % was observed in acid degradation study. In this stress study, well retained peaks were observed for Dacomitinib and its impurities and are well resolved from five unknown degradation compounds formed in acid stress study and the unknown compounds were retained at 2.71, 4.40, 6.30, 7.05 and 9.96 min along with impurity 1 and 2 [Fig. 3]. In base degradation study, four addition degradation compounds were observed at a retention time of 2.23, 4.45, 8.81 and 9.56 min and the % degradation of Dacomitinib was found to be 8.11 % and the two impurities studied were detected [Fig. 4]. A high % degradation of 9.27 % was observed in peroxide degradation study. In this, three additional degradation compounds were identified at a retention time of 2.71, 7.05 and 9.30 min [Fig. 5]. In photolytic (UV light) degradation, 7.32% degradation was observed for Dacomitinib and three additional degradation products were detected at a retention time of 3.28, 5.51 and 8.96 min [Fig. 6]. In very less % degradation of 5.06 % was observed in peroxide degradation study. In this, two additional degradation products were observed at retention time of 5.21 and 8.06 min along with imp 1 and 2 studied [Fig. 7]. The results of stress degradation study confirmed that the method can effectively separates the known and unknown degradation compounds observed in the stress degradation study.

The method developed for the analysis of Dacomitinib, impurity 1and 2 was applied for the estimation of drug and its impurities in formulation. The results of the formulation study confirmed that the % assay of 99.01, 0.32 and 0.14 % was observed for Dacomitinib, impurity 1and 2 respectively. In the formulation chromatogram (Fig. 8), both the impurities studied were detected along with Dacomitinib and there is no detection of other impurities and formulation excipients. Hence the method can be used for the identification and quantification of Dacomitinib and its impurity 1 and 2 in formulations.

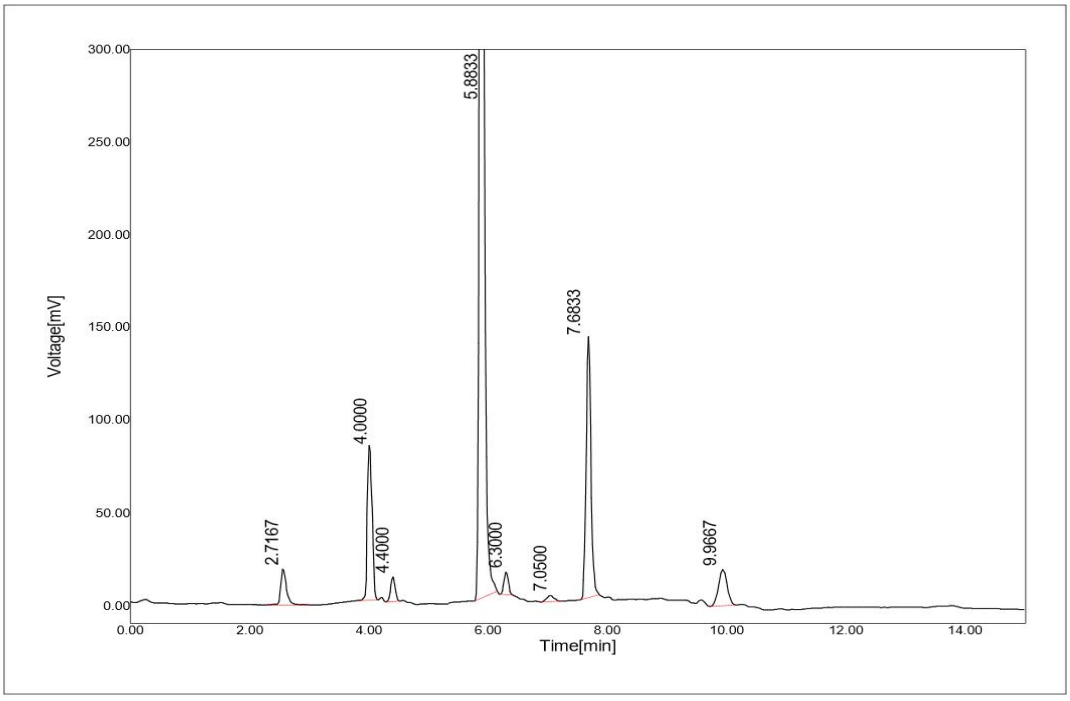


Fig. 3. Acid degradation chromatogram of Dacomitinib

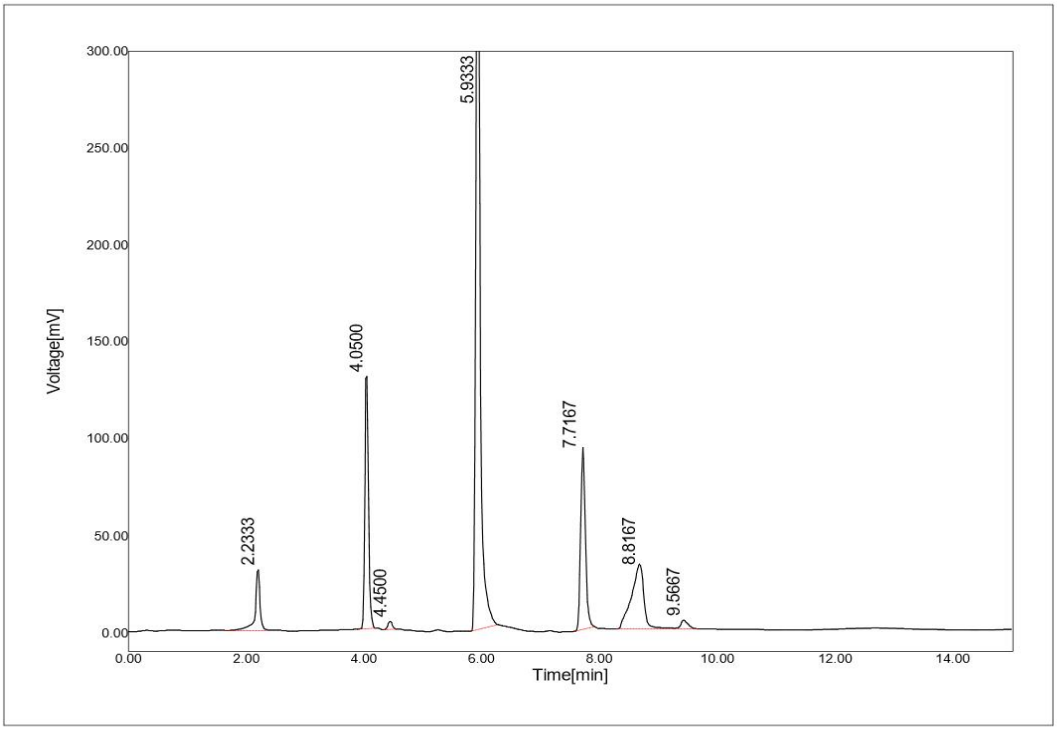


Fig. 4. Base degradation chromatogram of Dacomitinib

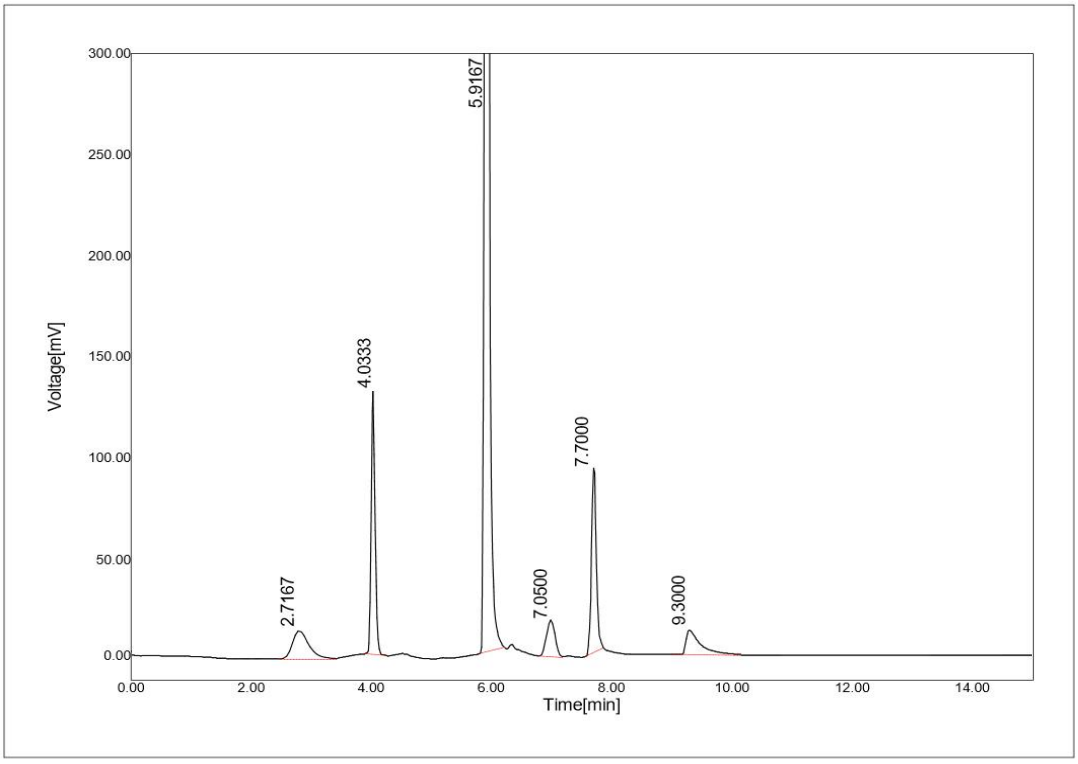


Fig. 5. Peroxide degradation chromatogram of Dacomitinib

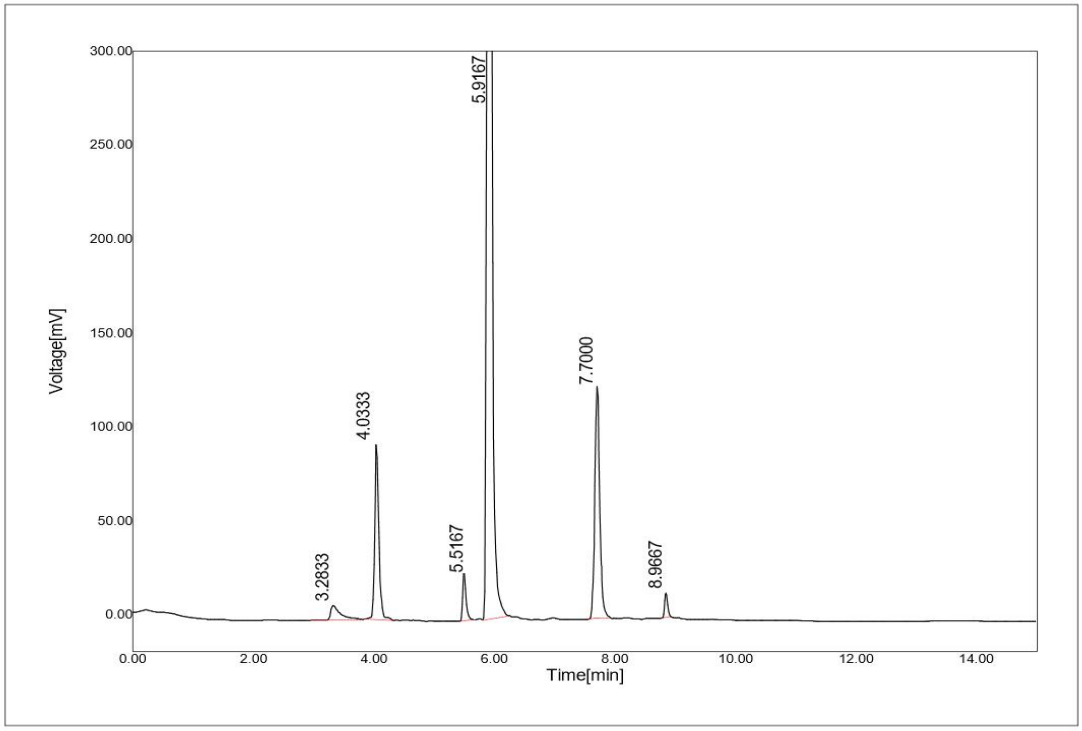


Fig. 6. Photolytic degradation chromatogram of Dacomitinib

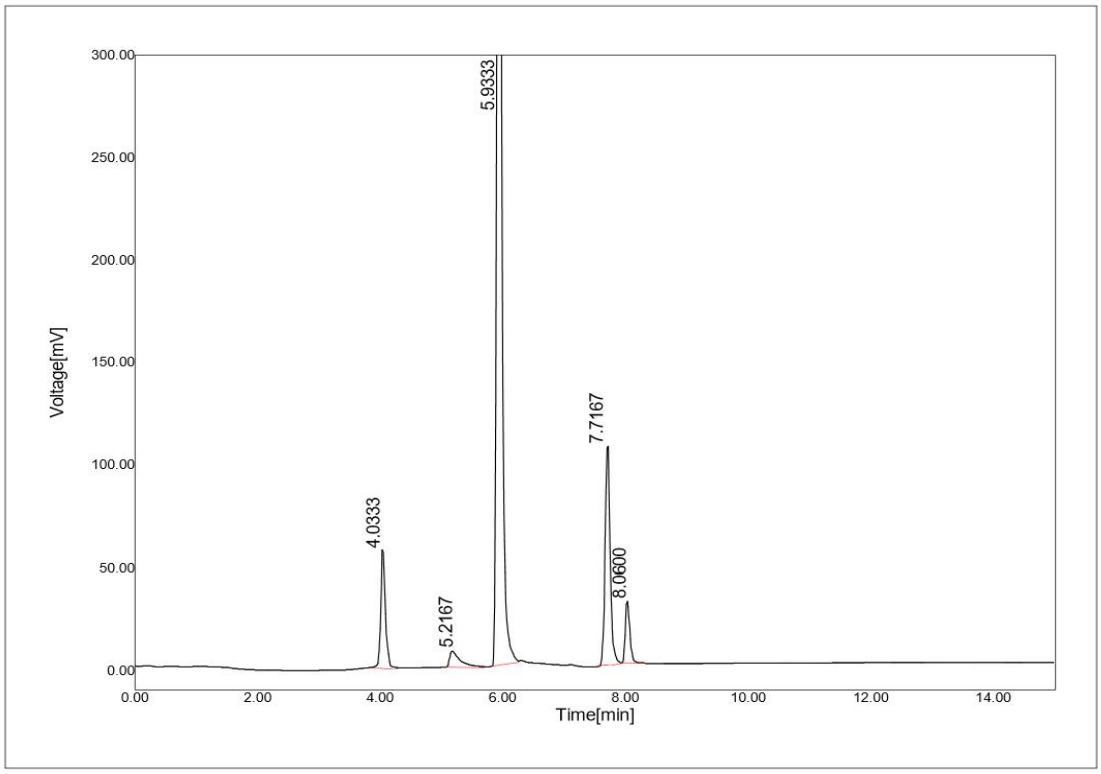


Fig. 7. Thermal degradation chromatogram of Dacomitinib

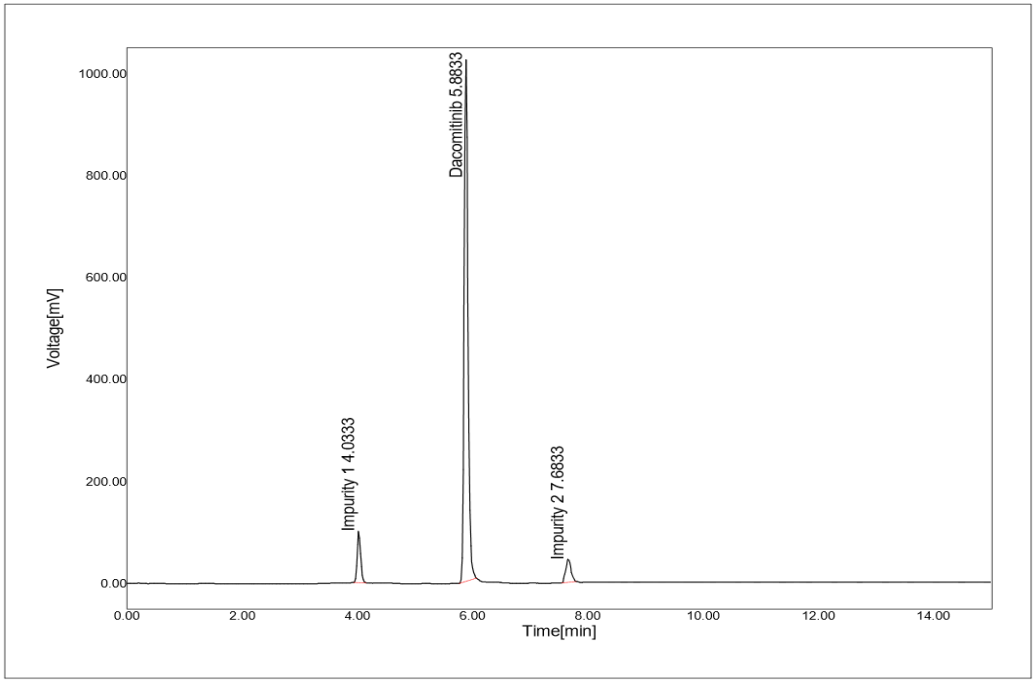


Fig. 8. Formulation chromatogram of Dacomitinib

4. CONCLUSION

A simple and novel HPLC method is proposed and developed for analysis of Dacomitinib and its impurities 1 and 2 in bulk drug and oral solid dosage forms as per ICH guidelines. The method found to be specific, selective, and sensitive for the quantification of known, unknown impurities and degradation products. The results observed for stability testing proves the stability indicating nature of the method. The assay utilized a previously unreported set of conditions, including an isocratic ramp, simple mobile phases, UV detection and less run time with high resolution without involving an ion-pair reagent. Sensitivity (LOD & LOQ) established by this method proved that the method is enough sensitive for the detection of impurities in formulation. The method is found to be accurate, precise, linear in the specified range, robust and may be used for routine and stability sample analysis of Dacomitinib and its impurities.

DISCLAIMER

Commonly, the products were used for this research and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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