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RESEARCH ARTICLE

New validated liquid chromatography-tandem mass spectrometry method for the determination of Dacomitinib in human plasma and its application to a pharmacokinetic study

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Abstract

Dacomitinib, a quinazoline compound, exhibits antineoplastic activity against brain metastasis activities in non-small cell lung cancer and the central nervous system. In this study, the liquid–liquid extraction method with high-performance liquid chromatography and tandem mass spectrometry detection method was established and validated for the determination of Dacomitinib in human plasma. Plasma samples were prepared and chromatographic separation was achieved on analytical column Discovery C_{18} (10 cm × 4.6 mm, 5 μm) with gradient elutes at a flow rate of 0.8 mL/min, using a mobile phase consisting of acetonitrile and ammonium formate. Dacomitinib and dacomitinib D_{10} (internal standard) were detected by multiple reactions. The method was fully validated according to the United States Food and Drug Administration guidelines. The calibration curve was linear with an excellent correlation coefficient (r^2 < 0.99). The method validation steps such as carry-over, matrix effect, extraction recovery, dilution effect, intra-inter accuracy, and precision were found

Article related abbreviations: AUC, area under the concentration-time curve; CC, calibration curve; HEGFR, human epidermal growth factor receptor; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography-tandem mass spectrometry; LLOQ, lower limit of quantitation; NSCLC, non-small cell lung cancer; QC, quality control; $T_{1/2}$, elimination half-life; UPLC, ultra-performance liquid chromatography; ULOQ, upper limit of quantitation.

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within acceptable limits. The method was then applied to a pharmacokinetic study in human plasma. After oral administration, the plasma concentration in different volunteers reached 0.5–250.01 ng/mL. The result established can be applied to the estimation of drugs in human plasma.

KEYWORDS
chromatography, dacomitinib, human plasma, liquid-liquid extraction, pharmacokinetic study

1 | INTRODUCTION

Dacomitinib (7-methoxyquinazoline-4, 6-diamine) a member of the class of quinazolines/piperidines/enamide, is a potent, irreversible pan-HER multi-tyrosine kinase receptor inhibitor used in the therapy of cases of non-small cell lung cancer (NSCLC) and central nervous system metastasis [1, 2, 12] that harbor active mutations in the human epidermal growth factor receptor (HEGFR). HEGFR is activated through homodimerization or heterodimerization to interact with downstream signaling pathways resulting in the formation of tumors.

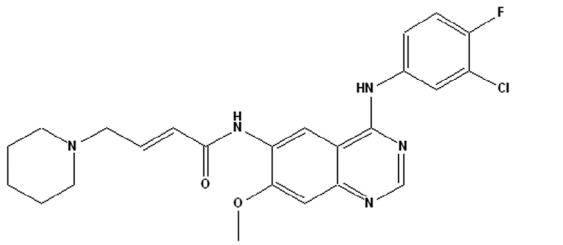
In addition, Dacomitinib has potential applications in patients harboring uncommon mutations [3]. The first time, it was developed by Pfizer Inc. and approved by the Food and Drug Administration on September 27, 2018. It has been approved in Germany since April 2019 for the treatment of locally advanced or metastatic NSCLC (https://www.ncbi.nlm.nih.gov/books/NBK546253). Previous literature suggests the therapeutic potential of Dacomitinib in the epithelial cancer model, although further investigations are needed. Numerous studies have reported that Dacomitinib exhibits significant growth inhibitory effects against NSCLC and also inhibits the proliferation and induces induction of apoptosis in HEGFR-expressing tumor cells by binding EGFR irreversibly and specifically [4, 13]. It was found to be more advanced than similar activity drugs such as afatinib, gefitinib, or erlotinib for the treatment of metastatic NSCLC with EGFR mutations L858R or del19 [5]. Some side effects are also observed with the use of Dacomitinib, that is, sourness in the mouth, weight loss, reduced appetite, swelling, infection around the nails, and skin dryness [6].

The quantity of various impurities (unwanted chemical compounds) in the drug/drug product will determine the ultimate safety of the drug product [7]. It may be formed during the synthesis or derived from precursors, intermediates, reagents, solvents, and catalysts [8]. Compared with the extensive literature on their pharmacological studies, little work has been done on the pharmacokinetics (ADME) of Dacomitinib. A better understanding of the ADME study of a drug is helpful for understanding its efficacy and toxicity [9]. In addition, there has been no bio-analytical method reported as per the available literature data for the analysis of Dacomitinib in bulk and pharmaceutical formulations. To the best of our knowledge, only liquid chromatography-mass spectrometry (LC-MS) and ultra-performance LC (UPLC) assays were recently published reporting the analysis of biological and pharmacokinetic characteristics of Dacomitinib in rat or dog plasma [10, 11]. Hence the present work aimed to develop an LC-tandem MS (LC-MS/MS) method for the determination of Dacomitinib (Figure 1) in K_2EDTAin human plasma. The validated assay has been successfully applied to the pharmacokinetic and bioavailability study of Dacomitinib in human plasma [14–19]. The results of this study will demonstrate the suitability of the developed method for the estimation of drugs in human blood plasma with adequate accuracy and precision (Figure 3).

2 | MATERIALS AND METHODS

2.1 | Drugs and reagents

Dacomitinib (100% purity, BST(I)—256-3291) was purchased from Bio-Organics, Bengaluru and Karnataka 560058, India whileDacomitinib D_{10} (99.3% purity, 3828-068A4) used as internal standard was also purchased from TLC Pharmaceutical Standards-L3Y 7B6. The



(E)-N-[4-(3-chloro-4-fluoroanilino)-7-methoxyquinazolin-6-yl]-4-piperidin-1-ylbut-2-enamide

FIGURE 1 Chemical structure of Dacomitinib.

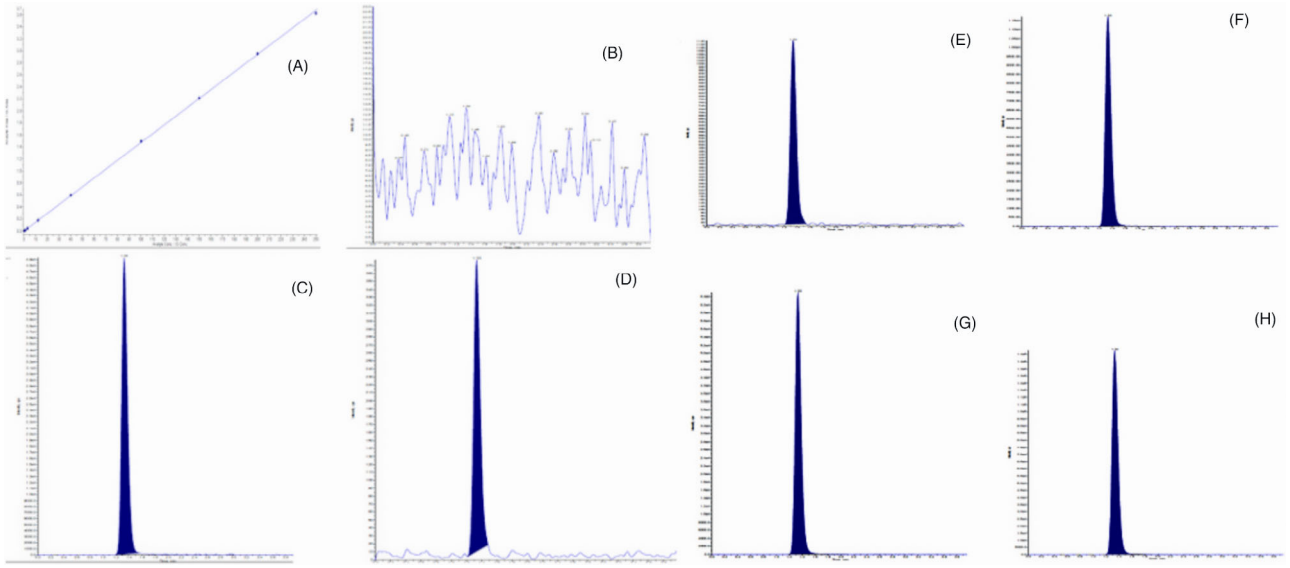


FIGURE 2 (A) Typical multiple reaction monitoring chromatograms of Dacomitinib and Dacomitinib (IS); (a) Calibration curve of Dacomitinib; (b) Blank plasma; (c) Standard Dacomitinib D10. (B) (d) 0.505 (LLOQC); (e) 1.463 (LQC); (f) 15.078 (AQC); (g) 80.632 (MQC); (h) 191.52 (HQC).

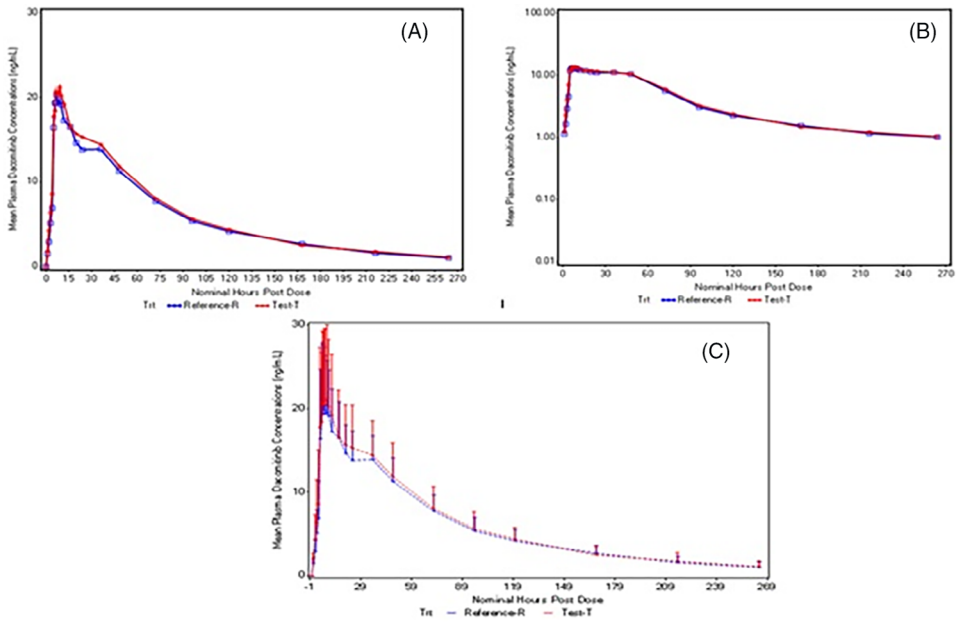


FIGURE 3 Mean plasma concentration curves (A): Dacomitinib concentrations versus time plot-linear scale; (B): Dacomitinib concentrations versus time plot-log linear scale; (C): Dacomitinib concentrations versus time profiles (Mean + SD plot).

chemical structures were confirmed by sophisticated techniques. Ultrapure water was prepared by the Milli-Qsytem (Millipore). High-performance liquid chromatography (HPLC) grade acetonitrile, ammonium formate was purchased from Sigma-Aldrich. All reference materials were stored in an airtight container at ambient temperature and protected from light.

Human plasma with K 2 EDTA as an anticoagulant, collected in-house in collaboration with Vasavi Medical and Research Centre, was further chromatographically screened for interfering substances and stored at −70°C prior to use. Liquid-liquid extraction was the method of extraction for preparing blank, calibration curve (CC), and quality control (QC) standard samples.

2.2 | plasma

The processed blank samples after the pretreatment stage were then reconstituted with 0.2 mL of aqueous samples as per the requirement, vortexed, and transferred into pre-labeled auto-sampler vials.

2.2.1 | Ethics approval and consent to participate

The clinical study protocol, including the final version of the subject informed consent form, was approved by the Institutional Review Board as per G.S.R 227(E) 2019 Indian GCP guidelines, before enrolment of any subjects into the study. All procedures performed in the clinical study involving human participants were in accordance with the ethical standards of the institutional and/or national research committees and the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

2.3 | LC-MS/MS conditions

Separation was achieved by HPLC and detection by tandem mass spectrometer (MS-MS). The chromatographic separation was achieved on analytical column Discovery C18 (10 cm × 4.6 mm, 5 µm) with mobile phase acetonitrile (10 mM): ammonium formate (70:30% v/v) with pH 3.00. A Turbo Ion spray interface in positive ion mode was selected to improve the selectivity and the sensitivity required for this application.

For MS/MS, Applied Biosystems/MDS Analytical Technologies was used. Multiple reaction monitoring mode was selected for quantitative analysis in positive ion mode transitions of *m/z* 470.2/385.1 for Dacomitinib and 480.2/385.1 for Dacomitinib D10 (IS) and are represented in Figures 4 and 5. Mass AB SCIEX (API 4500) Analyst 1.6.3 Software was used to acquire and process data. The lower limit of quantification was set for 0.5 ng/mL and linearity was verified for the curve range 0.5–250.42 ng/mL with linear $1/x^2$ regression analyses. Bio-analytical method SOP MS_21_033 (Draft) Version 01 was prepared and used for the full method validation.

2.4 | Preparations of stock solution, CC, and QC standard samples

Stock solutions were diluted in methanol and used for the preparation of CCs and QC samples. Stock solutions were stored at 2–8°C as per the method SOP.CCs and QCs were

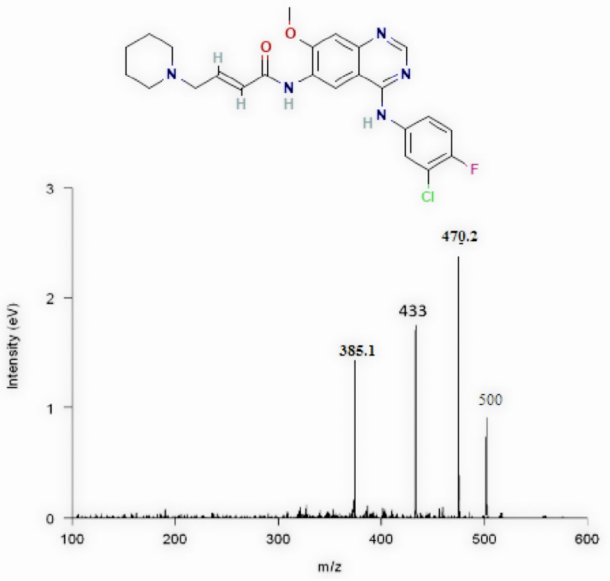


FIGURE 4 Mass spectra showing fragmentation of Dacomitinib (parent and daughter ion).

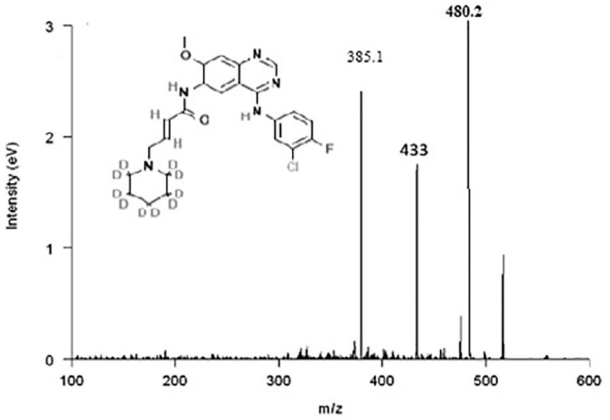


FIGURE 5 Mass spectra showing fragmentation of Dacomitinib D10 (parent and daughter ion).

prepared by spiking a known concentration of analyte into pooled plasma with plasma lots used for pooling as per the method SOP MS_21_033 (Draft) Version 01. The CCs and QCs were stored in the deep freezer at −70°C ± 10°C and −20°C ± 5°C for long-term stability evaluation.

2.5 | Sample preparation

The CC standards, QC samples, and subject samples (etc.) were retrieved from the deep freezer and kept in a water bath to thaw (maintained at room temperature). After thawing, the samples were vortexed briefly for

homogenization and processed with the following steps such as:

- 50 μL of ISTD dilution (about 100.0 ng/mL) was added into labeled polypropylene tubes (except blanks).
- Then added with 50 μL of 50% acetonitrile (diluent) to blank samples.
- 100 μL of the sample (CC standard/QC sample/Blank) was pipetted out to each tube and vortexed thoroughly.
- 100 μL of 0.1 N NaOH was added to each tube and vortexed briefly.
- Then added with 2.0 mL of TBME, capped, and vortexed for 10 min.
- All samples were centrifuged at 4000 RPM for 5 min at 10°C temperature.
- Then flash froze and transferred the supernatant into respective labeled polypropylene tubes.
- The above mixture was evaporated for the supernatant to complete dryness under a stream of nitrogen at 40°C.
- Finally, the dried residue samples with 0.2 mL of Mobile phase, were vortexed and transferred into respective labeled autosampler vials.

2.6 | Method validation

It was conducted according to the United States Food and Drug Administration Bio-analytical method validation guidelines. The parameters for validation included selectivity, carry-over, linearity, precision, accuracy, matrix effect, recovery, stability, and dilution integrity.

2.6.1 | Selectivity

This test was performed to assess the selectivity of the Dacomitinib and Dacomitinib D10. Screened human plasma including two Lipemic and two Haemolysed blanks were extracted along with the lower limit of quantitation (LLOQ) standard of respective lots. Response of interfering peaks at the retention time of analyte should be < 20% of the response of analyte in respective LLOQ standard and should be < 5% of CCs and QCs for each blank matrix.

2.6.2 | Linearity

The linearity was evaluated by analyzing calibration standard samples with concentrations of 10–250, respectively. A linear regression equation was established to provide the best fit for the concentration vs. detector response using $1/x^2$ as the weighting factor for the analyte. The back-calculated concentrations of the calibration standards should be within ± 15% of the nominal value, except for the LLOQ, for which it should be within ± 20%. At least 75% of the calibration standards, with a minimum of six calibration standards must full-fill this criterion including the LLOQ and upper limit of quantitation (ULOQ).

2.6.3 | Carry-over effect

Carryover was assessed by analyzing extracted LLOQ, blank, and ULOQ samples. The carryover in the subsequent injections of blank should not exceed 20% of the response of Dacomitinib in the extracted LLOQ standard and 5% of the response of internal standard(s), respectively.

2.6.4 | Accuracy and precision

The quantitative accuracy and precision of the assay were evaluated on a within-run and between-run basis. The analysis of matrix samples from accuracy and precision runs containing different concentrations of Dacomitinib was used for this evaluation. Each run included at a minimum, the calibration curve (LLOQ to ULOQ) and six replicates of each of the HQC, MQC, AQC, LQC, and LLOQQC quality control samples, where three accuracy and precision runs were processed and analyzed with freshly spiked calibration curve.

2.6.5 | Matrix effect and extraction recovery

Both tests (matrix and extraction recovery) were performed to assess the possible suppression or enhancement of the ionization of the Dacomitinib and dacomitinib D10 by co-eluting matrix components during mass spectrometric detection. The matrix effect was assessed by comparing the peak area of Dacomitinib obtained from the human plasma sample with that extracted from dacomitinib D10 solution at the same concentration.

2.6.6 | Stability

Stability exercises were performed to assess the stability of samples during expected conditions while handling, and storage including short-term stability (24 ± 4°C) and long-term stability (2–8°C) and after freeze-thaw cycles and processed sample stability. The mean concentration should be within ± 15% as compared to the freshly prepared solution.

2.6.7 | Dilution integrity

A dilution integrity standard prepared around 2.5 times the concentration of ULOQ was diluted and processed in replicates of six and then analyzed as per the analytical method. The dilution integrity standard concentration of Dacomitinib is 622.46 ng/mL, prepared in plasma and this was diluted 1/5th times and analyzed against a calibration curve. After applying the dilution factor, the mean concentrations of diluted samples (DQC) should be within ± 15% of the nominal concentration.

2.7 | Pharmacokinetic study

A pharmacokinetic study was performed on healthy male subjects (n = 12). The ethics committee approved the protocol and the volunteers provided their informed written consent. Blood samples were collected following the oral administration of Dacomitinib (45 mg tablet) and Vizimpro (45 mg) at the pre-dose, and 0.25, 0.5, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5,2.75, 3, 3.25, 3.5, 3.75, 4, 4.25, and 4.5 h, in K2 EDTA vacutainer collection tubes (BD). The tubes were centrifuged at 4000 rpm for 10 min and the plasma was collected. Immediately after collection, the plasma samples were subjected to flash–freezing and stored at −70 ± 10°C until their use. The plasma samples were spiked with the IS and processed as per the extraction procedure described earlier. Along with the clinical samples, the QC samples at low, middle 1, middle 2, and high concentration levels were also assayed in triplicate. The plasma concentration–time profile was analyzed by the non–compartmental method using PhoenixWinNonlin Software Version 8.3 (Pharsight Corporation,USA) or above. The pharmacokinetic parameters were computed using non-compartmental model of Phoenix Win-Nonlin Software Version 8.3 (Pharsight Corporation,USA). Pharmacokinetic study of human blood plasma was assessed by using these parameters, that is, maximum measured plasma concentration (C_{max}); Area under the plasma concentration versus time curvefrom time 0 to the last time point ($AUC_{0\text{-}t}$); Area Under the plasma concentration versus time curve from time 0 to time infinity ($AUC_{0\text{-}\infty}$) Time to achieve maximum plasma concentration (T_{max}); elimination half-life (T1/2); elimination rate constant (K_{el}) and percentage of $AUC_{0\text{-inf}}$ due to extrapolation from T_{last} to infinity ($AUC_{\_\%\ Extrap\_\ obs}$).

2.8 | Data analysis

The plasma concentrations are calculated according to the corresponding calibration curves. Pharmacokinetic parameters, such as the area under the concentration-time curve (AUC), total clearance, volume of distribution (V_d), and $T_{1/2}$, were calculated by using SAS software Version 9.4 or above (SAS Institute Inc.).

3 | RESULTS AND DISCUSSION

3.1 | Selectivity

This test is performed to assess the selectivity of the bioanalytical method for the analyte(s) and ISTD(s) of interest from the natural variation of endogenous matrix components among individuals for multiple separate matrix lots. Human plasma including two Lipemic (L) and two Haemolysed (H) blanks was extracted along with the LLOQ standard of respective lots. This demonstrates that the analyte(s) and ISTD(s) are free from significant interference from endogenous matrix components and also demonstrates the selectivity of the method at LLOQ with respect to accuracy. Selectivity met the SOP acceptance criteria. Results are presented in Table 1.

3.2 | Linearity, goodness of fit, and LLOQ

Method validation performance was evaluated using data generated from accepted calibration curves. The point calibration curve was found to be linear from 0.5 to 250.01 ng/mL for Dacomitinib. The goodness of fit (R^2) was consistently >0.99during the course of validation. The LLLOQ for Dacomitinib was found to be 0.5 ng/mL. The signal-to-noise (S/N > 10) of the extracted SEN LLOQ samples was calculated by comparing the signal of each SEN LLOQ sample to its baseline noise.

3.3 | Carryover

Carryover was assessed by analyzing extracted LLOQ, blank, and ULOQ samples. The results were evaluated for carryover in the run for blanks, which were injected following a ULOQ standard. The results met SOP acceptance (˂5% for LLOQ) criteria which suggested that the carryover effect was negligible under the current conditions.

3.4 | Accuracy and precision

Table 1 represents the intra- and inter-accuracy and precision of QC samples and it was present in the ranges of 91.8%–105.6% and 0.9%–8.28%, respectively.

TABLE 1 Intra- and inter-day precision and accuracy of Dacomitinib in the current method.

Quality control samples	Nominal concentration (ng/mL)	Mean ± SD (ng/mL)	Intra-run accuracy range (%)	Intra-run precision range (%)	Inter-run accuracy (%)	Inter-run precision (%)
LLOQQC	0.50	0.50 ± 0.04	91.88–108.71	3.83–5.69	100.40	8.28
LQC	1.46	1.47 ± 0.06	98.97–102.80	3.29–4.57	100.27	4.08
AQC	15.08	15.52 ± 0.31	101.70–103.96	1.51–2.4	102.96	2.01
MQC	80.63	85.15 ± 1.26	105.25–105.90	1.13–1.78	105.60	1.48
HQC	191.53	198.19 ± 3.78	101.21–104.72	0.90–1.32	103.48	1.91

TABLE 2 The extraction recoveries, matrix effects, and stabilities of Dacomitinib in human plasma.

Analyte	Nominal level (ng/ml)	Extraction recovery (%)	Matrix effect (%)	Stability (%)				
				Freeze-thaw	Bench-top	Processed sample @ Room Temperature	Processed sample @ Refrigerated Condition	Long term
Dacomitinib	1.46	73.52 ± 2.29	1.55	101.57 ± 4.99	100.00 ± 3.96	101.57 ± 2.24	99.38 ± 3.62	98.15 ± 2.33
	191.53	78.87 ± 3.42	0.86	98.34 ± 1.29	98.19 ± 1.06	98.59 ± 1.36	98.67 ± 2.00	101.42 ± 2.06
Dacomitinib (IS)	100.0	82.08 ± 9.10	–	–	–	–	–	–

3.5 | Matrix effect and extraction recovery

The matrix effect ($n = 6$) was from 0.86%–1.55% which suggested that no significant matrix effect affected the determination of dacomitinib. The extraction recovery ($n = 6$) was between 73.52% and 78.87%. The detail data of matrix effect and extraction recovery was described in Table 2.

3.6 | Stability

Calibration curve standards and quality control samples were used for bench top, processed sample stability at room temperature (24 ± 4°C), processed sample stability under refrigerated conditions (2–8°C), and freeze-thaw stability experiments. The freeze-thaw, short term and long term stabilities ($n = 6$) were detected by perming QC samples suffered to a series of stored conditions. As shown in Table 2, the relative recoveries were within limit. The results indicate that Dacomitinib was stable under the tested storage conditions.

3.7 | Dilution integrity

The dilution integrity standard concentration of Dacomitinib is 622.46 ng/mL, prepared in plasma and this was diluted 1/5 times and analyzed against a calibration curve.

3.8 | Pharmacokinetic study

The validated method was further successfully applied to a pharmacokinetic study of Dacomitinib in human plasma. All the above blank matrices were screened and no lot has shown any significant interference at the retention time of Dacomitinib and Dacomitinib d10 out of 16 lots. The profiles of the plasma concentration–time curve are expressed in Figure 2 and the pharmacokinetic study parameters accessed by the non-compartmental model are shown in Table 3 and represented in Fig.3.

The proposed method has lots of advantages over cited references 10 and 11 in the following ways such as:

(i) The current method is linear in the range from 0.5 to 250.01 ng/mL, which is less than the existing methods (2.00–500 ng/mL).
(ii) Intraday precision and accuracy were found to be 0.90%–1.32% and 100.4%, respectively which is supposed to be better than the existing methods (0.84%–3.58% and 92.2%–100.32%).
(iii) Cited reference 11 is all about the characterization of metabolites in which the objective is different and cannot be compared.
(iv) The proposed method is validated and the results were found better than the existing methods and pharmacokinetic parameters have been established, whereas existing methods lack.

TABLE 3 Mean pharmacokinetic parameters of Dacomitinib (ng/mL) for treatment T under fasting condition) for subjects considering PK and statistics analysis.

Parameter	Mean data
C_{max} (ng/ml)	22.5 ± 8.8
T_{max} (h)	9.0 ± 4.9
$T_{1/2}$ (h)	72.6 ± 18.2
MRT (h)	0.01 ± 0.03
$AUC_{0\text{-}t}$ (ng/h/L)	1603.4 ± 515.2
$AUC_{0\text{-}\infty}$ (ng/h/L)	1741.4 ± 576.1
R (%)	7.52 ± 3.52
T (%)	9.0 ± 4.97 (SD)

a) $\mathbf{C_{max}}$- Peak concentration, b) $\mathbf{T_{max}}$- Time to peak concentration, c) $\mathbf{T_{1/2}}$-elimination half-life, d) **MRT**- Mean residence time, e) **AUC**- area under the concentration-time curve, f) **R**- Oral bioavailability of Reference (Dacomitinib, D10), and g) **T**-Oral bioavailability of Test (Dacomitinib).

4 | CONCLUDING REMARKS

The results obtained from the validation, attest to the reliability of the analytical system and the reliability and reproducibility of the assay of Dacomitinib, K_2EDTA Human plasma over a range of 0.5–250.01 ng/mL. The assay is specific and results demonstrate freedom from any reasonably expected interference. The analyte measured is shown to be stable under stress conditions that may be encountered during the application of this method.

AUTHOR CONTRIBUTIONS

Nalini Kanta Sahoo, Maddela Rambabu, and M. Praveen conceived and designed all the experiments, and performed identification of the suitability of methods. Tinku Gupta, Shrikant Charde, and Madhusmita Sahu drafted and reviewed the manuscript. Nalini Kanta Sahoo, Arunaksharan Narayanankutty, and Tinku Gupta performed the bioanalytical section. Prasun Chakrabarti, Martin Margala, Bhuvan Unhelkar, and Bui Thanh Hung have done the analysis section. All authors have read and approved the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed during the current study are available with the corresponding author. Data can be acquired from the first author upon request.

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