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Development of a validated LC–ESI-MS/MS method for the quantification of tucatinib in plasma samples

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ABSTRACT

The aim of the work is to present a simple LC-MS/MS approach for a sensitive, specific, and quantitative determination of Tucatinib in human K2EDTA plasma. Tucatinib is used in the treatment of metastatic HER2-positive breast cancer. Linearity and a high r^2 value (>0.99) characterize the calibration curve, which spans 1–2,000 ng/ml. The quality control levels were executed with plasma blank to get 1, 3, 1,000, and 1,500 ng/ml for the lower limit of quantification, LQC,low quality control, MQC, and high quality control, respectively. The relative errors for the intra- and inter-batches were from 3.49% to 4.75% and 2.82% to 4.14%, correspondingly, with coefficient variation varying from −3.02% to 5.21% and 2.82% to 5.12%. During the retention period of Tucatinib and internal standard, there was no discernible interference from the endogenous peak. No matrix impact was seen in the test samples and was stable throughout the conditions exposed; moreover, recoveries were accurate across the whole calibration curve range. As per the USFDA bioanalytical technique validation guideline, the LC-MS/MS method was validated in terms of accuracy, linearity, precision, specificity, stability, dilution integrity, extraction recoveries, selectivity, and matrix effect. In conclusion, a new approach to evaluating Tucatinib in human K2EDTA plasma has been approved for use in clinical, bioavailability, and bioequivalence investigations, and it may be used to quantify Tucatinib.

1. INTRODUCTION

For people with advanced, non-resectable, or metastatic HER2-positive breast cancer, the recommended therapy regimen includes trastuzumab and capecitabine in addition to Tucatinib. Patients who have had brain metastases or who have been on anti-HER2-based treatment in the past are included in this category [1,2].

It is also approved for use in conjunction with trastuzumab to treat adult patients whose colorectal cancer has advanced after treatment with chemotherapy based on fluoropyrimidines, oxaliplatin, or irinotecan and is either unresectable or has spread. Confirmatory studies are required to confirm and describe the clinical benefit before this indication may be authorized under rapid approval [3].

Some forms of breast cancer are associated with HER-2 gene mutations. Tucatinib blocks the HER-2 gene's tyrosine kinase enzyme. Tyrosine kinase mutations in the HER-2 gene cause cancer by setting off a chain reaction that increases cell signaling and proliferation. It also blocks essential signaling routes such as PI3K/Akt/mTOR and RAS/RAF/MEK/ERK that promote the growth and longevity of cancer cells. Tucatinib stands out as one of the limited HER2-targeted agents capable of traversing the blood-brain barrier, offering therapeutic benefits for brain metastases in HER2-positive breast cancer. Molecular weight: 480.532 g•mol^{-1} and chemical formula [4–7]: 6-N-(4,4-dimethyl-5H-1,3-oxazol-2-yl)-4-N-[3-methyl-4-([1,2,4]triazolo[1,5-a]pyridin-7-yloxy)phenyl]quinazoline-4,6-diamine (Fig. 1).

No studies using high performance liquid chromatography (HPLC) with tandem mass spectrometry liquid chromatography tandem mass spectrometry (LC-MSMS)

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to quantify Tucatinib in human K2EDTA plasma have been published as far as we are aware. For the purpose of quantifying Tucatinib and characterizing its force degradation components utilizing LC-MSMS, there is a single described technique using reverse phase high performance liquid chromatography [8]. Developing and validating a fast, sensitive, and specific LC-MSMS technique for assessing Tucatinib in K2EDTA human plasma was the primary objective of this investigation.

2. MATERIALS AND METHODS

2.1. Reagents and chemicals

The pure Tucatinib and Lenvatinib standards of the purities of 99.81% and 99.87%, respectively, according to chromatographic (HPLC) methods. They are obtained from Shree Icon Lab in Vijayawada, India. Acetonitrile and formic acid that are suitable for HPLC were provided by Finar Chemicals in Ahmedabad, India. HPLC grade water (Millipore, USA) was made by filtering it through a Millipore MilliQ plus device.

2.2. Instrument

Quantum Discovery TSQ mass spectrometry analyzer (Thermo Finnigans, Sans Jose, CA) with an electrospray ionization interface was used for chromatography. It had an autosampling and degassing system and pumps connected to it. The test was done on a Thermo Scientific Hypersil Gold column with a reversed phase (50 × 2.1 mm i.d., 3 µm particle size). The Xcalibur program (version 1.4) was used to handle all the tasks, including gathering and analyzing data.

2.3. Mass and liquid chromatographic system conditions

It was possible to separate the samples using an isocratic mobile phase that was made up of 0.1%HCOOH and acetonitrile in the ratio of 15:85% v/v, with 0.5 ml/min flow rate and a column temperature of 35°C. The settings for tracking multiple reactions were set to 4,000 V spray voltage, 250°C vaporizer, and 350°C capillary temperatures. In multiple reaction monitoring mode, the best MS transitions for Tucatinib were m/z 481.2/382.1 and for Lenvatinib, they were 427.1/56.1 in positive ionization mode.

2.4. Processing of standard solution

The IS (2,000 µg/ml) and the stock solution of Tucatinib (10,000 µg/ml) were processed individually in acetonitrile and subsequently monitored at 5°C in a refrigerating system. To process the standards for working controls for Tucatinib and 1,000 ng/ml for lenvatinib (IS), appropriate dilutions were prepared in acetonitrile. The standard controls for Tucatinib and lenvatinib were executed when required and kept in the refrigerator at a temperature of 2°C–8°C.

2.5. Processing of calibration, and quality control (QC) standards

Linearity control solutions of Tucatinib were processed by introducing 1% quantities of control solutions into plasma blank. The calibration curve was determined to have eight levels. The plasma concentrations of Tucatinib were 1, 3, 30, 180, 520, 1,000, 15,00, and 2,000 ng/ml at the end of the study. The QC levels were similarly executed with plasma blank to get 1, 3, 1,000, and 1,500 ng/ml for the lower limit of quantification (LLOQ) low quality control (LQC), MQC, and high quality control (HQC), respectively. The plasma sample preparation procedure was followed for all contaminated samples.

2.6. Processing of sample solution

30 µl aliquots of each linearity level, Q C sample solutions, and test solutions were combined with 50 µl of an internal working standard solution (1 µg/ml) and shaken vigorously using a vortexer. Following vortex mixing, every solution was rapidly cooled by adding 800 µl of acetonitrile and subjected to mixing for 30 seconds. The mixture was then subjected to centrifugation at 14,000 revolutions per minute for at least 20 minutes at a temperature of 4°C. Following centrifugation, the liquid portion above the sediment was meticulously isolated, and 5 µl portion was introduced into an liquid chromatography-electro spray ionization-mass spectrometry (LC–ESI-MSMS) instrument for quantification [9].

2.7. Validation of the analytical method

The developed LC–ESI-MSMS technique to assess Tucatinib from biological matrices was validated as per the USFDA bioanalytical method validation guidelines (2018) [10]. The developed procedure was subjected to validation for the parameters selectivity, accuracy, linearity, specificity, matrix effect, extraction recoveries, precision, carryover, dilution integrity, and stability.

2.7.1. Selectivity

The evaluation of selectivity was conducted using the K2EDTA plasma without any substances present. The assessment of selectivity should indicate that there were no notable interferences detected for IS and Tucatinib retention times in blank plasma [11].

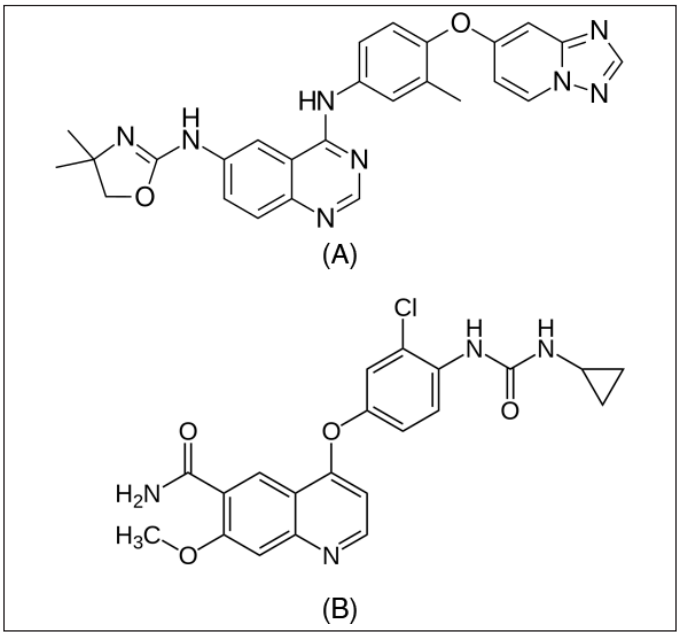

Figure 1. A) Tucatinib and B) Lenvatinib chemical structures.

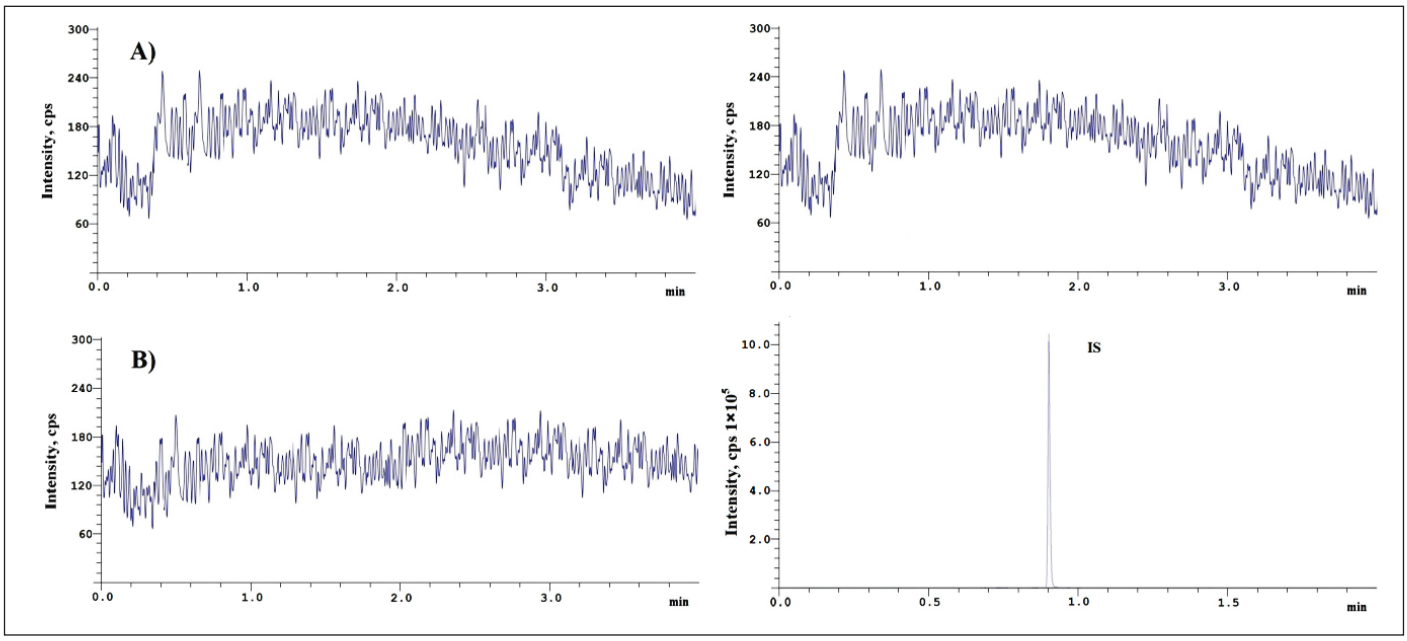

Figure 2. Tucatinib blank plasma (A), and blank plasma with IS (B) chromatograms.

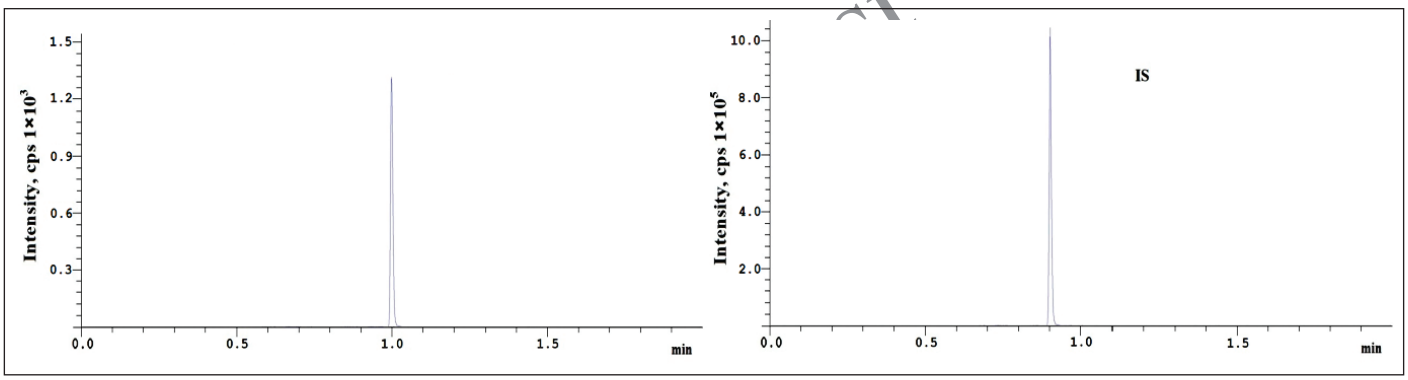

Figure 3. Tucatinib chromatogram at LLOQ (1 ng/ml) level with IS.

2.7.2. Calibration plot and sensitivity

Linearity was detected across eight calibration curves spanning a concentration range of 1 to 2,000 ng/ml for Tucatinib. The linearity plots were generated by graphing peak response fractions of Tucatinib to Lenvatinib against the control solutions of linearity controls [9].

2.7.3. Accuracy and precision

To ensure the method's precision and accuracy, every QC level was tested six times in three separate batches, both intra-day and inter-day. Precision and accuracy findings within a range of ±15% were deemed acceptable, with the exception of concentrations at LLOQ, for which a tolerance of 20% was deemed acceptable [12].

2.7.4. Matrix effect and extraction recoveries

The extraction recoveries were assessed by computing the fraction of response of QC levels containing known quantities of Tucatinib to the response of Tucatinib introduced at similar quantities to blank plasma after protein precipitation. This analysis was performed three times (n = 3) [13,14]. The matrix impact was assessed by comparing the quantities of

Table 1. Tucatinib linearity data.

LS-ID	Concentrations in ng/ml	Mean area	IS area	Analyte/IS area
LS1	1	1,359	1,167,354	0.001164
LS2	3	3,795	1,165,941	0.003255
LS3	30	39,478	1,165,367	0.033876
LS4	180	243,984	1,169,584	0.208608
LS5	520	712,847	1,165,741	0.611497
LS6	1,000	1,298,654	1,165,995	1.113773
LS7	1,500	2,018,745	1,164,664	1.733328
LS8	2,000	2,683,659	1,163,014	2.307504

LS: Linearity standard.

Table 2. Intra-day and inter-day precision and accuracy of tucatinib.

Level of drug spiked (ng/ml)		Intra-day[a]			Inter-day[b]		
		Concentrations found(mean ± SD; ng/ml)	Precision (%RSD)	%Accuracy	Concentration found(mean ± SD; ng/ml)	Precision (% RSD)	%Accuracy
	1	0.98 ± 0.05	5.12	97.56	0.96 ± 0.04	4.14	96.51
	3	2.91 ± 0.11	3.78	96.98	2.94 ± 0.11	3.74	97.91
	1,000	1,052.09 ± 24.32	2.31	105.21	1,047.56 ± 29.58	2.82	104.76
Tucatinib	1,500	1,477.32 ± 44.28	2.99	98.49	1,487.79 ± 47.84	3.21	99.19

a& b: 4×3 replicate experiments.

Tucatinib dissolved into matrix blank extract to those of pure standards (n = 3).

2.7.5. Dilution linearity

Dilution integrity refers to the evaluation of the diluting process of the sample to ensure that it does not affect the precision and accuracy of assessed concentrations of Tucatinib. The solutions diluted were tested and their precision and accuracy were evaluated to expected findings. Results that fell within a range of ±15% were deemed to be satisfactory in terms of both accuracy and precision [15–18].

2.7.6. Carryover

The carryover was evaluated by measuring peak responses of Tucatinib by injection of blank matrix samples in a sequential manner after the injection of the highest calibration standard sample [17,19].

2.8. Stability

The stability of the human K2EDTA plasma samples was examined by assessing them at two distinct concentration levels of QC samples. This analysis was conducted under various settings, comparing the samples against recently created calibration curves and QC samples. The concentrations of the QC samples were 3.0 and 1,500 ng/ml, with a total of six samples analyzed. The plasma samples underwent storage for a minimum of 6 hours at room temperature, at a temperature of −20°C for ten days, 3 cycles of freezing and thawing, and for 24 hours at a temperature of 4°C in autosampler [18–22].

3. RESULT AND DISCUSSION

3.1. Validation of the analytical method

3.1.1. Selectivity

Figures 2 and 3 demonstrate that there was no interference detected in retaining times of Tucatinib (1.02 minutes) and Lenvatinib (0.92 minutes) in chromatograms of plasma blank solutions taken from different six batches. Findings demonstrated that Tucatinib test exhibited a high degree of specificity and selectivity.

3.1.2. Calibration plot and sensitivity of tucatinib

Linearity controls were executed and examined at eight distinct concentration levels ranging from 1 to 2,000 ng/ml. The linearity graph for Tucatinib exhibited satisfactory linearity throughout the specified concentration range, as shown by a mean correlation coefficient (r^2) greater than 0.99. The curve was weighted using a factor of 1/x2. The equation for linear regression is y = 0.00115x - 0.00095, as shown in Table 1 (Fig. 4). These calculated concentrations fell within the acceptable range of ±15%, except for the LLOQ, where the acceptable range was ±20%.

Table 3. Tucatinib extraction recoveries.

QC level	*X*	*Y*	% Recoveries	%Mean recoveries	%RSD
LQC	4,107	3,914	95.31	98.31	2.96
MQC	1,350,984	1,315,588	97.38		
HQC	2,025,624	2,071,201	102.25		
IS	1,165,945	1,144,608	98.17		

X, average recoveries of unextracted samples; Y, average recoveries of extracted samples.

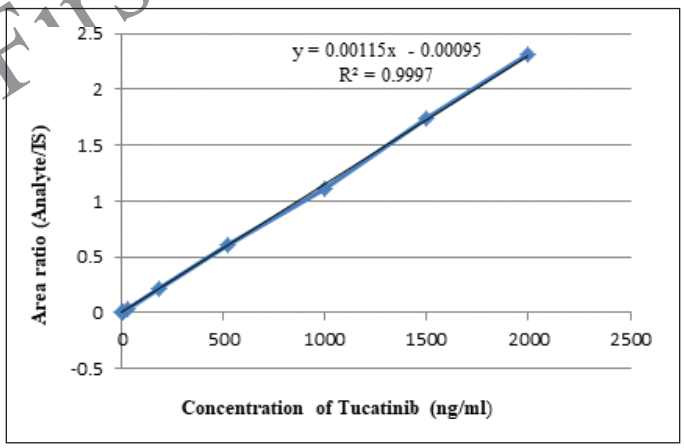

Figure 4. Calibration curve of tucatinib.

3.1.3. Precision and accuracies

The intra-batch accuracy was within −3.02% to 5.21% relative error and the precision was within 2.31% to 5.12%. The inter-batch accuracy was within −3.49% to 4.75% relative error and the precision was within 2.82% to 4.14%. The assay results, as shown in Table 2, were below 15% and met the approved

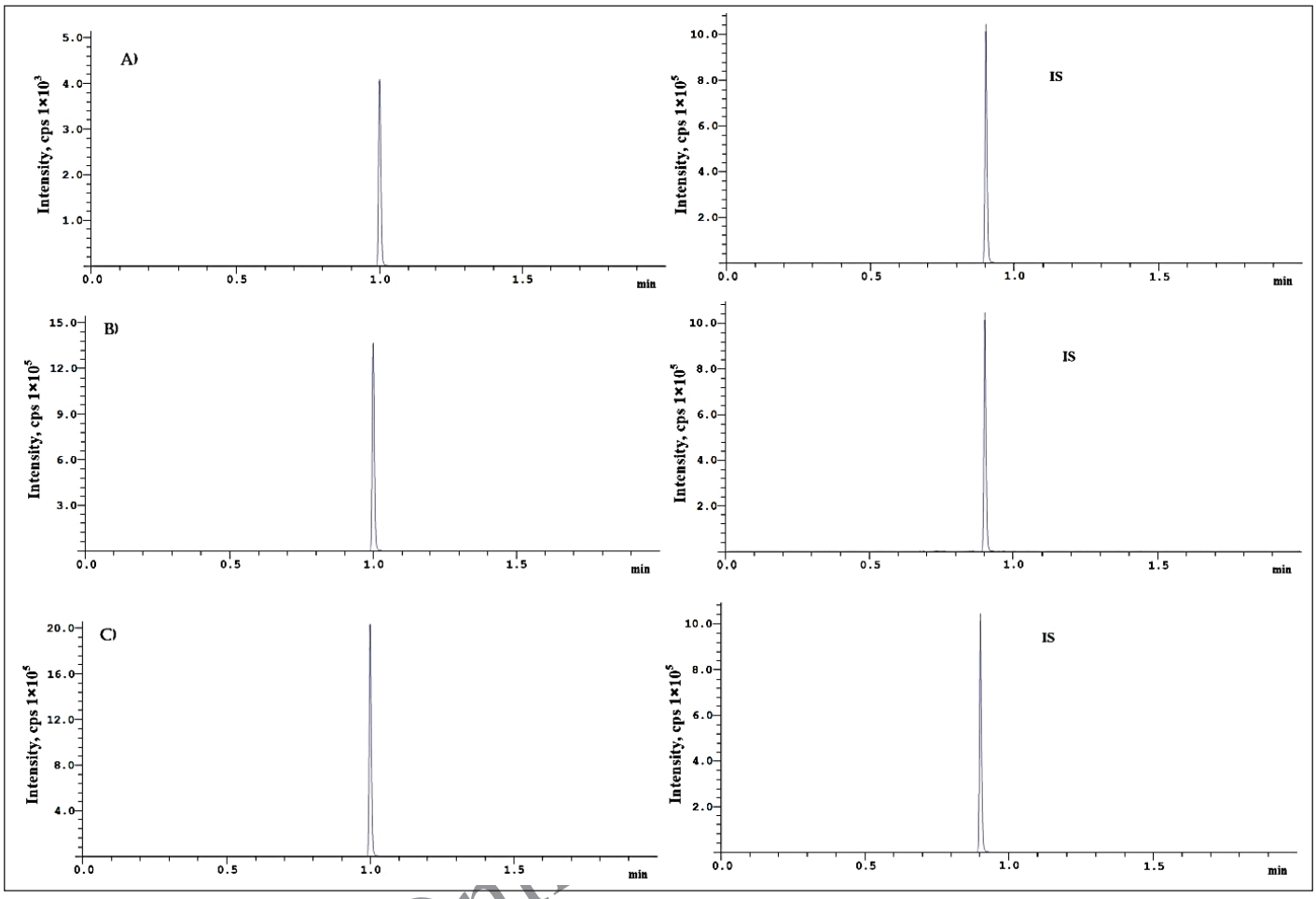

Figure 5. Tucatinib chromatograms at LQC (3 ng/ml) (A) MQC (1,000 ng/ml) (B) and HQC (1,500 ng/ml) (C) level

Table 4. Tucatinib matrix effect at LQC and HQC levels.

	LQC(3 ng/ml)			HQC(1,500 ng/ml)		
S.No	Peak responses in absence of matrices	Peak responses in existence of matrices	Matrix factor	Peak responses in lack of matrices	Peak areas in presence of matrices	Matrix factors
1	4,058	3,864.4334	95.23	2,025,541	1,889,425	93.28
2	4,147	4,264.7748	102.84	2,025,187	2,073,184	102.37
3	4,142	4,023.5388	97.14	2,025,379	1,965,630	97.05
4	4,031	3,821.7911	94.81	2,025,359	1,951,231	96.34
5	4,141	4,276.4107	103.27	2,025,718	1,909,847	94.28
6	4,028	3,843.5176	95.42	2,025,684	2,123,525	104.83
Mean			98.11833			98.025
± SD			3.907927			4.593843
% RSD			3.982872			4.686399

limit. This indicates that the quantification of Tucatinib in human K2EDTA plasma was accurate and precise.

3.1.4. Matrix effects and extraction recoveries

The analysis of extraction recoveries (Table 3 and Fig. 5) and matrix effect revealed that the extraction recoveries for Tucatinib satisfied the specified parameters and the matrix impact in this assay was found to be insignificant (Table 4).

3.1.5. Dilution integrity

Six duplicate samples, each containing Tucatinib at a concentration of 6 µg/ml, were diluted by factors of 5 and 10

Table 5. Stability findings of analytes (n = 3).

Storage temperature	LQC(3 ng/ml)		HQC(1,500 ng/ml)	
	%Accuracy	Precision	%Accuracy	Precision
6 hours at ambient temperature	96.38	3.29	94.21	2.69
4°C in autosampler	94.93	4.51	103.28	4.33
3 freeze-thaw cycles	103.27	3.27	96.31	4.51
−20°C for 10 days	94.32	5.29	102.66	3.93

using blank plasma. The analyte exhibited a precision (%CV) of less than 15% and accuracies within 85%–115%.

3.1.6. Carryover

Within the scope of this investigation, the blank matrix samples were evaluated in a sequential manner following the highest linearity concentration, and there was no evidence of a carryover effects.

3.2. Stability

Tucatinib demonstrated stability in human K2EDTA plasma under the following temperature and time conditions: a minimum of 6 hours at room temperature, storage at −20°C for 10 days, exposure to three freeze-thaw cycles, and stored at 4°C for 24 hours in autosampler. The stability test results are shown in Table 5.

4. CONCLUSION

Tucatinib is authorized for usage in conjunction with trastuzumab for the management of adult patients who have been diagnosed with RAS wild-type HER2-positive colorectal cancer that is either unresectable or metastatic and has progressed after receiving chemotherapy with fluoropyrimidine, oxaliplatin, or irinotecan. Within the context of human K2EDTA plasma, an LC–MS/MS approach that is extremely sensitive, specific, and straightforward was provided for the purpose of quantifying Tucatinib. With a linearity that was desired and an r^2 value that is more than 0.99, the linearity controls ranged from 1 to 2,000 ng/ml. The intra and inter batch accuracies were within −3.02% to 5.21% and 3.49% to 4.75% relative error with coefficients of variation 2.31% to 5.12% and 2.82% to 4.14%, respectively. In conclusion, a new approach to evaluating Tucatinib in human K2EDTA plasma has been approved for use in clinical, bioavailability, and bioequivalence investigations, and it may be used to quantify Tucatinib.

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6. AUTHOR CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be an author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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8. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

9. ETHICAL APPROVALS

The study protocol was approved by the Institutional Ethics Committee (Approval No.: DRSER: 0733/3, Date: 10/03/2025).

10. DATA AVAILABILITY

All data generated and analyzed are included in this research article.

11. PUBLISHER'S NOTE

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12. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declares that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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