Journal for Re Attach Therapy and Developmental Diversities
eISSN: 2589-7799
2023 November; 6(10s): 2067-2074

Method Development and Quantification of Cabozantinib in Human Plasma by Using LC-MS/MS

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ABSTRACT

The main aim of the research was to develop a fast and highly sensitive bioanalytical LC-MS/MS technique for the quantitation of Cabozantinib in human plasma. Chromatography has achieved on a Synergi polar column (75 mm x 4.6 mm ID, 4 µm) and mobile phase containing a mixture of 10 mM Ammonium acetate buffer with 0.2% formic acid were mixed with HPLC grade Acetonitrile in the proportion of 30:70, v/v. Chromatographic peaks were resolved with 0.40 ml/min flow rate. Drug was extracted by simple Protein Precipitation method. The precursor to product ion transitions is *m/z* 502.27 to 323.07 for Cabozantinib and *m/z* 231.25 to 185.17 for Naproxen (Internal standard) The retention time of Cabozantinib and Naproxen (Internal standard) was found to be 0.95 min and 1.50 min respectively Calibration curve of Cabozantinib was linear over 5-1000 ng/ml concentration range with a regression coefficient (r^2) value of>0.99. The % RSD values were less than 6.5% for inter-day and intra-day precision and accuracy. The method has excellent recovery and the percentage recovery values of lower quality control (LQC), median quality control (MQC) and higher quality control (HQC) samples were101.02 ,98.79 and 101.24 respectively. The drug was stable for more time at variable stability conditions and method was successfully applicable to the regular analysis of Cabozantinib in biological matrices.

Keywords; Cabozantinib, Acetonitrile, lower limit of quantification, human plasma, internal standard

INTRODUCTION

Bioanalysis is an essential part of drug discovery and development. Bioanalysis is related to the analysis of analytes (drugs, metabolites, biomarkers) in biological samples and it involves several steps from sample collection to sample analysis and data reporting.[1,2]The first step is sample collection from clinical or preclinical studies; then sending the samples to laboratory for analysis. Second step is sample clean-up (sample preparation) and it is a very important step in bioanalysis. [3,4] In order to reach reliable results, a robust and stable sample preparation method should be applied.[5] The role of sample preparation is to remove interferences from the sample matrix and improve analytical system performance. Sample preparation is often labor intensive and time consuming. The last step is the sample analysis and detection. For separation and detection, liquid chromatography-tandem mass spectrometry (LC–MS/MS) is a method of choice in bioanalytical laboratories [6,7.]According to literature survey, only one method was developed by using rat plasma and no work has been done in human plasma and other works has more retention time but when we have chosen the column Synergi polar column (75 mm x 4.6 mm ID, 4 µm) and mobile phase containing a mixture of 10 mM Ammonium acetate buffer with 0.2% formic acid were mixed with HPLC grade Acetonitrile in the proportion of 30:70, v/v,less retention time was achieved so that narrow peaks were obtained.In the present work a simple, precise and accurate method was developed and validated according to USFDA guidelines

Cabozantinib chemical formula is N-(4-(6,7-dimethoxyquinolin-4-yloxy) phenyl)-N'-(4-fluorophenyl) cyclopropane1,1-dicarboxamide, (2S)-hydroxybutanedioate. It's a white to off-white powder. It has a pKa of 5.9-13.46 [8-12]. Cometriq and Cabometyx are the brand names for Cabozantinib. It is used to treat thyroid medullary carcinoma [13,14], renal cell carcinoma [15,16], and hepatocellular carcinoma [17,18]. It is a small molecule that blocks c-Met, VEGFR2, AXL, and RET. Evelix's Inc. was responsible for its discovery and development. Cabozantinib is available in two doses. A capsule formulation has been used since 2012 to treat medullary thyroid cancer, while a tablet formulation has been utilized as a second-line treatment for renal cell carcinoma since 2016. Cabozantinib has not been evaluated in pregnant women, however it has been shown in rats to be harmful to the fetus [19-22]. This medication should be avoided by pregnant women and women who are already pregnant. Cabozantinib has not been shown to cross the placenta. Patients with a history of aberrant cardiac rhythms [23], particularly those with a prolonged QT interval, should be treated with caution. Plasma concentrations

approach a peak between two and five hours after taking an oral dose. This medicine has a half-life of around 55 hours The Chemical Structure as shown in the figure 1

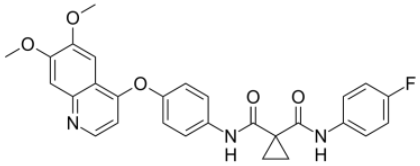

Figure 1: Chemical Structure of Cabozantinib

MATERIALS AND METHODS

Experimental Investigations

A LC-MS/MS method was performed on a liquid chromatographic system consist of Waters Acquity SDS LC system coupled with a Quattro Premier XE mass spectrometer with electrospray ionization (ESI) used for analysis and Mass Lynx 4.1 SCN 805 software for processing and data collecting. Synergi polar column (75 mm x 4.6 mm ID, 4 µm) is used as a stationary phase. An ultrasonic bath sonicator (Frontline FS 4, Mumbai, India), semi-micro analytical balance (India) and Whatman filter paper No. 41 is used in the study.

Reagents used

Cabozantinib and Naproxen (Internal Standard) were procured from Yarrow chemicals, Mumbai, India. Acetonitrile of HPLC grade were procured from Rankem Ltd., India. Water of HPLC grade was obtained from Merck Specialties Private Limited, Mumbai, India. Ammonium Acetate and formic acid of HPLC grade was procured from Merck Specialities Private Limited, Mumbai, India.

Bio-analytical conditions [23-35]

The chromatographic analysis was performed by using a mobile phase of 10 mM Ammonium acetate buffer with 0.2% formic acid were mixed with HPLC grade Acetonitrile in the proportion of 30:70, v/v with flow rate 0.4 mL/min by positive ion mode. Detection is performed by atmospheric pressure electrospray ionization (ESI) mass spectrometry in positive ion mode

Preparation of calibration curve standards and quality control (QC) samples

Calibration curve standard consisting of a set of eight non-zero concentrations ranging from 5 ng/mL to 1000 ng/mL of Cabozantinib was prepared. Prepared quality control samples consisted of concentrations of 5 ng/mL (lower limit of quantification quality control sample), 15 ng/mL (lower quality control sample), 420 ng/mL (middle quality control sample) and 780 ng/mL (higher quality control sample) for Cabozantinib. These samples were stored at -70 °C ± 10 °C until use. Twelve sets of LQC and HQC samples were stored at -20 °C ± 5 °C to check stability.

Preparation of plasma samples

For the preparation of plasma samples, human blood samples were collected into polypropylene tubes containing K_2-EDTA. Each tube was centrifuged for 15 min at 8500 rpm and the supernatant was collected in another tube. To the supernatant 1 mL of acetonitrile was added and kept for 10 min for the plasma proteins to precipitate and then the supernatant was collected for further use.

Procedure for Spiked Human Plasma

Liquid-liquid extraction was used to isolate Cabozantinib and Naproxen IS from human plasma. For this, aliquots of 20 µL of internal standard and 100 µL of plasma sample was added into labelled polypropylene tubes and vortexed briefly. Followed by addition of 20 µL of diluent and vortexed. Then 20 µL of 0.2 % formic acid was added to it and vortexed. Followed by addition of 5 mL of ammonium acetate and shaken for 30 min on reciprocating shaker at 500 rpm. Samples were centrifuged at 2000 rpm for 10 min at 5 °C. Then supernatant organic layer (5.0 mL) was transferred to pre-labelled glass dry test tubes and evaporated to dryness in turboVap at 40 °C. The samples were reconstituted in 1000 µL of mobile phase which contains 10 mM Ammonium acetate buffer with 0.2% formic acid were mixed with HPLC grade Acetonitrile in the proportion of 30:70, v/v and 20 µL of sample were injected to HPLC with MS-MS detection.

Method optimization

For the optimization of LC-MS method several parameters and mobile phase compositions were tried. A satisfactory separation and good peak symmetry for Cabozantinib were obtained with Synergi polar column (75 mm x 4.6 mm ID, 4

μm) and mobile phase containing a mixture of 10 mM Ammonium acetate buffer with 0.2% formic acid were mixed with HPLC grade Acetonitrile in the proportion of 30:70, v/v was delivered at a flow rate of 0.4 mL/min by positive ion mode (API 4000) with injection volume of 20 μL and a run time of 3 min. Detection is performed by atmospheric pressure electrospray ionization (ESI) mass spectrometry in positive ion mode. The precursor to product ion transitions is *m/z* 502.27 to 323.07 for Cabozantinib and *m/z* 231.25 to 185.17 for Naproxen (Internal standard) The retention time of Cabozantinib and Naproxen (Internal standard) was found to be 0.95 min and 1.50 min respectively.

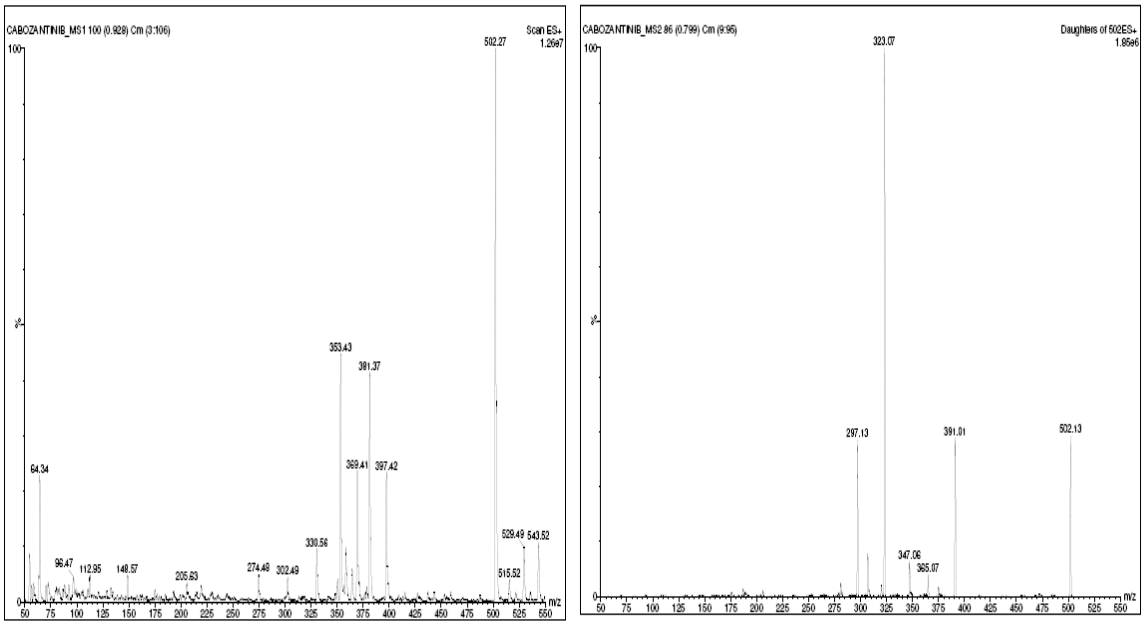

Fig. 2- Mass spectra of Cabozantinib for precursor MS1 and product ion masses MS2

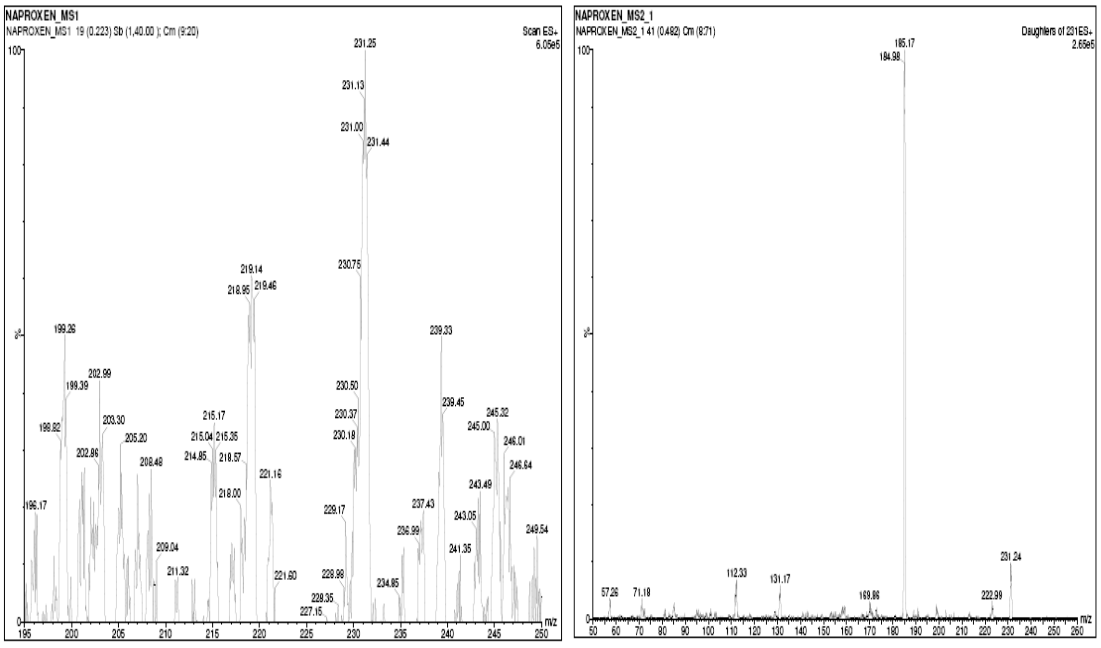

Fig. 3- Mass spectra of IS for precursor MS1 and product ion masses MS2

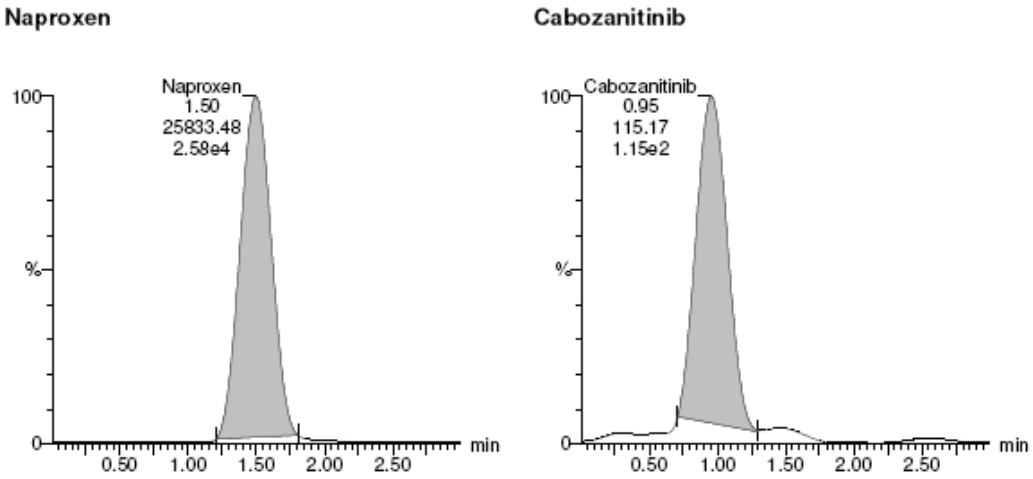

Figure 4: Chromatogram of LLOQ sample (Naproxen with Cabozantinib).

Method validation

The established LC-MS/MS method was validated for selectivity, specificity, sensitivity, linearity, accuracy, precision, recovery, stability and carry over test according to the principles of the FDA guidelines

Screening of plasma lots and specificity

The selectivity of the present method was evaluated by screening six different lots of blank plasma. All of them were found to have no significant endogenous interferences at the retention times of the analyte and the internal standard. The same human EDTA plasma lots free of interfering substances were used to prepare the calibration curve

Sensitivity

The lowest limit of reliable quantification (LLOQ) for Cabozantinib was set at the concentration of 5 ng/mL. The precision and accuracy for Cabozantinib at this concentration was estimated

Linearity

The linearity of Cabozantinib was assessed at eight concentration levels in the range of 5, 10, 25, 85, 400, 500, 800 and 1000 ng/mL in plasma samples. Peak area ratios for each solution against its corresponding concentration were measured and the calibration curve was obtained.

Extraction recovery

Ten blank matrix samples were processed and six sets of each blanks samples were reconstituted with the aqueous quality control dilutions at low, middle and high concentration without internal standard, which represents 100 % extraction of analyte(s) (non-extracted samples). Six blanks were reconstituted with the internal standard solution, which represents 100 % extraction of internal standard (Non-extracted sample). The non-extracted samples were injected. The recovery comparison samples of Cabozantinib were compared against extracted samples of LQC, MQC and HQC of PA Batch-I (Precision and accuracy). The recovery comparison samples of internal standard were compared against the response of internal standard in MQC level.

Accuracy and precision

Intra assay precision and accuracy were determined by analyzing six replicates at four different quality control levels in two runs on the same day. Inter-assay precision and accuracy were determined by analyzing six replicates at four different quality control levels on five different runs. The acceptance criteria included accuracy within ≤ 15 % deviation (SD) from the nominal values, except LLOQ quality control, where it should be ≤ 20 % and a precision of ≤ 15 % relative standard deviation (RSD), except for LLOQ quality control, where it should be < 20 %.

Stability

Stability of Cabozantinib in plasma was performed using six replicates of two quality control samples at low and high levels. Samples were prepared by spiking drug-free plasma with appropriate volumes of Cabozantinib standard solutions. The stability was evaluated with different studies such as room temperature stock solution stability, refrigerated stock solution stability, room temperature spiking solution stability, refrigerated spiking solution stability, freeze-thaw, short term stability, bench top stability etc. Stability tests were conducted to evaluate the analyte stability in stock solutions and in plasma samples under different conditions. The stock solution stability at room temperature and refrigerated conditions

(2-8 °C) was performed by comparing the area response of the analytes (stability samples) with the response of the sample prepared from fresh stock solution. Bench top stability (6 h), processed sample stability (auto sampler stability for 32 h), Samples were considered to be stable if assay values were within the acceptable limits of accuracy (≤15 % SD) and precision (≤15 % RSD).

Matrix effect test of Cabozantinib
Two sets of extracted blank plasma samples each containing six tubes (plasma taken from six different lots) are taken. One set of tubes are reconstituted with equivalent aqueous concentration of LQC and the other set of tubes are reconstituted with equivalent aqueous concentration of HQC.

RESULTS AND DISCUSSIONS

LC-MS analysis
A binary mixture of 10 mM Ammonium acetate buffer with 0.2% formic acid were mixed with HPLC grade Acetonitrile in the proportion of 30:70, v/v was proved to be the most suitable mobile phase of all the combinations since the chromatographic peaks obtained were well defined and resolved and free from tailing. A mobile phase flow rate of 0.4 mL/min with a splitness of 10/90 was found to be suitable in the study range of 0.3-1.0 mL/min. Detection of the ions were performed by multiple reaction monitoring (MRM) of the transitions *m/z* 502.27 to 323.07 for Cabozantinib and *m/z* 231.25 to 185.17 for Naproxen (Internal standard). The retention time of Cabozantinib and Naproxen (Internal standard) was found to be 0.95 min and 1.50 min respectively.

Linearity
The calibration curve was linear in the range of 5 ng/mL to 1000 ng/mL of the Cabozantinib A straight line fit made through the data points by least square regression analysis showed a constant proportionality with minimal data scattering. The correlation coefficient (r) was 0.994 for Cabozantinib

Precision and Accuracy
Intra and inter-batch % accuracy for Cabozantinib ranged between 99.79 to 100.24 and 98.79 to 100.24 % CV is 1.16 to 5.61 and 1.22-1.88 Results are presented in Tables 1 & **2**

Table 1: Within-batch precision and accuracy for Cabozantinib

Concentration (ng/mL	;mean ± S.D	% CV (n = 6)	% Accuracy
15	13.9±0.78	5.61	100.02
420	409.3±4.75	1.16	99.79
780	784.3±27.83	3.55	100.24

Table 2: Intra-day precision and accuracy for Cabozantinib

Concentration (ng/mL)	(n = 6;ng/mL; mean ± S.D	% CV (n = 6	% Accuracy
15	14.6±0.276	1.892	101.02
420	416.2±5.360	1.288	98.79
780	802.1±12.01	1.509	101.24

Stability
The processing and storage conditions of clinical samples need to maintain the integrity of a drug or at least keep the variation of pre-analysis as minimal as possible. For this reason, stability studies play an important role in a bio-analytical method development. In this study, the stability was assessed by considering different studies such as room temperature stock solution stability, refrigerated stock solution stability, the results show that Cabozantinib is stable under the studied conditions, since in all cases the international acceptance criteria (variation values for area smaller than 15 %) were met.

Table: 3 Stability studies of Cabozantinib

	Benchtop stability		Refrigerated Stock solution stability (at 2-8 °C)		Room temperature stock solution	
	6Hr		4 days		24 Hr	
Spiked Plasma Concentration (ng/mL)	*Concentration measured (n = 6n ng/mL;mean ± S.D*	*% CV (n = 6*	*Concentration measured (n = 6n ng/mL;mean ± S.D*	*% CV (n = 6*	*Concentration measured (n = 6n ng/mL;mean ± S.D*	*% CV (n = 6*
15	14.90 ±0.79	5.27	16.52±0.84	3.25	15.98 ±0.56	2.85

780	794.10±15.28	1.92	799.95±3.02	4.25	798.23±0.25	4.23

Matrix Effect

No significant matrix effect was observed in all the eight batches including haemolysis and lipemic plasma for Cabozantinib at low (LQC) and high (HQC) concentrations. The precision and accuracy for Cabozantinib at LQC concentration was found to be 1.55 % and 98.6 % respectively and at HQC concentration was found to be 2.93 % and 99.4 % respectively

Conclusion

In summary, a highly sensitive, specific, reproducible, rapid, green and high-throughput LC-MS/MS assay has been developed and validated to quantify Cabozantinib in human plasma as per the regulatory guidelines. The present method involved a simple protein precipitation method of sample preparation, which gave consistent and reproducible recoveries.

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