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Development and validation of and LC-MS/MS method to quantify Capmatinib in human plasma: Application to pharmacokinetic study in rabbits

Siddhartha Lolla*, Kumar Shiva Gubbiyappa

Department of Pharmaceutical Analysis, Gitam School of Pharmacy, GITAM Deemed to be University, Patancheru 502329, India.

ARTICLE INFO	**ABSTRACT**
	A novel, sensitive, and selective liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was developed and validated for the determination of Capmatinib in human plasma and its pharmacokinetic application in rabbits. Chromatographic separation of the Capmatinib and internal standard ([$^{13}CD_3$]Capmatinib) were achieved on Phenomenex Luna C18 column (50 mm × 2 mm × 5 μm) with 0.5 ml/minute flow rate and coupled with API6000 triple quadrupole MS in multireaction monitoring mode by applying mass transitions m/z 413.15–128.05 for Capmatinib and m/z 416.20–131.01 for the internal standard. The calibration curve exhibited linearity over the concentration of 1.0–28,000.0 ng/ml for Capmatinib. The LLOQ was 1.0 ng/ml. The validated LC-MS/MS method was effectively applied for the analysis of plasma in healthy rabbits for the determination of Capmatinib. From pharmacokinetic studies, Capmatinib showed average AUC_{last} of 12,964.14 ± 635.97 hour*ng/ml and C_{max} of 2,537.94 ± 12.42 ng/ml in the subjects. In summary, the developed method has been successfully validated and pharmacokinetic parameters were demonstrated after oral administration of Capmatinib to healthy rabbits.

INTRODUCTION

Mesenchymal-epithelial transition (*MET*), the proto-oncogenea receptor tyrosine kinase which binds to high-affinity ligand hepatocyte growth factor for activating downstream cell signal pathways (Bang *et al*., 2020; Esaki *et al*., 2019; Wu *et al*., 2021). Abnormal activation of the *MET* pathway might arise due to high-level *MET* gene amplification, protein over expression in cancer cells (Baltschukat *et al*., 2019; Esaki *et al*., 2019; Wu *et al*., 2021). One of these activation mechanisms involves the gaining of gene mutations which lead to *MET*exon 14 skipping (*MET*ex14) through mRNA splicing. The mutation that leads to *MET*ex14 are observed in about 3%–4% of patients suffering from nonsmall cell lung cancer (NSCLC) (Moreno *et al*., 2021; Wu *et al*., 2021). The

NSCLC is responsible for almost 85% of lung cancers (Upadhya *et al*., 2020; Wu *et al*., 2021).

Capmatinib is an oral drug for small-molecule MET inhibition with potent *activity* against preclinical cancer models across various tumors including NSCLC (Baltschukat *et al*., 2019; Esaki *et al*., 2019; Glaenzel *et al*., 2020; Liu *et al*., 2011; Vansteenkiste *et al*., 2019; Wolf *et al*., 2020).

Tabrecta™ (Capmatinib) is used for treating adults diagnosed with NSCLC where tumors possess mutation resulting in METex14. Capmatinib designated chemically as 2-fluoro-N-methyl-4-{7-[(quinolin-6-yl)methyl]imidazo[1,2-b][1,2,4]triazin-2-yl}benzamide with molecular formula of $C_{23}H_{17}FN_6O$ and having molecular weight of 412.43 g/mol (Fig. 1) (FDA, 2020; Novartis, 2020; PubChem, 2021).

Literature on Capmatinib revealed that only one analytical method was developed for the estimation of Capmatinib in rat plasma by LC-MS/MS (Fan *et al*., 2020). The method was reported for the analysis of rat plasma. There is a need of LC-MS/MS technique for the analysis of biological samples, which will be useful in pharmacokinetic, pharmacodynamics, and forensic

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*Corresponding Author
Siddhartha Lolla, Gitam School of Pharmacy, GITAM Deemed to be University, Patancheru, India.
E-mail: Siddupharma1989 @ gmail.com*

studies. In the present work, we developed a method based on the human plasma and applied the same method for healthy rabbits.

MATERIALS AND METHODS

Materials

Capmatinib (99% purity), [$^{13}CD_3$] Capmatinib (98% purity) were procured from Novartis, India. Drug free human plasma having K_2-EDTA was obtained from Red Cross blood bank, Hyderabad, India. Milli-Q water purification system (Millipore, USA) was utilized for HPLC-water in the research work. HPLC grade methanol, acetonitrile, ammonium acetate and formic acid (HCOOH) were obtained from local market. The pharmacokinetic study on healthy rabbits was approved by the Institutional Ethical Committee with Ethical no: 1447/PO/Re/S/11/24/A.

Equipment

A modular LC system (Shimadzu LC-20ADvp, Japan) with an SIL-HTC auto sampler, comprising of LC-20AD solvent delivery module coupled with API 6000 applied Biosystems/sciex tandem MS, Canada was used for the research work. The software, version: 1.4.2 applied bio system was used.

Calibration standards

The stock solution of Capmatinib and [^{13}C, D_3] Capmatinib (IS) were prepared separately in acetonitrile. The
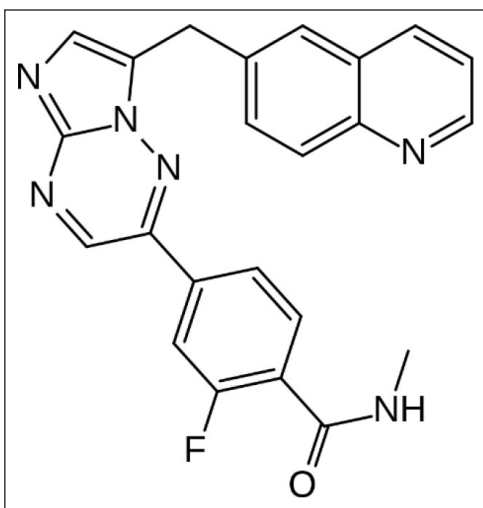

Figure 1. Structure of Capmatinib.

serial dilution of the stock was prepared by adding 20 μl of the diluted samples of Capmatinib to 960 μl of K_2EDTA pooled samples. Then, 20 μl of each IS sample was added to obtain 1.0–28,000.0 ng/ml concentration and stored at −20°C in a freezer.

Quality control (QC) standard

Three levels of low quality control (LQC), median quality control (MQC), and highest quality control (HQC) were prepared. The drug-free plasma is spiked with Capmatinib to get the concentration (conc.) of 3.0, 14,000.00, and 21,000.00 ng/ml for LQC, MQC and HQC, respectively, and stored at −20°C.

Chromatography condition

The separation performed on Phenomenex Luna C18 column (50 mm × 2 mm, 5 μm particle size) with 0.1% HCOOH, methanol and ACN as mobile phase in the ratio of 10:20:70 with a flow rate of 0.5 ml/minute and quantity of 10 μl. The run time was 2.00 minutes at oven temperature of 40°C and sample temperature of 5°C.

Mass system parameters

Mass spectrometry was performed with an electro spray ionization (ESI) source in the +ve ionization mode with multiple reaction monitor (MRM) using the following conditions (Table 1) : auxiliary gas flow 30 psi and nebulizer gas flow 25 psi; capillary voltage—3,500 (V); and tube lens voltage—110 (V). Source temperature was set at 280°C. Quadrupoles Q1 and Q3 were fixed at unit resolution. The MRM transitions observed were m/z 413.15–128.05 for Capmatinib and m/z 416.20–131.01 for the internal standard. The samples evaluated by linear regression analysis using the analyst software 1.4.2. Data evaluated by peak area ratio (Fan *et al*., 2020; He *et al*., 2018; Saraner *et al*., 2019).

Sample preparation

For sample preparation, 100 μl of samples, 50 μl of internal standard working solution were mixed and vortexed for 5.0 minutes. The drug was extracted using 3 ml of 0.5% ammonium hydroxide in water and centrifuged at 2,000 rotations per minute for 15 minutes at 4.0°C. After solid phase extraction, the extract was evaporated to dryness. The sample was diluted with 300 μl of ACN, and evaluated by injection of 10 μl of each sample into LC-MS/MS equipment using ESI technique.

Method validation

The developed method was validated as per FDA (2001) and EMA (2011) for following parameters.

Table 1. Mass spectrometric parameters.

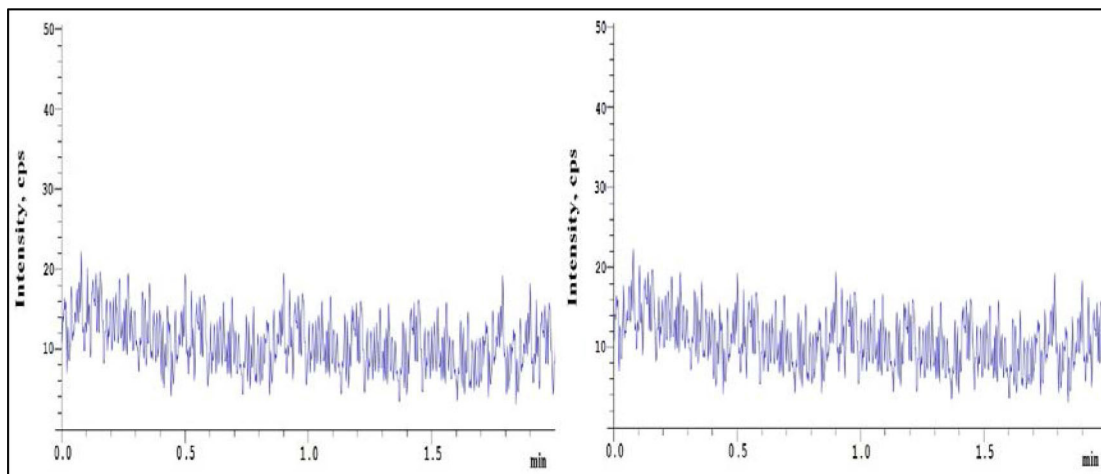| Parameters	Capmatinib	Internal standard
Declustering potential (DP) (V)	40	35
Dwell time (MS)	200	200
Entrance potential (EP) (V)	10	10
Curtain gas flow (CUR) (psi)	30	30
Collision energy (CE) (V)	16	20
Ion source voltage (V)	4,000	4,000

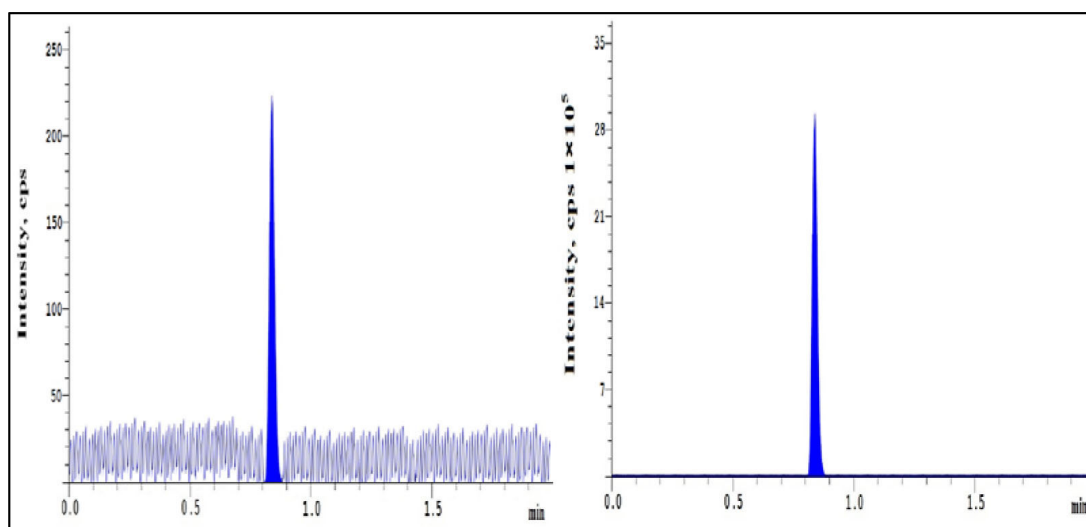**Figure 2.** Blank chromatograms (CHR) of sample and IS.

Figure 3. LLOQ CHR of sample and IS.

Selectivity

Eight different human K_2 EDTA plasma samples were analyzed to demonstrate the lack of interferences at the retention time (RNT) of analyte and IS (Saraner *et al*., 2019).

Linearity and sensitivity

The calibration plot constructed among the peak area ratios of analyte and IS against nominal concentration (NOC) of the analyte standards with analyte concentration ranging from 1.0 to 28,000.00 ng/ml. The curve was plotted for blank sample and eight different concentration samples (Bhatt and Rajkamal, 2017; Fan *et al*., 2020).

Recovery studies

Recovery was determined by the comparison of results of extracted sample with those of spiked plasma samples after extraction. Recovery analyzed at three levels and comparative study carried out between mean analyte responses of six extracted samples and diluted standard solutions (Saraner *et al*., 2019).

The precession and accuracy (P and A)

The P and A were analyzed by injection of QC samples in six replicates in three batches. This process was carried out on three successive days in order to evaluate inter-day P and A (IN P and A) (Fan *et al*., 2020; Saraner *et al*., 2019).

Matrix effect

Six plasma samples (including hemolytic and lipemic plasma) free from interference at RNT of analyte and IS. Evaluations carried out at LQC and HQC concentration in six replicates (Saraner *et al*., 2019).

Carryover effect

Carryover effect was analyzed by determination of peak area by injection of blank matrix in sequence post injection of highest calibration standard sample.

Table 2. Extraction recovery rates of Capmatinib and internal standard.

S. No.	LQC	MQC	HQC	IS
1.	96.37	94.16	102.99	95.25
2.	96.87	93.39	99.71	96.14
3.	96.37	100.63	100.09	101.68
4.	103.18	99.61	100.90	94.60
5.	97.14	95.87	100.69	97.92
6.	93.56	93.91	100.22	96.03
Mean % recovery	97.13	96.26	100.77	96.94
Standard deviation	3.18	3.12	1.17	2.58
%CV	3.27	3.24	1.16	2.66

Stability studies

The plasma samples at two QC concentrations analyzed at various conditions and plotted against fresh samples (3.0 and 21,000 ng/ml, $n = 6$) as follows:

Freeze thaw stability

The samples were frozen at −70°C. After three freeze thaw cycles, the stability was estimated.

Short term temperature stability

Solutions of Capmatinib and IS were prepared in acetonitrile (Stability Samples) and were kept at 25°C for 24 hours. A freshly prepared solution of Capmatinib and stability sample were diluted to similar analyte concentrations and evaluated for six replicate injections.

Stock solution stability

The Capmatinib and stability samples were stored at −20°C 20 days. A fresh solution of Capmatinib and stability samples were approximately diluted to analyte concentration and analyzed for six replicate injections and analyzed.

Bench-top stability

This was examined by storing six samples of spiked plasma with LQC and HQC at 25°C for about 5 hours and processed with freshly prepared calibration standards.

Auto sampler stability

The LQC and HQC of each sample were placed in auto-sampler at 10°C for 24 hours and stability of the samples examined.

Wet extract stability

The LQC and HQC samples of ever analyte were placed at 25°C for 6 hours. The mean concentration for stability samples should be 85%–115% of the mean concentration of freshly prepared samples (Bhatt and Rajkamal, 2017).

Pharmacokinetic evaluation

The study was carried on six healthy white rabbits (subjects) of both sex (2–3 kg). Animals were housed at 25°C, RH 45% with 12 hours alternating light/ dark cycles, 100% fresh air swap. The rabbits were provided with standard diet and water. Post oral administration of 25 mg/kg of Capmatinib, the blood samples collected into polypropylene tubes filled with EDTA solution at specified time slots till 24.0 hours following administration. The plasma isolated by centrifugation of samples at 6,000 rpm for 10 minutes and preserved at −20°C. About 10 µl of plasma samples loaded into LC-MS/MS system and the pharmacokinetic parameters were evaluated by a non-compartmental method analysis using Win Nonlin 3.3® pharmacokinetic software (Pharsight Mountain View, CA) (Fan *et al*., 2020; Glaenzel *et al*., 2020; Zhou et al., 2020).

RESULTS AND DISCUSSION

Method validation

Selectivity

Selectivity of the method shows the lack of interferences at RNT of analyte and IS when peak response in blank samples were compared to response of spiked LLOQ samples which contain IS mixtures (Figs. 2 and 3).

Linearity and sensitivity

Calibration curve was linear with linearity equation $y = 0.0016x + 0.05234$ and coefficient of correlation (r^2) value > 0.999 (0.9992). The LLOQ concentration of the method was 1.0 ng/ml for Capmatinib. The results shown the sensitivity of the method. The superior signal-to-noise ratio indicated at this concentration shown that the LLOQ can further be reduced.

Recovery and matrix effect

The mean overall recovery around QC levels for Capmatinib was 96.26%–100.77%. The recovery of IS was measured in a comparable manner using corresponding medium QC samples as reference. Mean recovery of IS was 96.94% and the results were presented in Table 2 (Figs. 4–6). The % CV of LQC and HQC were 4.94% and 4.30% for Capmatinib (Table 3).

The P and A

The intra-batch P and A was within 97.61%–101.56% and the precision was within 1.28%–4.03%. The inter-batch accuracy ranged between 94.59% and 106.00% and the precision was within 1.86%–4.72% (CV). The inter-batch accuracy ranged between 97.33% and 108.78% with a *p* value of 1.06%–4.04% (CV). The values, were <15% for all the concentrations, which are within the acceptable limit (Table 4).
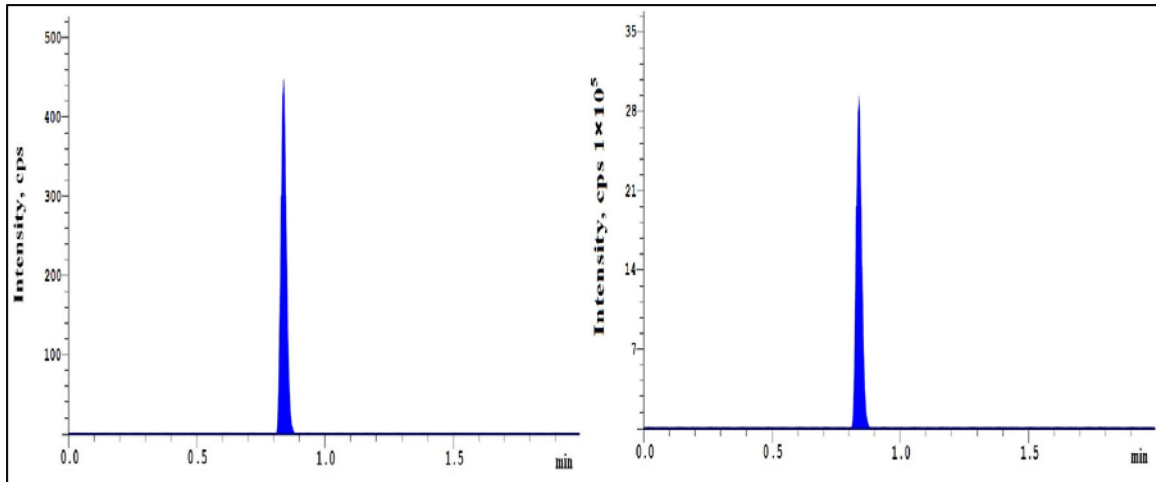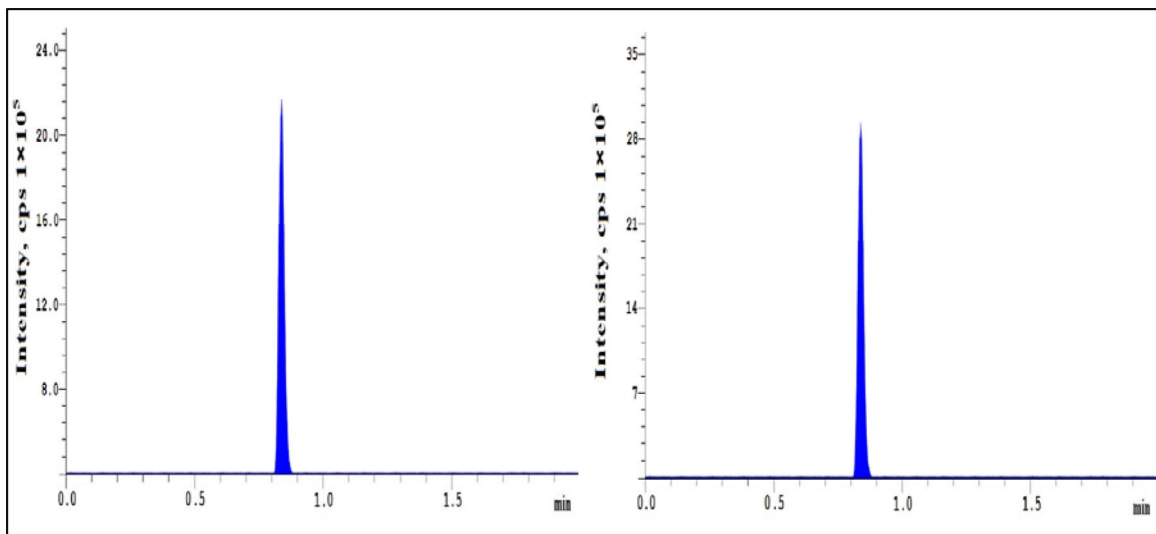
Figure 4. CHR of Capmatinib at LQC and IS.

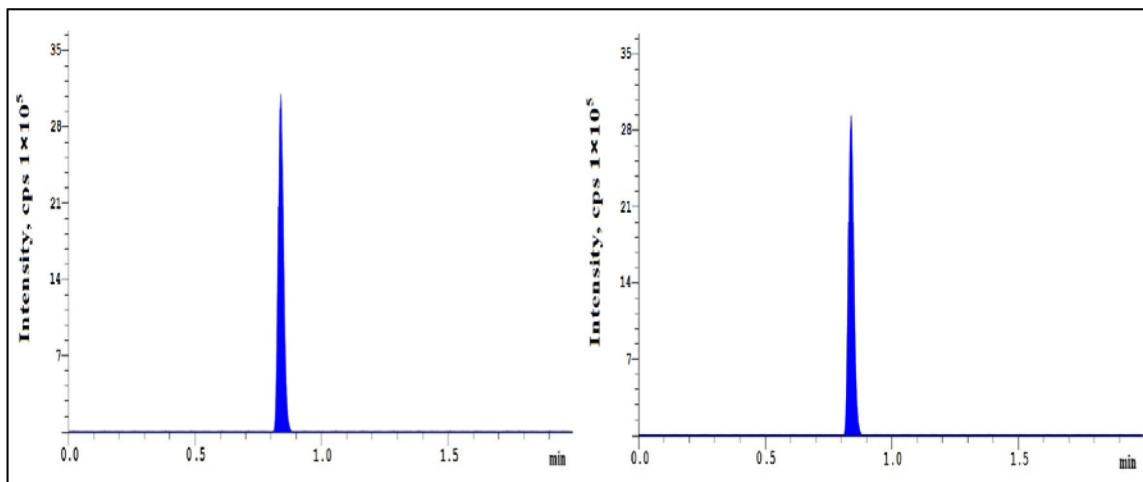
Figure 5. CHR of Capmatinib at MQC and IS.

Figure 6. CHR of Capmatinib at HQC and IS.

Table 3. Results of Capmatinib matrix effects.

S. No	LQC			HQC		
	Analyte	IS	IS normalized	Analyte	IS	IS normalized
1	1.02	1.08	0.94	1.08	1.03	1.05
2	1.21	1.16	1.04	1.06	1.1	0.96
3	1.05	1.08	0.97	1.08	1.02	1.06
4	1.03	1.06	0.97	1.16	1.21	0.96
5	1.1	1.06	1.04	1.08	1.07	1.01
6	1.13	1.04	1.08	1.03	1.08	0.95
Mean			1.01			0.991
± SD			0.05			0.04
% CV			4.94			4.30

Table 4. Intra-batch and inter-batch P and A.

	Conc.	NOC (ng/ml)	Conc. found[a] (ng/ml) ± SD	% A	% CV
	LLOQ	1	1.06 ± 0.05	106.00	4.72
	LQC	3	2.94 ± 0.09	98.00	3.06
Intra-batch	MQC	14,000	13,895 ± 259	99.25	1.86
	HQC	21,000	19,865 ± 896	94.59	4.51
	LLOQ	1	1.04 ± 0.04	104.00	3.85
	LQC	3	2.92 ± 0.08	97.33	2.74
Inter-batch	MQC	14,000	14,135 ± 150	100.96	1.06
	HQC	21,000	22,845 ± 924	108.78	4.04

[a] Average of 6 replicates.

Table 5. Stability results of Capmatinib.

Parameter	QC level	NOC (ng/ml)	Mean concentartion (ng/ml) of analyte	%CV	% Stability
Freeze–thaw stability	LQC	3.00	2.89	3.85	104.00
	HQC	21,000	20,453	4.51	97.39
Benchtop stability	LQC	3.00	2.86	2.79	95.33
	HQC	21,000	20,027	1.06	95.37
Wet extract stability	LQC	3.00	2.91	2.75	97
	HQC	21,000	22,257	4.15	105.98
Autosampler stability	LQC	3.00	3.11	2.577	103.67
	HQC	21,000	14,135	1.067	100.967

NOC, Nominal concentration.
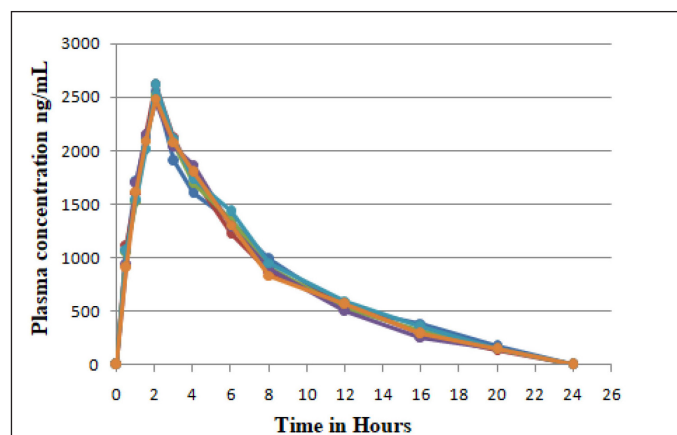
Figure 7. Plasma concentration-time graph of six healthy subjects.

Carryover effect

The blank matrix samples were evaluated in sequence post evaluation of highest calibration standard sample. No carryover effect was observed.

Stability

From the stability studies, Capmatinib was found to be stable at the studied conditions and the stability results were shown in Table 5. The p value was <15% and % stability was between 85% and 115% for the analyte.

Pharmacokinetic studies

The study was carried out in rabbits (subjects) and plasma concentration–time curve of Capmatinib post oral administration was shown in Figure 7 and Table 6. The mean of C_{max} and T_{max}

Table 6. Plasma conc. at various time interval of six rabbits (subject).

Concentration (ng/ml)								
Time in hours	Subject -1	Subject -2	Subject -3	Subject -4	Subject -5	Subject -6	Mean	SD
0	0	0	0	0	0	0	0	0
0.5	1,062.63	1,123.06	1,058.35	936.6	1,061.63	908.64	1,025.15	13.47
1	1,704.15	1,607.84	1,530.74	1,692.64	1,540.63	1,620.74	1,616.12	11.05
1.5	2,122.45	2,158.34	2,096.44	2,139.61	2,013.6	2,095.21	2,104.28	15.73
2	2,550.06	2,610.04	2,504.71	2,463.62	2,609.75	2,489.46	2,537.94	12.42
3	1,907.92	2,110.725	2,068.07	2,036.85	2,102.86	2,079.84	2,051.04	11.90
4	1,603.14	1,750.65	1,700.75	1,870.85	1,730.93	1,799.38	1,742.62	9.64
6	1,340.08	1,221.15	1,357.58	1,291.27	1,428.05	1,309.38	1,324.59	10.39
8	986.22	876.56	903.44	890.78	954.97	834.76	907.79	14.76
12	523.34	567.9	523.44	502.65	598.87	565.34	546.92	12.18
16	390.49	290.54	325.75	256.485	359.94	291.66	319.14	9.59
20	173.1	130.54	150.467	149.06	151.32	147.71	150.37	10.56
24	0	0	0	0	0	0	0.00	0.00

SD, Standard deviation.

Table 7. Pharmacokinetics data of rabbits (subject).

Parameters	Subject -1	Subject -2	Subject -3	Subject -4	Subject -5	Subject -6	Mean	SD
C_{max}	2,550.06	2,610.04	2,504.71	2,463.62	2,609.75	2,489.46	2,537.94	12.42
$\log C_{max}$	3.41	3.42	3.40	3.39	3.42	3.40	3.40	0.01
T_{max}	1.98	2.01	1.97	2.02	2.05	2.01	2.01	0.03
$\log T_{max}$	0.30	0.30	0.29	0.31	0.31	0.30	0.30	0.01
$t_{1/2}$	10.51	9.58	10.36	9.42	10.06	10.23	10.03	0.44
$\log t_{1/2}$	1.02	0.98	1.02	0.97	1.00	1.01	1.00	0.02
Ke	0.066	0.072	0.067	0.074	0.069	0.068	0.069	0.003
log Ke	−1.18	−1.14	−1.17	−1.13	−1.16	−1.17	−1.16	0.02
$AUC_{0→last}$	13,190.05	12,980.66	13,250.65	11,823.54	13,717.65	12,822.30	12,964.14	135.97
$\log AUC_{0→last}$	4.12	4.11	4.12	4.07	4.14	4.11	4.11	0.02

SD, Standard deviation.

were 2,537.94 ± 12.42 ng/ml and 2.01 ± 0.03, respectively. Plasma concentration reduced with $t_{1/2}$ of 10.03 ± 0.44. $AUC_{0→Last}$ value obtained was 12,964.14 ± 635.97 ng.hour/ml, respectively (Table 7).

CONCLUSION

A new, effortless, and sensitive LC-MS/MS technique was developed for the estimation of Capmatinib in human plasma by solid phase extraction and reproducible recoveries for analyte and IS with insignificant interference and matrix effect. The technique was validated in according with FDA guideline within concentration of 1.0–28,000.00 ng/ml for Capmatinib with the correlation coefficient value of 0.9992. The reported method was established for the analysis of rat plasma. There is a need for the analysis of Capmatinib in human plasma samples. The linearity ranges in the reported method also less. In the present work, we developed a method based on artificial human plasma and also applied the same method to pharmacokinetic study in healthy rabbits. The intraday and inter-day P and A within 4.72%

and the assay accuracy was 96.73%–102.34% of the nominal values. Matrix effect was within 1.21 with a %CV of 4.94 for analyte at LQC and at HQC, the matrix effect was within 1.16 with a %CV of 4.30. Stabilities revealed that the method has high degree of stability. From the pharmacokinetic data, the mean of C_{max} and T_{max} were 2,537.94 ± 12.42 ng/ml and 2.01 ± 0.03, respectively. Plasma concentration decline with $t_{1/2}$ of 10.03 ± 0.44. $AUC_{0→Last}$ value obtained was 12,964.14 ± 635.97 ng.hour/ml, respectively. The developed method was effectively applied for pharmacokinetics study of Capmatinib in biological matrix for future studies.

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.

CONFLICTS OF INTEREST

The authors report no conflicts of interest in this work.

FUNDING

There is no funding for the research.

ETHICAL APPROVALS

The pharmacokinetic study on healthy rabbits was approved by the Institutional Ethical Committee with Ethical no: 1447/PO/Re/S/11/24/A.

DATA AVAILABILITY

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

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