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Original article

UPLC–MS/MS assay for quantification of an inhibitor of kinases (Foretinib) in plasma: Application to a pharmacokinetic study in rats

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ABSTRACT

Foretinib, an oral multikinase inhibitor, is known to have anti-tumor effects against cancers. The doses and the levels of foretinib vary based on the type of cancer to be treated. An accurate and precise method is required to determine the level of foretinib and its pharmacokinetics. Here, we developed such a method, which was validated based on the guidelines of the FDA and EMA. Foretinib and ibrutinib (the internal standard (IS)) were extracted using tert-butyl methyl ether. Foretinib and IS were eluted in approximately 1.2 min. Thus, a linear, fast, accurate, and precise method was developed. The calibration curve was linear ($r^2 > 0.997$) in the range of 0.5–400.0 ng/mL and the lowest limit of quantitation was 0.5 ng/mL. The average recovery, accuracy, and precision were 87.9%, 88.7%, and ≤7.8%, respectively. The analyte was deemed stable using various stability tests. The validated assay was then fruitfully applied to a pharmacokinetics study in rats, which revealed that foretinib was absorbed and the maximum concentration achieved at 4.0 h after the administration of a single dose of foretinib.
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1. Introduction

Foretinib (GSK1363089 or XL880), an oral multikinase inhibitor, targets the hepatocyte growth factor (HGF)/Met signaling pathway to exert its therapeutic effects. Endometrial carcinoma and uterine corpus cancer are two of the most common cancer types affecting women, and are accountable for thousands of female deaths in the US (Lachance et al., 2008). In experimental and clinical studies, foretinib has been shown to exhibit anti-tumor effects against some types of cancers (e.g., uterine corpus cancer, head and neck squamous cell cancer, hepatocellular carcinoma, papillary renal-cell carcinoma, gastric cancer, breast cancer, and non-small cell lung cancer) (Sharma and Adjei, 2011; Kogata et al., 2018) and to reduce tumor growth in ovarian cancer by affecting tumor function (Zillhardt et al., 2019). A dose escalation study using foretinib (four dosing levels; 28 days) showed that the maximum tolerated dose is 80 mg/kg, with the steady state achieved after two weeks. The maximum concentration of foretinib is attainable at approximately 4.0 h with an average concentration and trough concentration of 46.0 and 24.0 ng/mL, respectively (Shapiro et al., 2013). Foretinib can penetrate the blood-brain barrier; thus enabling its effectiveness when used to target primary and metastatic tumors. Reducing primary tumor growth and the incidence of metastases, and prolonging host survival in mouse xenografts and transgenic models of metastatic medulloblastoma, are some of the effects achieved using foretinib (Faria et al., 2015). Hypertension, fatigue, diarrhea, vomiting, and elevations in AST and lactate dehydrogenase are the most common observed adverse events of foretinib administration. Generally, these symptoms have a grade of 1 or 2 and are resolved with programmed dose delay. Hypertension and proteinuria are related to the inhibition of VEGF-mediated angiogenesis (Shah et al., 2013; Leighl et al., 2017). Results obtained from a relative bioavailability study with a single dose of foretinib in two dosage forms (free base tablet versus bisphosphate salt capsule) showed

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that the confidence interval exceeded the acceptable range of bioequivalence; however, a clinical difference was not observed (Naing et al., 2012). Singh et al., (2015) found that the bisphosphate salt capsules and free base tablets had a relatively higher bioavailability of 37% and 20%, respectively, in comparison with the solution formulation. Pancreatic cancer is one of the lethal malignancies occurring globally (Chen et al., 2015) and the therapeutic effects of foretinib have been explored in pancreatic islet cancer (You et al., 2011). Foretinib was found to directly inhibit the islet cancer (Di Renzo et al., 1995; Kiehne et al., 1997) and was up-regulate in pancreatic cancer (Camp et al., 2007). Foretinib inhibits angiogenesis, lymphangiogenesis and tumor growth in pancreatic cancer in vivo by decreasing VEGFR-2/3 and TIE-2 signaling (Chen et al., 2015).

Foretinib is a narrow therapeutic index dug with high inter-individual variability. Hence, individualization of the dose is crucial to ensure that patients are receiving the maximum benefit, with very few side effects (Crumbaker and Gurney, 2017). To achieve this aim, a very sensitive analytical method is essential to evaluate the plasma concentration of foretinib, which can be used to determine the actual rate and extent of drug absorption via therapeutic drug monitoring (TDM). Therefore, we aimed to develop a fast, precise, sensitive, and accurate LC-MS/MS method with full validation parameters and an analytical procedure to determine foretinib concentrations in plasma. The sensitivity of this method was 12-fold higher compared to Attwa et al (2018) method. In addition, this method was successfully applied to a pharmacokinetic study in rats.

2. Experimental

2.1. Instrumentation

We used the following instruments: "Waters Acquity UPLC" system connected to a TQ detector and an ESI source (Waters Corp. MA, USA) operated by Mass Lynx software version 4.1; An Acquity BEH C_{18} column (100 × 201 mm, 1.7 μm) for chromatographic separation; A Speedvac concentrator "Savant SC210A, Thermo scientific, MA. USA"; an ultra-freezer (−80 °C) "Thermo scientific, MA. USA"; and a cooling centrifuge (Hermle Z 383K, Hermle Labortechnik GmbH, Germany). For drug and IS separation, a series of experiments using different columns such as the Acquity BEH C_{18} and Acquity CSH Phenyl Hexyl was performed. Finally, we selected the Acquity BEH C_{18} column (100 × 201 mm, 1.7 μm) in the present experiment

2.2. Materials

Foretinib (≥97%) was obtained from Enzo Life Sciences, LTD (Exeter, UK). Ibrutinib was obtained from Beijing Mesochem (Beijing, China) and purified water obtained from Milli Q purification system, Millipore, (Bedford, MA, USA). Ammonium acetate, tert-butyl methyl ether, formic acid, and acetonitrile (HPLC grade) were purchased from Sigma Aldrich (St. Louis, MO, USA).

2.3. Animals

Eight Male Wistar rats (weighing 250–270 g) were obtained from the Animal House of "the National Organization for Drug Control and Research, Giza, Egypt". Rats were fed standard sufficient food and water. The experiments were performed under the Guide for Care and use of Laboratory Animals. The experimental protocols were approved by the ethics committee of the "Faculty of Pharmacy, Al-Azhar University, Cairo, Egypt".

2.4. Preparation of stock solution, quality control samples and calibration standard

Accurate weight of foretinib standard was dissolved in methanol for preparation of foretinib stock solution (5 mg/mL). The working solutions were prepared for quality control sample (QC) and calibration curve samples (CC). A working solution of IS was prepared in methanol and then diluted in acetonitrile to yield a concentration of 10 μg/mL.

2.5. Sample preparation

Foretinib was extracted from plasma by liquid–liquid extraction using tert-butyl methyl ether as the extraction solvent. To 50 μL of plasma, 10 μL of IS (10 μg/mL) and 1 mL of *tert*-butyl methyl ether were added. The samples were then mixed by vortex for 30 s and centrifuged at 10,000*g* at 8 °C for 10 min. The organic layer was then transferred to test tubes and dried using a vacuum concentrator. The dried residues were then reconstituted in 100 μL of acetonitrile, and a 5 μL aliquot injected into the LC–MS/MS system.

2.6. Method validation

Method validation was performed according to the "guidelines for bioanalytical method validation" of the USFDA and EMA (USFDA, 2018; EMA, 2012).

2.6.1. Selectivity, matrix factor, carry over and recovery

Selectivity was assessed by comparing the chromatogram of the blank (plasma without drug) obtained from different sources to the chromatogram of the samples (plasma spiked with the lower limit of detection (LLOD) of foretinib and 100 ng/mL of ibrutinib (IS). Quality control samples (QC) from different sources were used to determine the matrix factor. The lower control samples (LQC), medium control (MQC) and high control (HQC) samples of foretinib were analyzed, with the precision calculated for the matrix factor not exceeding 15%. The efficiency of the method or recovery was determined by comparing the analyte response (peak area) of adding foretinib to the blank (plasma without drug) and extracted with the procedure used, to those obtained when foretinib is added post-plasma extraction at three QC levels. The amount of carry-over was determined by injecting blank samples after injecting the high QC sample. The method developed was deemed acceptable if the response (carry-over percentage) was less than 20% of the LLOQ.

2.6.2. Linearity

Standard calibration curves were constructed using eight different concentrations (0.5, 1.0, 10.0, 20.0, 50.0, 100.0, 200.0 and 400.0 ng/mL) and analyzed to estimate the method linearity. The linearity acceptance criteria were met when the correlation coefficients (r^2) were higher than 0.99; the back-calculated concentrations were less than 20% at the LLOQ and ≤15% at the higher concentrations; and a minimum of 75% of the nonzero calibration was within the range of the acceptance criteria.

2.6.3. Lower limit of quantitation (LLOQ)

LLOQ is the lowest measurable concentration and should be 5-fold greater than the blank sample response. The average value of the accuracy of the LLOQ needs to be within 20% of the nominal concentration and not exceeding ±20% CV% for precision.

2.6.4. Stability

The method stability was evaluated by the evaluation of the short-term, long-term, auto-sampler and freeze/thaw stability using LQC and HQC. An aliquot of the two levels of the QC samples

(maintained at room temperature, 20 °C) was used to determine the short-term stability. The Long-term stability was evaluated by storing the QC sample in an ultra-freezer (−80 °C) for 8 weeks. Moreover, post-operative stability was determined by keeping the QC samples in the auto sampler at ambient temperature for 24 h. The stability of the analytical method was determined after three cycles of freeze/thaw. Aliquots of the LQC and HQC samples were kept in the freezer for 24 h, thawed at room temperature and then returned to the freezer; this cycle was performed three times. Evaluation of the stability was then performed by comparing the peak area ratio of the stored samples with those of the freshly prepared samples at the same concentration levels. The change in the concentration should not have exceeded 15% of the nominal concentration.

2.7. Pharmacokinetic application

The method was applied to pharmacokinetic study in rats. After 10 h of overnight fasting with sufficient water, six rats were orally administered 10 mg/kg (equivalent to the average therapeutic dose in human (Sharipo et al., 2013) as a single dose of foretinib suspension using 1% carboxy-methyl cellulose as a suspending agent. The blood samples were drawn, under anesthesia, from the *retro*-orbital vein into heparinized tubes at pre-dose, 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 h post dosing. Plasma separated by centrifugation. The samples stored in deep freezer till transferred for analysis. The forelimb plasma levels determined applying the validated UPLC–MS/MS method described above. From the foretinib plasma concentration–time curve, pharmacokinetic parameters were evaluated. The Extravascular non-compartmental analysis model was applied to calculate pharmacokinetic parameters and trapezoidal rule was chosen to calculate AUC. All experimental data were represented as mean ± SD. It is noteworthy to mention that the foretinib dose selected in this study is equivalent to the average dose in human (Shapiro et al., 2013). The conversion from the human dose to the rat's dose was based on the body surface area.

Table 1
Mass Optimization Parameters for Foretinib and IS.

Parameters	Foretinib	Ibrutinib
I. Compound Parameters		
Precursor	633.1	441.1
Product ion	128.4	84.0
Dwell time (s)	0.025	0.025
Cone voltage (V)	50.0	52
Collision energy eV	34.0	46
II. Instrument Parameters		
Collision gas flow rate (mL/min)	0.1	0.1
Nitrogen flow rate	600 L/h	600 L/h

3. Results and discussion

3.1. Mass spectrometry optimization

The mass spectrometry conditions were optimized using a standard solution of foretinib and IS to obtain the best signal that reflects the method sensitivity. We tested both the negative and positive ion modes and found that the positive ion mode to be more efficient. The precursors ion for foretinib and the IS were obtained. The optimum MS/MS parameters for detecting foretinib and IS are shown in Table 1. The spectra of the precursor to the product ion [M + H +] for foretinib and the IS are shown in Fig. 1. A series of UPLC–MS/MS experiments with different columns were used for separation and determination of the drug and IS. We observed a good retention time and peak shape following separation. We then attempted to use several constituent mobile phases in different ratios. Good chromatographic peak characteristics with a short retention time for foretinib and IS Good chromatographic peak characteristics with a short retention time for foretinib and IS using a suitable buffer solution from formic acid and ammonium acetate (see experimental Section 2.1) (Fig. 2).

3.2. Method validation

3.2.1. Linearity

Linearity was evaluated over the range, 0.5–400.0 ng/mL and a calibration curve constructed by plotting the peak area ratio of

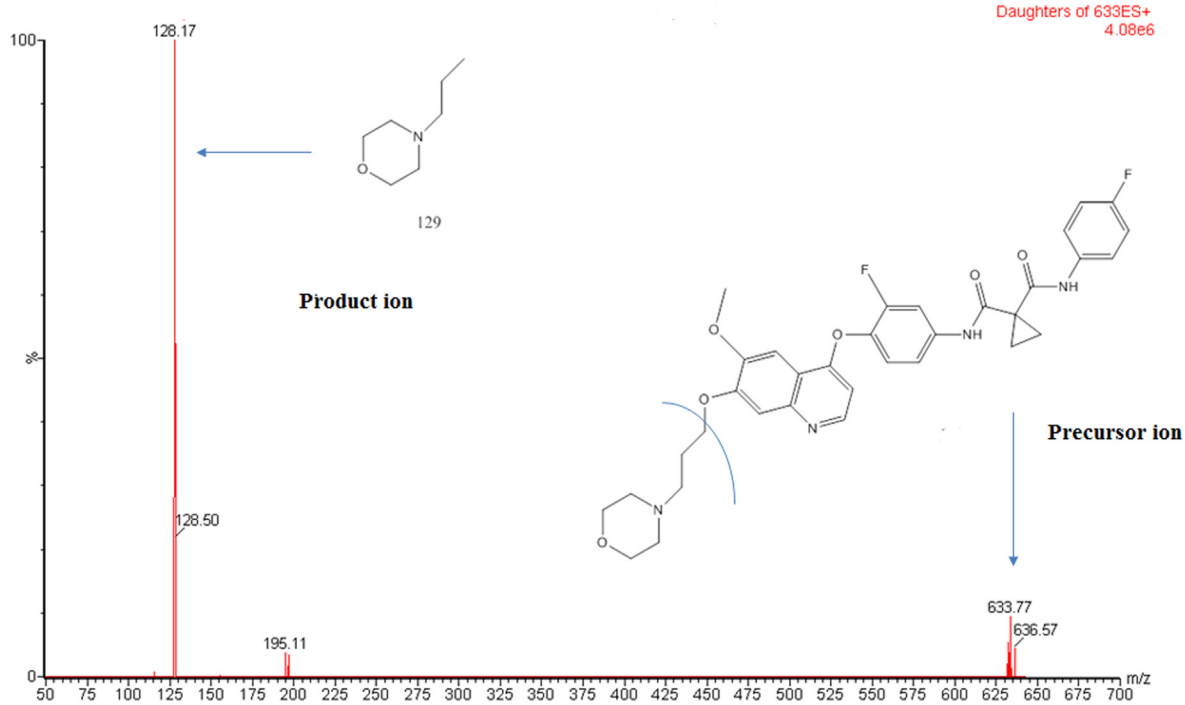

Fig. 1. Typical Representation of Precursor to Product Ion Spectra of Foretinib (A) ESI Positive Ionization Mode.

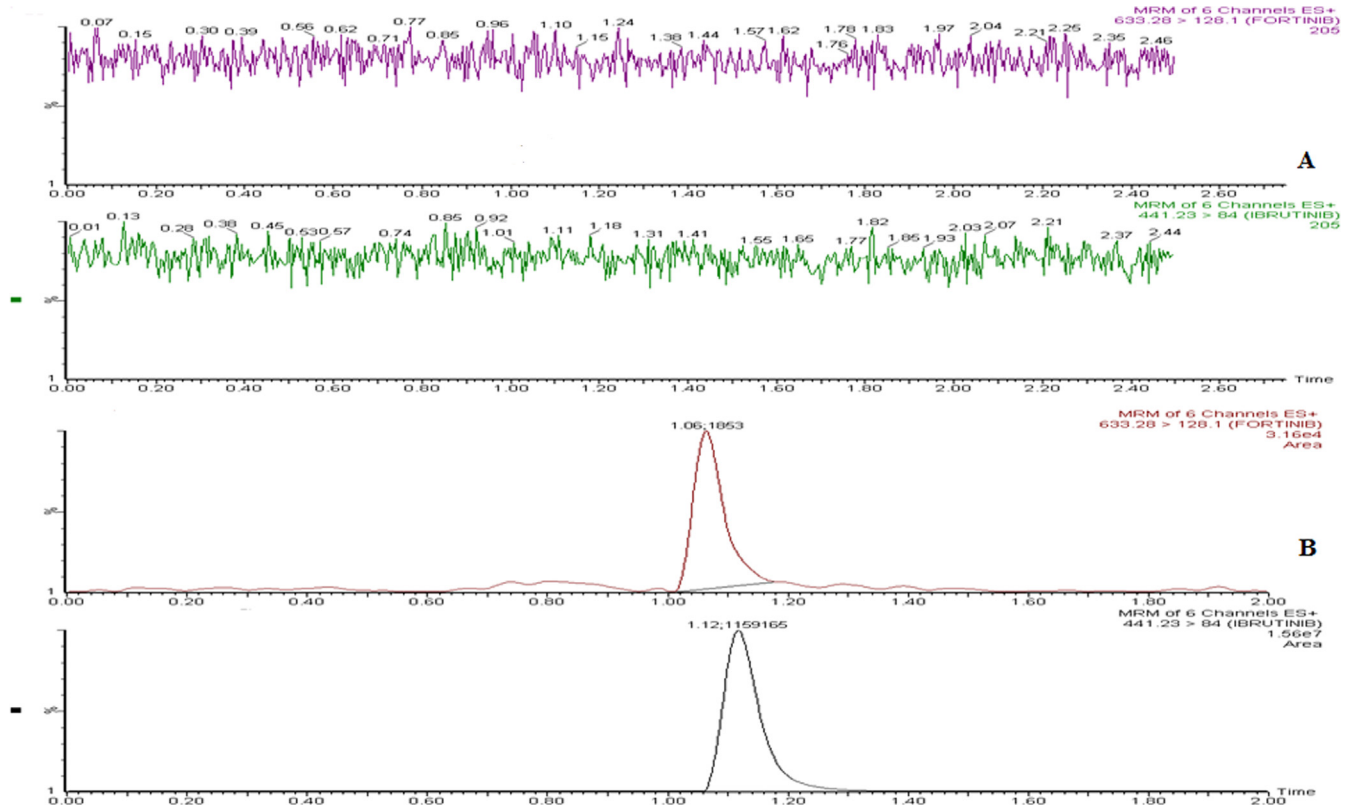

Fig. 2. MRM Chromatograms of Foretinib and Internal Standard in Blank Rat Plasma (A), and Plasma Spiked at LLOQ Level (B).

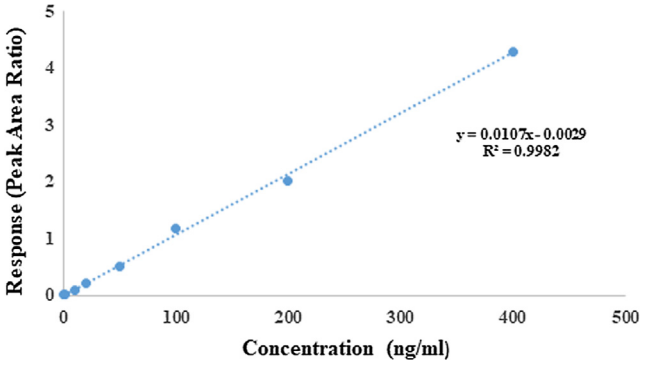

Fig. 3. Plasma Calibration Curve of Foretinib.

foretinib versus IS against the nominal concentration of the calibration standard. The calibration curves were linear in the range of 0.5–400.0 ng/ml and the correlation coefficient was ≥0.998 (Fig. 3).

3.2.2. Precision and accuracy

Inter-day and intra-day precision and accuracy were evaluated by analyzing three different concentrations of the QC samples (1.5, 50 and 300.0 ng/mL) in addition to LLOQ (0.5 ng/mL). The precision in the term of CV % ranged from 3.1% −10.9% and 4.9–10.6% for Inter-day and intra-day, respectively (Table 2). The inter-day and intra-day accuracy were ranged from 86.7% to 92.0% and from 87.0% to 92.0%, respectively (Table 2). These results indicated that the precision and accuracy of foretinib by proposed method was

Table 2
Inter-and Intraday Precision and Accuracy of Foretinib in Rat Plasma.

Conc. (ng/mL)	Inter-day			Intra-day		
	Mean ± SD	Precision (CV %)	Accuracy (%)	Mean ± SD	Precision (CV %)	Accuracy (%)
0.5	0.46 ± 0.04	8.7	92.0	0.46 ± 0.05	10.9	92.0
1.5	1.30 ± 0.04	3.1	86.7	1.33 ± 0.09	6.7	88.7
50	43.60 ± 3.4	7.8	87.2	43.50 ± 2.70	6.2	87.0
300	274.14 ± 29.9	10.9	91.4	263.34 ± 12.8	4.9	87.8

Table 3
Recovery % and Matrix Effects Foretinib and IS.

Compound	Nominal Conc. (ng/mL)	Extraction Recovery		Matrix effects	
Foretinib		Mean (%)	RSD (%)	Mean (%)	RSD (%)
	1.5	86.7	8.3	90.0	10.9
	50	86.4	4.9	87.2	6.0
	300	87.8	12.8	88.2	7.1
IS	100	89.6	2.6	88.1	2.7

Table 4
Stability of Foretinib in Rat plasma under Different Storage Condition.

Stability	Nominal Con. (ng/mL)	Measured Con. (ng/mL)	Precision (%)	Accuracy (%)
Short-term (6 h)	1.5	1.35 ± 0.20	**14.84**	**90.0**
	300	267.0 ± 21.5	8.05	89.0
Long-term (8 weeks)	1.5	1.40 ± 0.10	7.14	93.3
	300	255.96 ± 7.65	2.99	85.3
Thaw and freeze (Three cycle)	1.5	1.30 ± 0.10	7.69	86.7
	300	258.81 + 21.05	8.14	86.2
Auto-sampler (24) h	1.5	1.60 ± 0.20	12.50	106.7
	300	260.53 ± 20.15	7.73	86.9

Table 5
Mean Pharmacokinetic Parameters Following Administration of Foretinib (10 mg/kg P.O) to Rats.

Parameters	Mean ± SE
C_{max} (h)	59.6 ± 3.6
T_{max} (h)	4.0
AUC $_{0\text{-}24}$ (ng.h/mL)	1065.81 ± 75.31
AUC $_{0\text{-}inf}$ (ng.h/mL)	1243.80 ± 56.01
$t_{1/2}$ (h)	21.03 ± 5.50
MRT (h)	30.71 ± 8.80
Kel (h)	0.04 ± 0.01

C_{max}: Maximum (peak) plasma drug concentration, t_{max}: Time to reach maximum (peak) plasma concentration following drug administration, AUC: Area under the plasma concentration-time curve, $t_{1/2}$: Elimination half-life, MRT: Elimination rate.

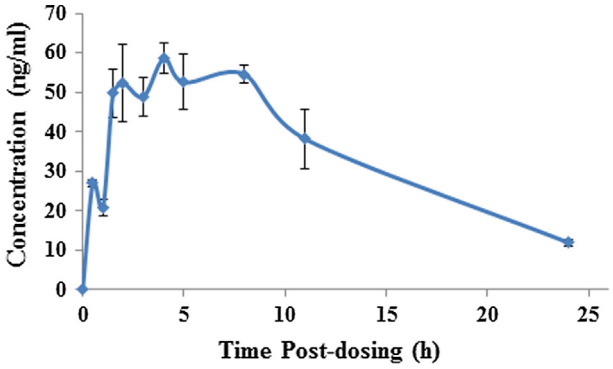

Fig. 4. The Mean ± SD Concentration Versus Time Profile of Foretinib after Oral Administration of 10 mg/kg.

precise and accurate and were within the acceptable limits as per guideline.

3.2.3. Selectivity

We did not observe any peak interference of the retention time of foretinib and IS. Moreover, the blank response was <20% for foretinib and <5% for IS which met the requirement for method validation. The typical chromatogram of an extracted blank plasma of foretinib and IS are presented in Fig. 2.

3.2.4. Lower limit of quantitation (LLOQ)

LLOQ, the minimum concentration that can be quantitated, was determined as 0.5 ng/mL. The accuracy and precision was 5-fold greater than that of signal/noise (S/N); this value represented the lowest point in the calibration curve (Fig. 2).

3.2.5. Matrix effects and recovery

Matrix effects were evaluated by comparing the peak of spiked-post extracted blank plasma with that of the standard solution. The

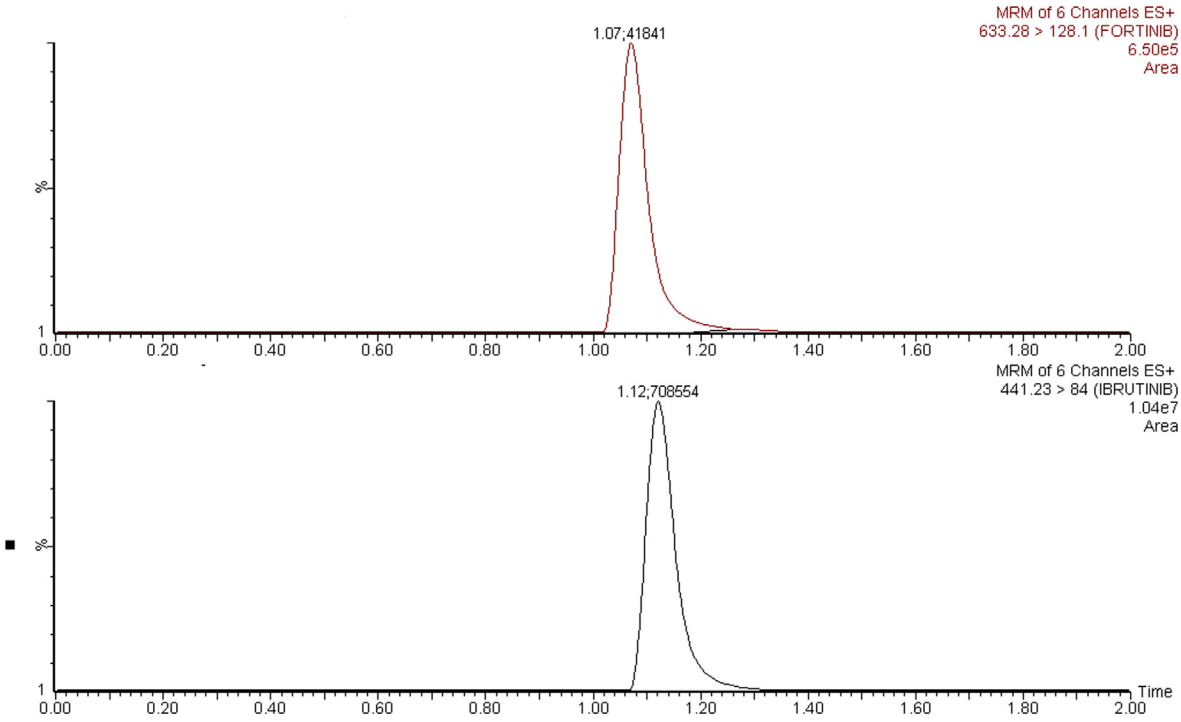

Fig. 5. MRM Chromatograms of Foretinib and Internal Standard in Real Rat Plasma Sample Obtained at 1.0 h Following Oral Administration of 10 mg/kg Foretinib.

range of the matrix effects was 87.2 – 90.0% for foretinib and 88.1% for IS. The extraction recovery of foretinib and IS are described in Table 3. The recovery ranged from 86.4% to 87.8%.

3.2.6. Stability

Table 4 shows the stability of foretinib under various conditions of processing and storage. The samples of long-term, short-term, under freeze/thaw conditions and during the analysis process were stable (see Table 5).

3.3. Pharmacokinetic application

The method was fruitfully applied in a single dose pharmacokinetic study of foretinib. Blood was withdrawn in 10-time intervals over 24 h. The maximum concentration achieved was 59.6 ± 3.6 ng/mL at 4.0 h. The concentration of foretinib versus time profile is shown in Fig. 4. The MRM chromatogram of foretinib with IS in rat plasma, 1.0 h following administration of 10 mg/kg, is shown in Fig. 5

4. Conclusion

A novel, simple, reliable, highly sensitive, and fast method was developed and validated to assess the concentration of foretinib in plasma. The calibration curve generated was observed to occupy a wide concentration range of 0.5–400.0 ng/mL. A simple liquid–liquid (one-step) extraction method was used for sample preparation. The LLOQ was 0.5 ng/mL, a 12-fold greater sensitivity than the previously published method. The method developed was also successfully applied in a pharmacokinetic study in rats. The precise evaluation of the lowest concentration of foretinib and the wide range of the calibration curve enable this method to apply in future therapeutic drug monitoring and pharmacokinetic/pharmacody namic relationship studies. Therefore, dose adjustment to meet individual requirements and the consequent minimization of side effects can be achieved using the method developed and described herein.

Declaration of Competing Interest

Authors declare that there is no conflict of interest.

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