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Development of UPLC–MS/MS method for studying the pharmacokinetic interactions of pexidartinib with antifungal drugs in rats

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ABSTRACT

Pexidartinib was approved in the USA for targeted therapy of adult patients with symptomatic tenosynovial giant cell tumour (TGCT) by the FDA. The purpose of our study was to develop and establish a quick assay based on ultra performance liquid chromatography tandem mass spectrometry (UPLC–MS/MS) for the measurement of pexidartinib concentrations in plasma and to survey whether antifungal drugs (isavuconazole, posaconazole, fluconazole and itraconazole) could change the pharmacokinetic parameters of pexidartinib in rats. After the quick protein crash with acetonitrile, the chromatographic separation of pexidartinib and upadacitinib (used as the internal standard in this study, IS) were conducted on an Acquity BEH C18 (2.1 × 50 mm, 1.7 μm) column, and the detection of the analyte was also accomplished with a Xevo TQ-S triple quadrupole tandem mass spectrometer in the positive ion electro-spray ionization (ESI) interface. The assay showed good linearity in the range of 1–7000 ng/mL. The accuracy and precision were all within the acceptable limits in the bioanalytical method, and the results of recovery, matrix effect, stability, and carry-over were also met the requirements. The application of the validated UPLC–MS/MS bioanalytical method was further successfully involved in the drug-drug interactions study from rats. It was found that fluconazole and itraconazole significantly increased the concentration of pexidartinib and had the inhibitory effect on the metabolism of pexidartinib, while not isavuconazole and posaconazole. Thus, more attention should be paid to the concurrent use of pexidartinib with fluconazole or itraconazole to reduce the risk of unexpected clinical outcomes.

1. Introduction

As a novel, orally available small molecule tyrosine kinase inhibitor (TKI), pexidartinib (Fig. 1A) inhibits the colony-stimulating factor 1 (CSF1) receptor [1], and has potent and selective activity against the receptors KIT and FMS-like tyrosine kinase 3 internal tandem duplication mutation (FLT3-ITD) [2,3]. Recently, it was approved in the USA by the FDA for its first systemic treatment of adult patients with symptomatic tenosynovial giant cell tumour (TGCT) associated with severe morbidity or functional limitations and not amenable to improvement with surgery [4,5], which is a rare and locally aggressive neoplasm that overexpresses CSF1 [6].

After oral administration of a single dose of pexidartinib, it is primarily metabolized by CYP3A4 [7]. In clinical studies, exposure of pexidartinib was influenced by coadministration with CYP3A4 inhibitors or inducers, potentially affecting the safety profile or efficacy of pexidartinib [7]. Therefore, it is valuable to develop, optimize and fully validate a robust and sensitive method for the quantitation of pexidartinib in biological fluids in order to assess the pharmacokinetic profile and potential drug-drug interactions (DDIs) for its clinic application.

Up to now, there were three papers reported to describe the pharmacokinetic profile of pexidartinib in subjects using bioanalytical methods [8–10]. However, these mentioned bioanalytical methods were not perfect, and did not involve important parameters and lack sufficient experimental data for repeating in other laboratories. In other words, there was no report using HPLC or LC–MS/MS techniques to determine the concentration of pexidartinib in biological fluids.

Therefore, the purpose of this study was to develop, optimize and fully validate a robust, simple and sensitive ultra performance

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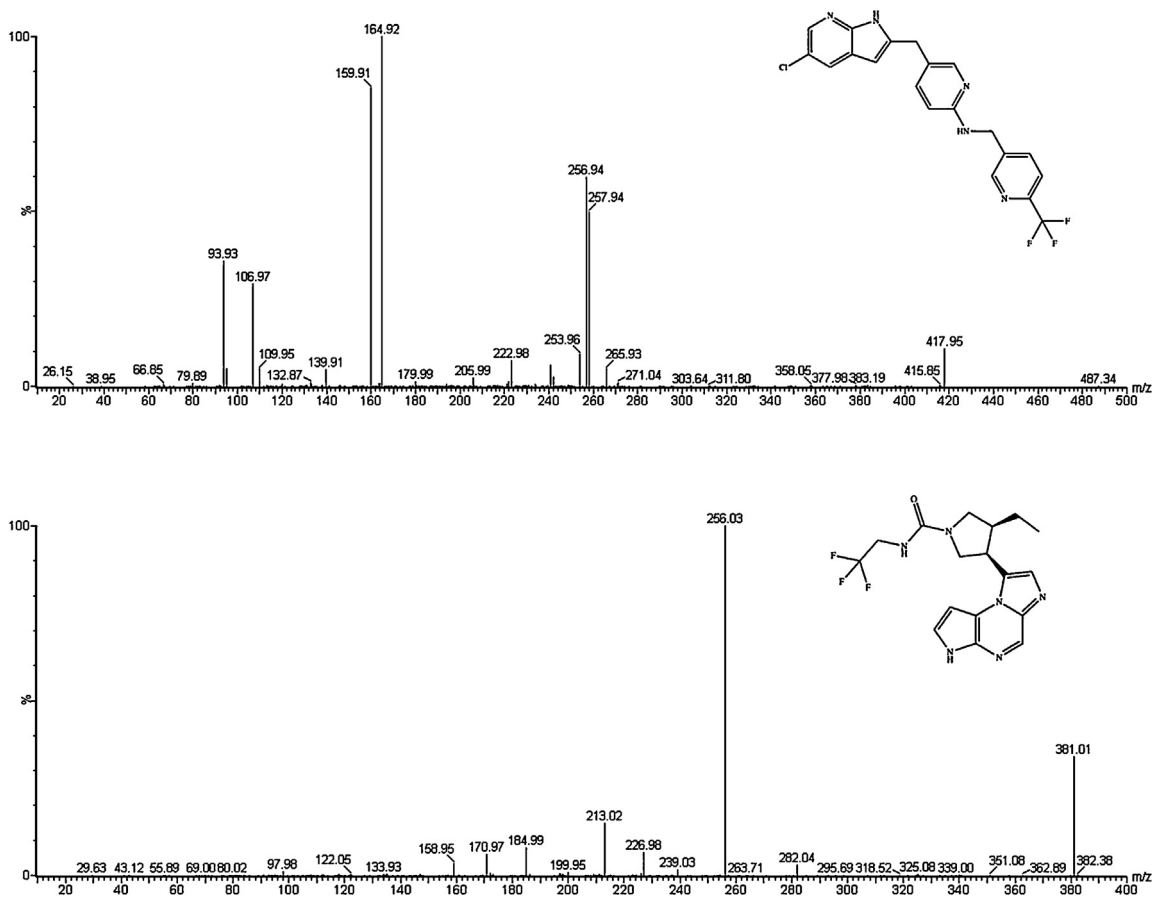

Fig. 1. Mass spectra of pexidartinib (A) and upadacitinib (IS, B) in the present study.

liquid chromatography tandem mass spectrometry (UPLC–MS/MS) method for analysing the concentration levels of pexidartinib in rat plasma. Considering opportunistic fungal infections are common in cancer patients with low immune function, especially under chemotherapy, antifungal drugs such as isavuconazole, posaconazole, fluconazole and itraconazole had shown certain inhibition on CYP enzymes [11,12]. So, the novel developed UPLC–MS/MS method was set up to assess the changes of the exposure and pharmacokinetic parameters of pexidartinib by different antifungal drugs (isavuconazole, posaconazole, fluconazole and itraconazole) in rats.

2. Experimental

2.1. Chemicals materials and reagents

Pexidartinib, isavuconazole, posaconazole, fluconazole, itraconazole (all purity > 98 %) and upadacitinib (IS, purity > 98 %, Fig. 1B) were provided by Beijing sunflower and technology development CO., LTD (Beijing, China). HPLC grade of acetonitrile and methanol were obtained from Merck Company (Darmstadt, Germany). Formic acid was analytical grade and supplied from Beijing sunflower and technology development CO., LTD (Beijing, China). Ultrapure water was prepared using a Milli-Q Water Purification System (Millipore, Bedford, USA).

2.2. Animal experiments

Healthy male Sprague-Dawley (SD) rats (body weight of 200 ± 20 g) were provided by Laboratory Animal Center of Wenzhou Medical University (Wenzhou, China). Rats were raised under humidity, standard temperature, and light conditions, and fed standard rodent diet and water. This experiment was approved by the Animal Care and Use Committee of Wenzhou Medical University.

Pexidartinib, isavuconazole, posaconazole, fluconazole, and itraconazole were all suspended in 0.5 % carboxymethyl cellulose sodium (CMC-Na). After fasting with free access to water for 12 h, 30 SD rats were randomly divided into five groups (n = 6) and orally administered the approximate equivalent volume solutions: the control group (0.5 % CMC-Na, Group A), isavuconazole group (20 mg/kg, Group B), posaconazole group (20 mg/kg, Group C), fluconazole group (20 mg/kg, Group D) and itraconazole group (20 mg/kg, Group E). Thirty minutes later, 20 mg/kg pexidartinib was orally administered to each rat. At the time points of 0, 0.333, 0.667, 1, 2, 4, 6, 12, 24, and 48 h, approximately 0.3 mL of blood samples were then collected from the rats' tail veins into heparinized 1.5 mL polythene tubes. Subsequently, 100 μL plasma was obtained after centrifugation of the blood samples at 4000 g for 10 min at room temperature, and all samples were stored at −20 °C until analysis.

2.3. Instrumentations and analytical conditions

The UPLC–MS/MS system was consisted of the Waters ACQUITY UPLC I-Class system (Milford, MA, USA) and Waters Xevo TQ-S triple quadrupole tandem mass spectrometer which was equipped with an electrospray ionization (ESI) source (Milford, MA, USA). All experimental data were acquired in centroid mode and processed using Masslynx 4.1 software and Quanlynx programme (Milford, MA, USA).

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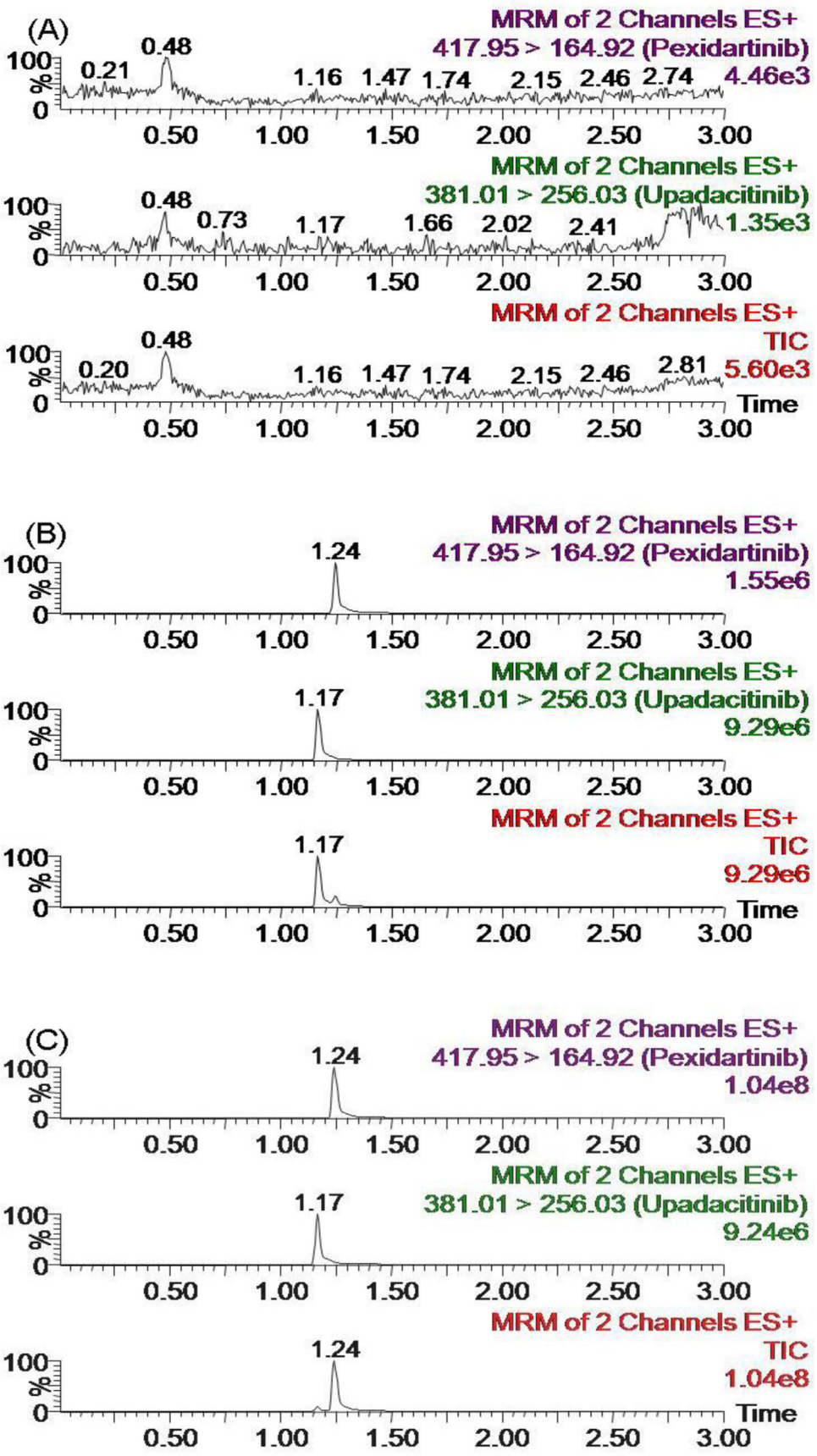

Fig. 2. Representative MRM chromatograms of pexidartinib and IS in rat plasma sample: blank plasma (A), blank plasma spiked with standard solution (B) and real plasma sample collected from a rat after oral administration of 20 mg/kg pexidartinib (C).

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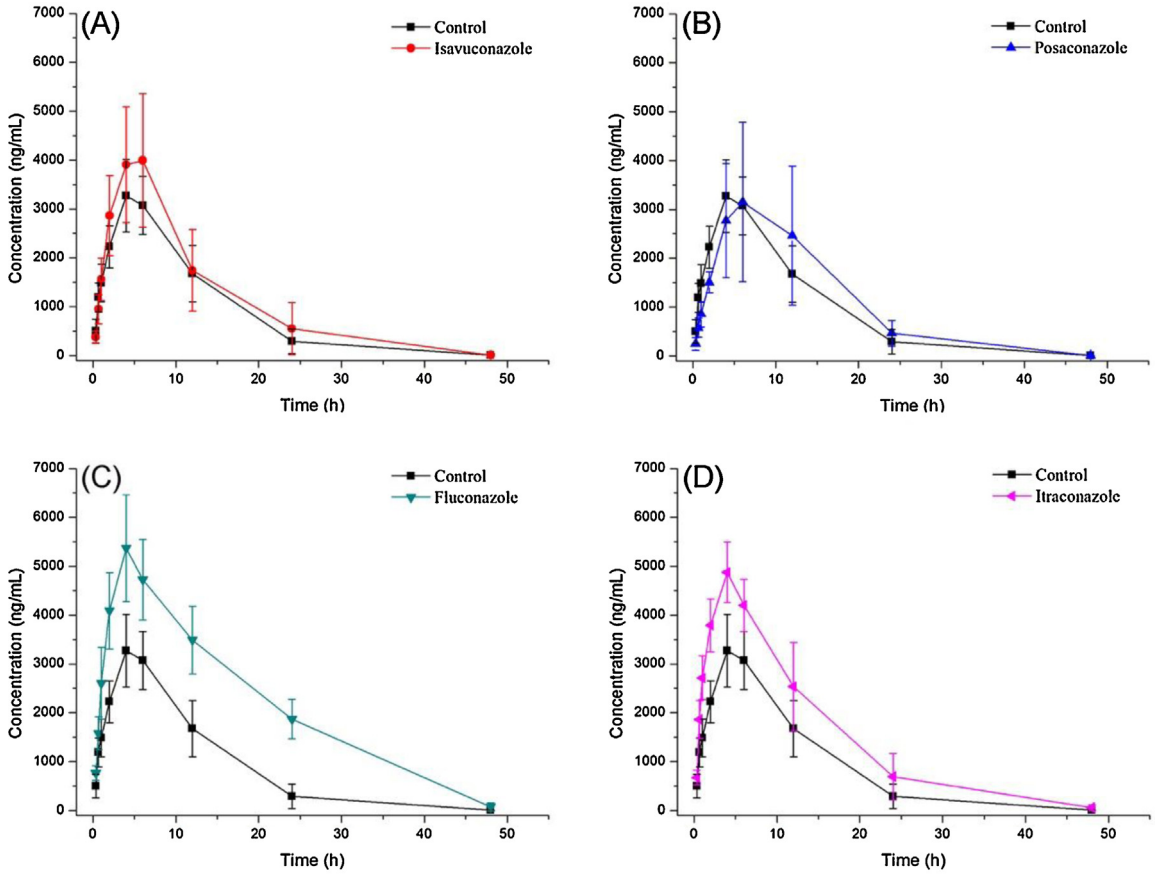

Fig. 3. Mean plasma concentration-time curves of pexidartinib in different treatment groups of rats (n = 6).

The chromatographic separation of pexidartinib and IS was achieved on an Acquity UPLC BEH C18 column (2.1 × 50 mm, 1.7 μm). Meanwhile, the mobile phase used for the analysis in this study was composed of acetonitrile (solvent A) and 0.1 % formic acid in water (solvent B) with 0.40 mL/min flow rate. Linear gradient elution was achieved and conducted as follows: 0–0.5 min (A, 10–10%); 0.5–1.0 min (A, 10–90 %); 1.0–2.0 min (A, 90–90%); and 2.0–2.1 min (A, 90–10%). Then, 10 % A from 2.1–3.0 min was maintained for equilibration. The entire run time was 3.0 min for an injection volume of 2.0 μL. The auto-sampler was maintained at 10 °C for all samples, while the temperature of the column was set at 40 °C.

Analyses were performed by an ACQUITY UPLC system coupled to a Xevo TQ-S triple quadrupole tandem mass spectrometer in the positive ion mode. Multiple reaction monitoring (MRM) mode was selected and operated for the detection, in which the ion transitions for pexidartinib and IS were m/z 417.95 → 164.92 and m/z 381.01 → 256.03, respectively. The cone voltage and collision energy were 30 V and 35 eV for pexidartinib and were 30 V and 25 eV for IS, respectively.

2.4. Preparation of the standard solutions

Standard stock solution of pexidartinib in the experiment was operated in methanol at the concentration level of 1.00 mg/mL. A serial corresponding dilution from the prepared stock solution was operated to obtain the working solution of the calibration curve and quality control (QC) samples through methanol. Calibration standard was prepared by spiking blank rat plasma with appropriate volumes of the working solution to obtain the following concentrations of the analyte: 1, 5, 10, 50, 100, 500, 1000, and 7000 ng/mL. Similarly, QC samples at four different concentrations in this study were produced at 1 ng/mL (lower limit of quantification, LLOQ), 3 ng/mL (LOQ), 200 ng/mL (MOQ), and 5000 ng/mL (HOQ). In addition, IS working solution at the concentration level of 200 ng/mL was achieved by the dilution of its stock solution (1.00 mg/mL) with methanol. All solutions were placed at −20 °C until further use.

2.5. Sample preparation

A 100 μL aliquot of plasma sample was mixed with 20 μL of IS working solution (200 ng/mL) and 300 μL of acetonitrile for protein precipitation. The mixture was vortexed for 1.0 min and centrifugated at 13,000 g for 10 min. The clear supernatant (100 μL) was collected and moved into a clean auto-sampler vial. Finally, 2.0 μL was injected directly into the system for further LC–MS/MS analysis.

2.6. Method validation

The present study was validated in compliance with the US FDA principles for the validation of bioanalytical methods [13]. The calibration curve, selectivity, LLOQ, accuracy, precision, matrix effect, recovery, stability, and carry-over were evaluated during the method validation process.

2.7. Statistical analysis

In the present experiment, the mean concentration levels of pexidartinib in rat plasma versus time profile was explored by Origin 8.0 (Originlab Company, Northampton, MA, USA) after

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Table 1
The precision, accuracy and recovery of pexidartinib in rat plasma (n = 6).

Analyte	Concentration (ng/mL)	Intra-day		Inter-day		Recovery
		RSD%	RE%	RSD%	RE%	(Mean ± SD %)
Pexidartinib	1	11.1	−4.0	13.4	6.4	88.7 ± 10.5
	3	10.2	−5.3	12.1	−0.3	90.4 ± 12.7
	200	4.7	−1.5	4.8	0.6	92.5 ± 4.8
	5000	1.7	2.3	2.1	4.1	94.1 ± 2.1

Table 2
Stability results of pexidartinib in rat plasma under different conditions (n = 5).

Analyte	Concentration(ng/mL)	Ambient temperature, 2 h		Auto-sampler 10 °C, 4 h		3 freeze-thaw		−20 °C, 30 days	
		RSD (%)	RE (%)	RSD (%)	RE (%)	RSD(%)	RE(%)	RSD(%)	RE(%)
Pexidartinib	3	6.8	−11.6	11.4	0.1	8.5	7.1	8.1	−1.7
	200	4.6	7.5	5.7	7.2	6.0	8.3	5.3	8.4
	5000	1.9	5.9	2.1	6.6	1.7	6.8	0.9	7.8

Table 3
The pharmacokinetic parameters of pexidartinib in different treatment groups of rats. Group A: the control group (0.5 % CMC-Na), Group B: 20 mg/kg isavuconazole, Group C: 20 mg/kg posaconazole, Group D: 20 mg/kg fluconazole, and Group E: 20 mg/kg itraconazole. (n = 6, Mean ± SD).

Parameters	Group A	Group B	Group C	Group D	Group E
$AUC_{0\to t}$ (μg/mL•h)	44.99 ± 10.48	55.19 ± 11.80	52.59 ± 10.78	104.58 ± 18.62**	71.47 ± 12.21*
$AUC_{0\to\infty}$ (μg/mL•h)	45.04 ± 10.52	55.27 ± 11.85	52.65 ± 10.79	105.83 ± 19.43**	72.10 ± 12.70*
$t_{1/2}$ (h)	4.13 ± 0.75	4.72 ± 0.71	4.73 ± 0.81	6.84 ± 1.56**	5.78 ± 1.20*
T_{max} (h)	4.88 ± 1.03	5.33 ± 1.03	5.03 ± 1.08	6.00 ± 1.45	5.01 ± 1.20
CLz/F(L/h/kg)	0.46 ± 0.10	0.40 ± 0.11	0.50 ± 0.16	0.21 ± 0.06*	0.29 ± 0.08
C_{max} (μg/mL)	3.65 ± 0.62	4.22 ± 0.66	3.47 ± 0.53	5.88 ± 1.30**	5.07 ± 0.55*

Compared with Group A, *P < 0.05, **P < 0.01.

the measurement of the analyte concentration, and the main pharmacokinetic parameters of pexidartinib were analyzed in non-compartmental mode using the Drug and Statistics (DAS) 2.0 software (Shanghai University of Traditional Chinese Medicine, China). Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) 17.0 software in one-way analysis of variance (ANOVA) followed by Dunnett's test was employed to compare the main pharmacokinetic parameters among different groups. Anyway, if the value of P was below 0.05, it was considered to be of statistical significance.

3. Results and discussion

3.1. Method development and optimization

As we known, the selection of column is necessary for efficient separation, short chromatographic retention time and peak symmetry, so different analytical columns were evaluated and compared. It was proved to be that BEH C18 (2.1 × 50 mm, 1.7 μm) column indicated superiority to other columns. Considering the addition of formic acid might enhance the chromatographic signals of the analyte and IS in this study, thus, we added 0.1 % formic acid into water to optimize the mobile phase. Finally, the excessive numbers of plasma samples generated in pharmacokinetic or drug-drug interaction study, a simple and quick sample preparation method is always preferable. Although plasma protein precipitation may introduce endogenous components that cause matrix effects during LC–MS/MS analysis, a gradient elution could remove endogenous substances and overcome matrix effects to some extent. In addition, a simple protein precipitation met the requirements of high-throughput testing as we had reported [14]. Therefore, acetonitrile was employed for sample preparation in this study.

3.2. Method validation

3.2.1. Selectivity

Three plasma samples of blank plasma obtained from six different rats, blank plasma sample containing the target analyte of pexidartinib and IS, and a real sample of rat plasma from the drug-drug interaction study were processed, and their chromatograms were harvested and compared for potential interferences and chromatographic integrity. The results showed that no interference peak from endogenous substance was observed near the retention times with the peaks of the analyte being detected and IS, which respectively were 1.24 and 1.17 min from the chromatograms (Fig. 2).

3.2.2. Calibration curve and LLOQ

Eight different concentrations of calibration curves ranging from 1 to 7000 ng/mL spiked into blank samples from rat plasma were processed and then evaluated at three consecutive days by UPLC–MS/MS. A weighted ($1/x^2$) linear regression of pexidartinib versus IS peak area ratios was operated to define the calibration curve. It was turned out that the regression equation of pexidartinib obtained in this bioanalytical assay was $Y = 0.0281478 \times X \pm 0.0340183$ ($r^2 = 0.9992$), where Y represents the peak area ratio of analyte to IS, and X indicates the concentration level of pexidartinib in nominal. LLOQ was established as the sensitivity of this method, for which the value was 1 ng/mL with acceptable RE% and RSD% (Table 1).

3.2.3. Precision, accuracy and recovery

6 replicates of QC samples at LLOQ, LOQ, MOQ and HOQ four different concentration levels were evaluated over three consecutive days, to calculate the accuracy and precision for inter-day, while on the same day for intra-day. The extraction recovery of pexidartinib from the plasma matrix was assessed by comparing the chromatographic peak areas of pexidartinib in QC plasma samples

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in six replicates with those of the analyte in processed blank plasma samples at the corresponding concentration levels. A summary of the data were listed in Table 1, and met the requirements.

3.2.4. Matrix effect

Peak area ratios of pexidartinib spiked into the extracted blank matrix to the neat reference standard solutions at three different concentrations of 3, 200 and 5000 ng/mL was defined as the matrix effect and had been investigated. The matrix effect of pexidartinib was calculated to be ranged from 99.1%–112.0%, indicating no significant effect existed from the endogenous materials in the rat plasma for the entire procedure.

3.2.5. Stability

The stability of the analyte was assessed for plasma samples in various storage and processing conditions at three QC levels (Table 2). It was found to be stable when plasma pexidartinib samples were processed and kept in the auto-sampler at 10 °C for more than 4 h. Moreover, the stability of short term and long term was investigated after storage at ambient temperature for 2 h and kept at −20 °C for at least 30 days, respectively, of which the results passed the required accuracy and precision and met the requirement. Finally, 3 complete freeze thaw cycles (from −20 °C to ambient temperature) was also stable.

3.2.6. Carry-over

Carry-over was assessed by analysing blank plasma samples injected after use of upper limit of quantification (ULOQ) samples. In our study, the peak area in the blank sample was lower than 20 % of the areas in the LLOQ and less than 5% of the IS, which were consequently considered acceptable.

3.3. Animal study

The newly established UPLC–MS/MS method for bioanalysis was successfully employed to investigate the study of DDIs among pexidartinib and four antifungal drugs (isavuconazole, posaconazole, fluconazole and itraconazole) in rats. After oral administration of a single dose of 20 mg/kg pexidartinib, the mean concentration levels of pexidartinib in rat plasma versus time profiles in different groups were illustrated in Fig. 3, and the main pharmacokinetic parameters of pexidartinib were also demonstrated in Table 3 by non-compartment model analysis.

From the data of our study, when pexidartinib was co-administered with isavuconazole in Group B or posaconazole in Group C, the main pharmacokinetic parameters ($AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, $t_{1/2}$,T_{max}, CLz/F, and C_{max}) of pexidartinib have no significant differences compared with the control Group A. Thus, isavuconazole and posaconazole did not affect the pharmacokinetic parameters of pexidartinib to a clinically relevant extent. Therefore, adaptation of the dose of pexidartinib might not be required when administered concomitantly with isavuconazole or posaconazole. However, for fluconazole in group D, $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, $t_{1/2}$,and C_{max} of pexidartinib increased significantly ($P < 0.01$), while CLz/F decreased obviously ($P < 0.05$). It demonstrated that fluconazole had an obvious inhibitory effect on the metabolism of pexidartinib in rats. As for itraconazole in group E, the values of $AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, $t_{1/2}$,and C_{max} of pexidartinib also increased greatly ($P < 0.05$) when compared with Group A, while less than Group D. Therefore, fluconazole had a more significant inhibitory effect on the metabolism of pexidartinib than itraconazole. As the investigation of the inhibitory effect of antifungal drugs on the metabolism of pexidartinib was performed in rats with a few, further researches should be done.

4. Conclusions

In conclusions, the presented method based on UPLC–MS/MS technique was simple, fast, and accurate for the detection of pexidartinib in rat plasma. The application of this bioanalytical assay was conducted in the animal study of DDIs among pexidartinib and different antifungal drugs (isavuconazole, posaconazole, fluconazole and itraconazole) in rats, where fluconazole and itraconazole increased the exposure of pexidartinib and had obvious inhibitory effect on the metabolism of pexidartinib. Therefore, the combination use of pexidartinib with fluconazole or itraconazole should be monitored to avoid the occurrence of adverse reactions in clinic.

CRediT authorship contribution statement

Lu Shi: Writing - original draft, Conceptualization, Data curation, Formal analysis. **Zheli Jiang:** Investigation, Methodology, Resources, Supervision. **Bowen Zhang:** Visualization, Writing - original draft. **Congrong Tang:** Writing - review & editing. **Renai Xu:** Project administration, Resources, Software, Supervision, Writing - review & editing, Validation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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