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ORIGINAL ARTICLE

Determination and metabolism of brexpiprazole following baicalin to rats by a novel developed UPLC-MS/MS

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Abstract The prime purpose of this research currently being done was to set up an acceptable and high-operational ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS) method, which could simultaneously analyze the concentration levels of brexpiprazole, assisted medication for treating depression, and DM-3411, the principal metabolite of brexpiprazole in rats, and to examine the impact of baicalin on the metabolism of brexpiprazole in rats. After quick sample preparation using acetonitrile as a protein precipitating agent, the chromatograms of brexpiprazole, DM-3411 and aripiprazole (internal standard, IS) were successfully separated by Acquity BEH C18 (2.1 mm × 50 mm, 1.7 μm) column. The concentrations of the analytes were detected through a Xevo TQ-S triple quadrupole tandem by the positive ion scanning. The ranges of calibration curves for both brexpiprazole and DM-3411 were 0.5–100 ng/mL, and the approach represented fine linearity in the ranges. The lower limit of quantification (LLOQ) of brexpiprazole and DM-3411 could reach 0.5 ng/mL in the study. The range of intra-day and inter-day accuracy of the two analytes was between −10.6% and 12.3%, while the precision was ≤ 11.5%. The recovery rate of each compound was greater than 81.0%, and no obvious matrix effects were observable. In addition, the plasma sample quantitative detection of the compounds in the study remained stable under all

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conditions. Then, we used this assay to detect the plasma levels of brexpiprazole and DM-3411 from a herb-drug interaction investigation, in which 200 mg/kg baicalin remarkably increased the plasma concentration of brexpiprazole and changed brexpiprazole pharmacokinetics. This study will contribute to a better understanding of the pharmacokinetic properties of brexpiprazole when concurrent use with baicalin, and to an understanding of the unanticipated clinical risks.

1. Introduction

Increasing number of people are taking herbal products which replace some western drugs in the worldwide (Foster, Arnason, & Briggs, 2005). Approximately 80% of the world's population was reported to use herbal products to meet their demand for drugs (Soligard, Bratlid, Cao, Liang, & Nilsen, 2011). Baicalin is a kind of flavonoids isolated from Scutellaria baicalensis' root, which is widely used with other herbal drugs in traditional Chinese medicine (Yang, Yang, & Zou, 2013). It produces a variety of pharmaceutical effects, particularly for depressive disorders (Li et al., 2013; Zhong, Li, Xu, Wang, & Shi, 2019). In addition, it demonstrated that baicalin inhibits rat hepatic CYP2D and CYP3A activities on the metabolism of dextromethorphan in a concentration-dependent manner (Tian, Cheng, He, Jia, & Qiao, 2013), as well as midazolam metabolism in rats (Tian, Cheng, Jin, Gao, & Qiao, 2013).

Brexpiprazole (Fig. 1A) is a novel modulator of 5-hydroxytryptamine-dopamine activity, pharmacologically acting as a partial agonist of 5-hydroxytryptamine 1A (5-HT_{1A}) and dopamine D2 receptors, and a powerful antagonist of 5-HT_{2A} receptors and norepinephrine α1B/α2C receptors (Maeda, Lerdrup, et al., 2014, Maeda, Sugino, et al., 2014). In July 2015, the US FDA approved oral brexpiprazole for use as an assisted therapy to antidepressants in major depressive disorder (MDD) and schizophrenia in accordance with the four randomized, placebo-controlled phase III trials (Greig, 2015). CYP3A4 and CYP2D6 are the main metabolizing enzymes of brexpiprazole whose major metabolite is DM-3411 (Fig. 1B) after S-oxidation (Sasabe et al., 2021). Therefore, any combined application with herbs those influence the CYP isozymes must be performed carefully. Considering the effect of baicalin on depressive disorder, co-administration of brexpiprazole with baicalin may be happen when both of them are used for patients with MDD diseases. However, potential herb-drug interactions between brexpiprazole with baicalin have not been investigated in detail.

As far as we know, several analytical assays are reported to evaluate brexpiprazole concentrations (Feng et al., 2020; Yu et al., 2020; Zou, Yan, Liu, & Wei, 2018) or its metabolite DM-3411 alone (Chen et al., 2020) in biological samples. Although it has been reported that an analytical approach through liquid chromatography tandem mass spectrometry (LC-MS/MS) allows simultaneous determination of brepiprazole and DM-3411 in animal and human for pharmacokinetics, it is non-repeatable in other laboratories for lack of sufficient LC-MS/MS parameters (Sasabe et al., 2021). In other words, there is no literature reported for the simultaneous determination of brepiprazole and DM-3411 in biological fluids.

For these facts, the article aimed to set up a precise and highly operational method for simultaneously detecting of brexpiprazole and its major metabolite DM-3411 in plasma of rats by ultra performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS), and to search for the influence of baicalin on the pharmacokinetic profiles of brexpiprazole and DM-3411 in Sprague Dawley (SD) rats.

2. Experimental

2.1. Chemicals, materials and reagents

The purity of brepiprazole, DM-3411 and aripiprazole (internal standard, IS, Fig. 1C) were greater than 98%, which were from Shanghai Chuangsai Technology Co., Ltd. (Shanghai, China), as well as the formic acid (AR grade) in this study. LC-grade of acetonitrile and methanol were provided by Merck Company (Darmstadt, Germany). Ultrapure water was supplied by Milli-Q Reagent System (Millipore, Bedford, USA).

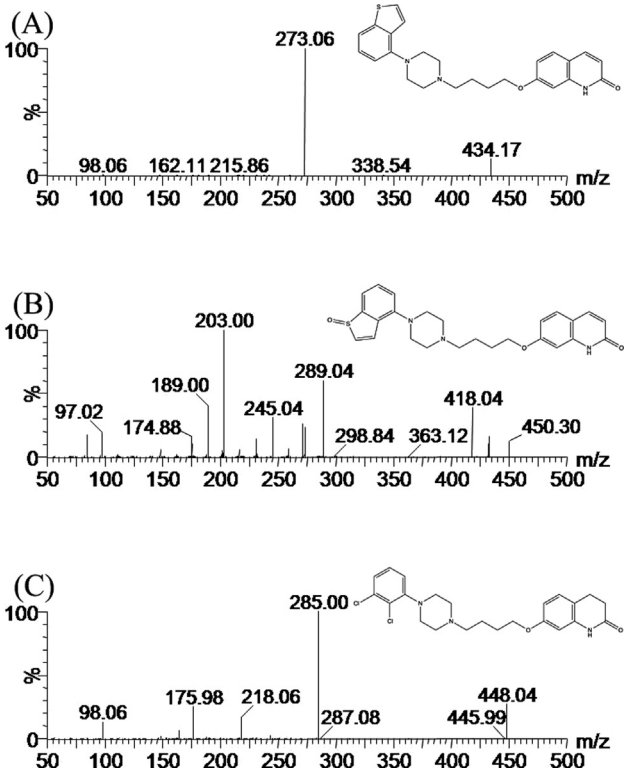

Fig. 1 Mass spectra of brexpiprazole (A), DM-3411 (B), and aripiprazole (IS, C) in the present study.

2.2. Animal experiments

Twelve rats (weighing 200 ± 20 g) adapted to diet about seven day before the initiation of experimentation, which were purchased from the Animal Experimental Center of Wenzhou Medical University (Zhejiang, China). The animal experimental operations were carried out according to the Operational Regulations of Laboratory Animals of Wenzhou Medical University (Zhejiang, China).

The two analytes, baicalin and brexpiprazole were prepared in a 0.5% solution of carboxymethyl cellulose sodium (CMC-Na). After at least of 12 h fasting, equal volume of 0.5% CMC-Na and baicalin were respectively given to two groups: control group (Group A, 0.5% CMC-Na solution), and administration group (Group B, baicalin 200 mg/kg), which were divided randomly (n = 6). Blood collection from the tail vein of rats (about 0.3 mL) at each fixed time point (0, 0.333, 0.667, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, and 48 h) was placed in a 1.5 mL heparined-polyethylene tube.

The supernatants were collected after centrifugation (4 °C, 8000 × g for 10 min), and then were put into −80 °C refrigerator for the next operation. According to the UPLC-MS/MS method established in the study, the plasma concentration at each time point was calculated, and the pharmacokinetic parameters of non-compartmental analysis were calculated by Drug and Statistics (DAS) 3.0 software (Mathematical Pharmacology Professional Committee of China, Shanghai, China).

2.3. Instrumentations and operating conditions

The system named Waters Acquity ultra performance liquid chromatography (UPLC) (Milford, MA, USA) was applied in the research, equipped with an I-CLASS delivery manager of binary solvent, a 40 °C thermostatted column and an autosampler at 10 °C (FTN). The solid phase of the chromatographic separation was the Acquity UPLC BEH C18 (2.1 mm × 50 mm, 1.7 μm) column, and a pre-column. The chromatographic analysis was performed by optimized gradient elution consisting of acetonitrile and 0.1% formic acid solution. The procedure of gradient elution was set up as below: 10% acetonitrile at 0–0.5 min, increase to 90% acetonitrile at 0.5–1.0 min, maintain 90% acetonitrile at 1.0–1.4 min, decrease to 10% acetonitrile at 1.4–1.5 min, and maintain 10% acetonitrile at 1.5–2.0 min.

The MS/MS triple quadrupole system of Xevo TQ-S (Milford, MA, USA) and the electro-spray ion (ESI) with positive ion scanning were performed in multiple reaction monitoring (MRM) mode. The ion conversions for brexpiprazole, DM-3411 and IS were m/z 434.17 → 273.06, m/z 450.30 → 203.00 , and m/z 448.04 → 285.00, respectively, with the cone voltage and collision energy of 30 V and 25 eV for all the three analytes. General parameters of the re-improved MS method were indicated as below: desolvation temperature 600 °C, capillary voltage 2.0 kV, cone gas 150 L/h, desolvation gas 1000 L/h, collision gas 0.15 mL/min. The control and data acquisition of the MS system is mastered by Masslynx 4.1 software (Milford, MA, USA).

2.4. Preparation of standard and quality control (QC) samples

The reference substances of brepiprazole, DM-3411 and IS were dissolved in methanol respectively, reaching the concentration of 1.00 mg/mL, and used as stock solutions. The working solution was formulated by diluting the mixture of the corresponding stock solutions with methanol. Additionally, level of IS working solution was 100 ng/mL diluted with methanol. 10 μL standard working solution was mixed with 90 μL rat blank plasma to prepare eight calibration standards, the concentration of which were 0.5, 1, 2, 5, 10, 20, 50, and 100 ng/mL. The quality control (QC) samples were prepared from blank plasma with four concentrations of lower limit of quantification (LLOQ), low (LQC), medium (MQC) and high (HQC), with the levels of 0.5, 1.0, 8, 80 ng/mL, respectively. After sample preparation, the solutions containing reference substances were put into − 80 °C refrigerator for next operation.

2.5. Extraction procedure

300 μL acetonitrile was added into the mixture of 100 μL plasma sample and 20 μL IS working solution to precipitate protein, and prepare calibration standards, plasma samples and QC samples. After centrifugation (4 °C, 13,000 × g for 10 min) and vorticity (2.0 min), 100 μL supernatant was extracted to the autosampler vials for UPLC-MS/MS analysis at an injected amount of 6.0 μL.

2.6. Method validation

The improved UPLC-MS/MS assay could simultaneously determine the content of brepiprazole and its metabolite DM-3411 in rat plasma, verified by the principles of FDA bioanalysis method validation (and Research of the U.S, 2018, http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064964.htm, Accessed: August 2, 2018.), including selectivity, carry-over, accuracy, recovery, precision, LLOQ, matrix effect, calibration curve and stability.

For the measurement of the selectivity in this method, six individual batches of control, drug-free rat plasma were processed and analyzed according to the described procedure. Responses of the analytes at the LLOQ concentrations were compared with the response of the blank samples. The responses of the interfering peaks in the blank sample should not exceed 20% of the responses for the analytes and 5% of the response for the IS, in an LLOQ sample. Carry-over was assessed by analyzing blank plasma samples injected after use of upper limit of quantification (ULOQ) samples.

Linearity range was established on the basis of the concentrations of 8 calibration samples. The calibration curves covering a range of 0.5–100 ng/mL for both brexpiprazole and DM-3411 were generated by diluting calibration standard working solutions with rat blank plasma and analyzed in three successive runs. The calibration curves were plotted utilizing peak area ratio of analyte/IS versus actual concentrations of analytes, and the result was described by a correlation coefficient (r^2) as the weighting factor. The LLOQ was determined as the lowest concentration in a calibration curve that could be quantified with the accuracy of 80–120% and the precision within ± 20%.

Intra-day precision refers to the changes of samples on the same day, while inter-day precision refers to the changes for three consecutive days. The precision results were expressed as relative standard deviation (RSD) and the accuracy results

were described as relative error (RE). The precision in the principle of FDA is within 15%, and the accuracy between the measured values and theoretical values is within ± 15%, but for LLOQ, it should be within 20%.

Three different processed QC samples (LQC, MQC and HQC) were obtained and used to evaluate the extraction recovery and matrix effect of brepiprazole and its metabolite DM-3411 in this study. The comparison of the peak areas of

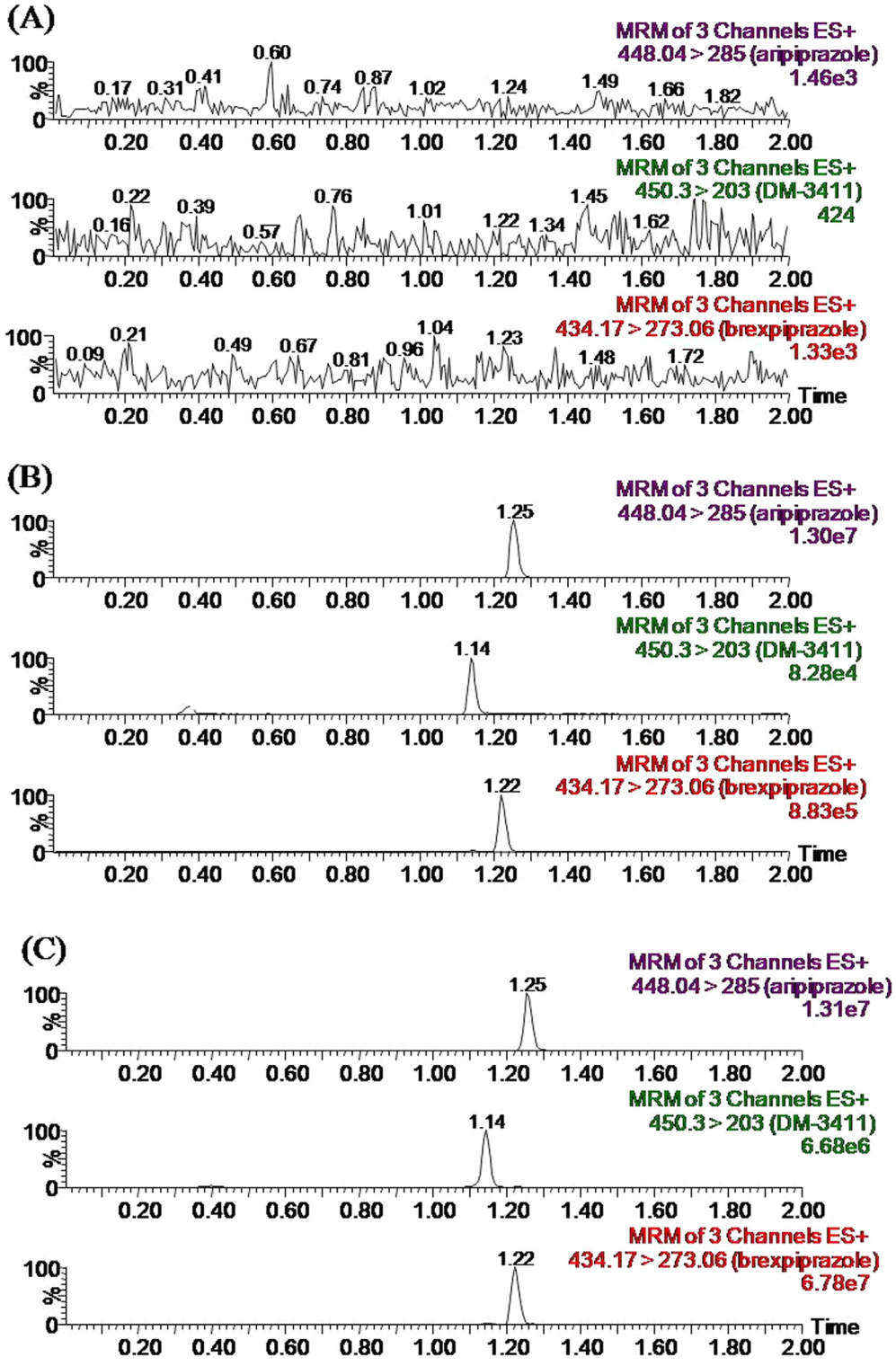

Fig. 2 Representative MRM chromatograms of brexpiprazole, DM-3411 and IS in rat samples: blank plasma (A), blank plasma spiked with low concentration of standard solutions (B) and blank plasma spiked with high concentration of standard solutions (C).

samples extracted from plasma (A), post- extracted blank plasma spiked samples (B), and the corresponding pure reference standard solutions (C) were done, where A/B*100 was calculated as the extraction recovery and B/C*100 was considered as the matrix effect, respectively.

The stability of brexpiprazole and DM-3411 in four different conditions were measured at three QC concentrations (LQC, MQC and HQC, n = 5). Among them, room temperature stability was evaluated by assessing the QC plasma samples under ambient temperature for 2 h as the short-term stability. In addition, QC plasma samples after extraction and being kept in the autosampler at 10 °C for at least 6 h were quantified to calculate the stability of the post-preparation. Moreover, the freeze–thaw stability was measured by determining the QC plasma samples from frozen (−80 °C) to thawed (room temperature) three times. Finally, the stability of long-term was analyzed and determined by testing the QC plasma samples for at least 21 days after stored at −80 °C.

3. Results and discussions

3.1. Method development and optimization

The optimized chromatographic conditions in the research performed with gradient elution verified its superior sensitivity and resolution, short peak time, high and efficient repeatability. In the pre-experiment, different organic buffers (such as methanol and acetonitrile) and water buffers (such as formic acid and ammonium acetate) on different chromatographic columns were evaluated, and the chromatographic elution in gradient programming mode was also investigated. However, the supernatant of precipitated samples produced asymmetric peaks with poor sensitivity, which did not satisfy the method requirement. Finally, it was found that the interference of impurity peaks was less, and a better resolution was obtained when operating gradient elution using acetonitrile and 0.1% formic acid aqueous solution as mobile phase and an Acquity BEH C18 (2.1 mm × 50 mm, 1.7 μm) column as solid phase.

Previous work reveals that protein precipitation (PPT) is one of the more straightforward, simple, one step and cost-effective approach for sample preparation and used for generating clean extracts for LC-MS/MS quantitation from samples (Tang et al., 2020; Xu et al., 2019). Methanol and acetonitrile are the preferred precipitants for plasma protein precipitation. However, it was found that during PPT, the volume of acetonitrile was less, so that pH value would not change significantly and the particle size of precipitation was smaller. Therefore, acetonitrile was selected for PPT in the study.

3.2. Method validation

3.2.1. Selectivity and carry-over

As shown in Fig. 2, the impurity peaks in blank plasma had no obvious interference with brepiprazole, DM-3411 and IS, indicating that the method used in the research was selective. The chromatograms of brexpiprazole, DM-3411 and IS were completely separated from each other with the retention times of 1.22, 1.14 and 1.25 min, respectively. In addition, no carry-over was observed for either analyte or IS in rat plasma, since there was no interference peak detected following injection of ULOQ samples.

Table 1 The accuracy and precision of each analyte in rat plasma (n = 6).

Analytes	Concentration (ng/mL)	Intra-day		Inter-day	
		RSD%	RE%	RSD%	RE%
Brexpiprazole	0.5	10.8	−10.6	10.9	−6.2
	1.0	7.3	1.0	9.3	2.8
	8	5.8	9.6	6.5	12.3
	80	4.5	−4.3	4.9	−4.9
DM-3411	0.5	11.5	−1.3	11.3	−3.1
	1.0	9.4	5.0	8.6	6.2
	8	6.6	6.3	8.5	11.1
	80	4.6	0.2	4.7	2.6

Table 2 Recovery and matrix effect of each analyte in rat plasma (n = 6).

Analytes	Concentration (ng/mL)	Recovery (%)		Matrix effect (%)	
		Mean ± SD	RSD (%)	Mean ± SD	RSD (%)
Brexpiprazole	1.0	81.0 ± 7.6	9.4	113.8 ± 10.5	9.2
	8	82.4 ± 3.1	3.8	112.7 ± 10.2	9.1
	80	88.0 ± 6.3	7.2	111.4 ± 6.1	5.5
DM-3411	1.0	82.6 ± 9.1	11.0	104.9 ± 10.5	10.0
	8	85.2 ± 5.7	6.7	89.0 ± 4.2	4.7
	80	93.1 ± 6.1	6.5	87.7 ± 10.4	11.9

Table 3 Stability results of each analyte in rat plasma under different conditions (n = 5).

Analyte	Added (ng/mL)	Room temperature, 2 h		Autosampler 10 °C, 6 h		Three freeze–thaw		−80 °C, 21 days	
		RSD (%)	RE (%)	RSD (%)	RE (%)	RSD(%)	RE(%)	RSD(%)	RE(%)
Brexpiprazole	1.0	8.4	−2.3	12.0	−2.4	8.6	0.5	8.1	4.4
	8	5.9	1.2	8.7	10.4	8.0	14.2	7.1	14.0
	80	5.4	−13.7	5.1	−6.8	5.1	−4.6	4.6	−3.7
DM-3411	1.0	12.5	−4.4	13.2	−6.0	11.6	−2.5	13.6	−7.0
	8	5.6	−3.0	6.6	3.6	6.1	6.5	7.2	2.3
	80	5.4	2.2	4.0	10.3	5.1	11.2	5.8	8.7

3.2.2. LLOQ and linearity of calibration curve

The concentration range of brepiprazole and DM-3411 was 0.5–100 ng/mL in the calibration curves including eight points, with the regression coefficient (r^2) greater than 0.99. The regression equation demonstrated in this research was Y = 2.888 × X ± 0.458843 (r^2 = 0.9983) for brexpiprazole, and Y = 0.249471 × X ± 0.0467125 (r^2 = 0.9987) for DM-3411, respectively. The LLOQ of brepiprazole and DM-3411 was both 0.5 ng/mL. According to the requirements of FDA, the precision and accuracy met the standard (within 20%, presented in Table 1).

3.2.3. Accuracy and precision

The intra-day and inter-day accuracy and precision of brexpiprazole and DM-3411 were revealed in Table 1, analyzed at four concentrations including LLOQ and three QC concentrations. As listed in Table 1, the accuracy and precision met the principles of FDA, of which was < ±15% and < 15%, respectively. The improved biological analysis to simultaneously quantitative detect the contents of brexpiprazole and DM-3411 in rat plasma was believed to be dependable with high reproduciblility.

3.2.4. Recovery and matrix effect

As demonstrated in Table 2, the range of the average extraction recoveries of brexpiprazole and DM-3411 at the three QC levels in rat plasma was between 81.0% and 93.1%. The matrix effect of all analytes in rat plasma was 87.7%-113.8%, and no obvious matrix effect was found.

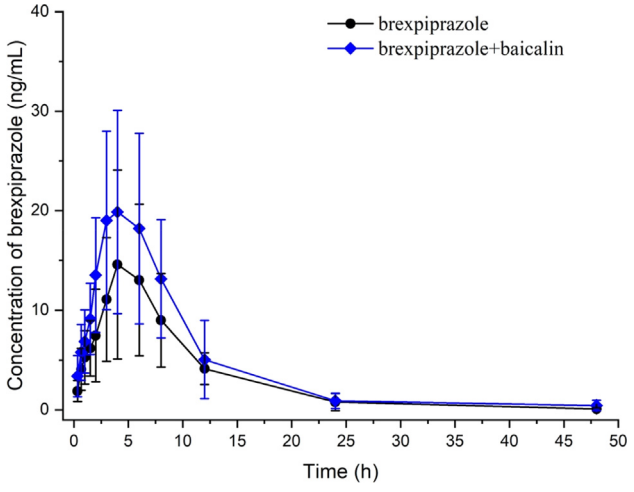

Fig. 3 Mean plasma concentration–time curves of brexpiprazole in rats after orally administrated of 1.0 mg/kg brexpiprazole alone or with 200 mg/kg baicalin. (n = 6, Mean ± SD).

4. Stability

Research of stabilities were operated at three QC concentration under four conditions, such as ≥ 2 h in room temperature, ≥21 days at −80 °C, ≥6h in the automatic sampler (10 °C) and the three whole freeze–thaw circles. The results exhibited that the QC samples held favorable stability under the four different conditions (Table 3).

4.1. Animal experiments

After intragastric administration of 1.0 mg/kg brepiprazole in rats, the newly optimized UPLC-MS/MS method was only available for measuring concentration of brepiprazole in plasma because the main metabolite of brepiprazole, DM-3411, couldn't be detected (illustrated in Fig. 3). The general pharmacokinetic parameters of non-compartment model were revealed in Table 4.

In the animal experiments, brexpiprazole was slowly absorbed and reached to the peak concentration (C_{max}) within 5.25 ± 1.60 h post-medication after a single oral gavage of 1.0 mg/kg brexpiprazole to rats. Additionally, the half-life ($t_{1/2}$) of brexpiprazole was 5.69 ± 1.33 h. These parameters were close to the previous report in rats (Yu et al., 2020), and were different from another research (Sasabe et al., 2021). For Group B, when brexpiprazole was co-administered with 200 mg/kg baicalin, the principal pharmacokinetic parameters ($AUC_{0\to t}$, $AUC_{0\to\infty}$, and C_{max}) of brexpiprazole had significant differences compared with the control

Table 4 The main pharmacokinetic parameters of brexpiprazole in rats after orally administrated of 1.0 mg/kg brexpiprazole. (n = 6, Mean ± SD).

Parameters	Group A	Group B
$AUC_{0\to t}$ (ng/mL•h)	147.39 ± 72.69	207.64 ± 80.25*
$AUC_{0\to\infty}$ (ng/mL•h)	148.32 ± 73.69	210.59 ± 81.94*
$MRT_{0\to t}$ (h)	8.81 ± 1.29	8.99 ± 2.63
$MRT_{0\to\infty}$ (h)	9.04 ± 1.54	10.23 ± 3.06
$t_{1/2}$ (h)	5.69 ± 1.33	6.32 ± 1.96
T_{max} (h)	5.25 ± 1.60	5.17 ± 1.47
CLz/F (L/h/kg)	9.44 ± 2.09	5.51 ± 1.41*
C_{max} (ng/mL)	16.37 ± 6.33	23.68 ± 9.87*

Compared with Group A, *P < 0.05.

Group A, while decreased CLz/F ($P < 0.05$), indicating that the total brexpiprazole systemic exposure increased. Thus, baicalin exhibited inhibitory effect on the metabolism of brexpiprazole in rats. Since the concentration of DM-3411 was lower than that of LLOQ in this pharmacokinetic study, detail pharmacokinetic profiles and parameters of its metabolite DM-3411 had not been found. Given that pharmacokinetic variations among different species, the absorption, distribution, metabolism and excretion of the drugs may be affected. The pharmacokinetics curves and parameters of the two analytes in human body need to be further investigated due to the low number of SD rat samples and species variations between human and rats.

5. Conclusions

In general, it was the first optimized analytical method to simultaneously quantitative measure the concentrations of brexpiprazole and its principal metabolite DM-3411 in plasma, and to examine the influences of baicalin on their pharmacokinetics in rats. In addition, the improved approach through UPLC-MS/MS was demonstrated to be more reliable and easier to operate, reducing retention time and improving sensitivity and accuracy (Sasabe et al., 2021). Besides, it was found that baicalin could exhibit inhibitory effects on the metabolism of brexpiprazole in rats. While considering the complex and varied clinical factors of MDD patients, further human clinical trials should be investigated to confirm their accuracy interaction and be meaningful.

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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