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Determination of perospirone by liquid chromatography/electrospray mass spectrometry: Application to a pharmacokinetic study in healthy Chinese volunteers

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Abstract

Perospirone is a novel atypical antipsychotic with a unique combination of 5-HT_{1A} receptor agonism as well as 5-HT_{2A} and D_2 receptor antagonism. A simple rapid and selective LC–MS method utilizing a single quadrupole mass spectrometer was developed and validated for the determination of perospirone hydrochloride in human plasma. *N*-hexane was used to extract perospirone hydrochloride and amlodipine benzenesulfonate (internal standard (IS)) from an alkaline plasma sample. LC separation was performed on a XTerra ® MS C_{18} column (100 mm × 2.1 mm, i.d. 3.5 μm) using methanol −10 mM ammonium acetate (84:16, v/v) as a mobile phase. The quantification of target compounds was obtained by using a selected ion monitoring (SIM) at *m/z* 427.5 $[M+H]^+$ for perospirone hydrochloride, and at *m/z* 431.4 $[M+Na]^+$ for IS (amlodipine benzenesulfonate). Perospirone and IS eluted as sharp, symmetrical peaks with retention times of 3.11 ± 0.01 min and 4.15 ± 0.2 min, respectively. Calibration curves of perospirone hydrochloride in human plasma at concentrations ranging from 0.10 to 21.1 ng/mL exhibited excellent linearity ($r^2 = 0.9997$). The mean absolute recovery of the drug from plasma was more than 85%. Intra- and inter-day relative standard deviations were less than 6.43% and 11.9% for perospirone hydrochloride at the range from 0.32 to 10.6 ng/mL. Stability characteristics of the drug-containing plasma were thoroughly evaluated to establish appropriate conditions to process, store and prepare for chromatographic analysis without inducing significant chemical degradation. The following pharmacokinetic parameters were elucidated after administering a single dose of 8 mg perospirone hydrochloride. The area under the plasma concentration versus time curve from time 0 to 24 h (AUC_{0-24}) was 15.48 ± 4.23 μg/L h; peak plasma concentration (C_{max}) was 2.79 ± 0.78 μg/L; time to C_{max} (T_{max}) was 1.79 ± 0.45 h; and elimination half-life ($t_{1/2}$) 6.78 ± 1.38 h. The described assay method showed acceptable precision, accuracy, linearity, stability, and specificity and can be used for pharmacokinetic studies, therapeutic drug monitoring, and drug abuse screening.
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Keywords: Perospirone; Pharmacokinetic; LC-ESI/MS

1. Introduction

Perospirone(*cis*-*N*-[4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl]cyclohexane-1,2-dicarboximide monohydrochloride dehydrate (Fig. 1A) is a novel atypical antipsychotic drug. It has been reported that perospirone is effective in the treatment of positive and negative symptoms in schizophrenia, and is well tolerated compared with haloperidol treatment [1]. Like other atypical antipsychotics, perospirone is a more potent antagonizer of the 5-HT_{2A} receptor than of the D_2 receptor. In addition, perospirone displays a good affinity towards the 5-HT_{1A} receptor and is a 5-HT_{1A} receptor agonist [2,3]. The latest studies indicate that perospirone is effective in improving aggressive and agitated behavioral symptoms in demented patients [4]. Therefore, it is clinically important for a pharmacokinetic and pharmacodynamic study to detect perospirone in human plasma. Because perospirone has the potential to be abused, accurate drug-screening methods are needed for its analysis.

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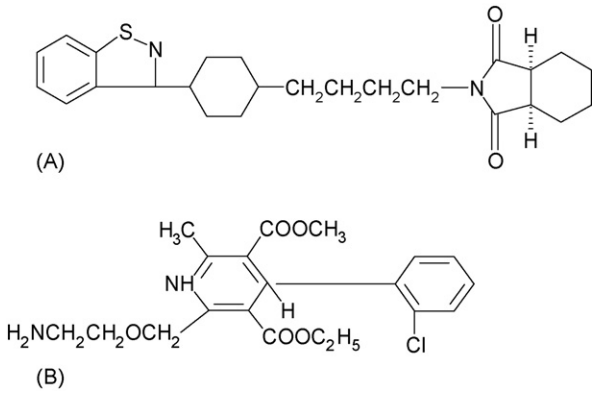

Fig. 1. Chemical structures of perospirone (A) and amlodipine (B).

To our knowledge, only one method has previously been reported for analysis of perospirone in human plasma [5]. The method had been used primarily for therapeutic drug monitoring of perospirone and its metabolite (ID-15036). HPLC coupled with column-switching techniques and fluorescence detector had been used. It performed too complicated procedure, needed special apparatus and took too long run time to adapt to high sample throughput and rapid determination in clinic and pharmacokinetic analysis, which was only suitable for routine analysis as the author indicated [5].

Our study focused on LC-single quadrupole MS because of its wider availability in ordinary laboratories as well as its sufficient sensitivity, selectivity and effectivity for the present study. The developed method was validated in terms of selectivity, linearity, limit of quantification, precision and accuracy and has been successfully applied to a pharmacokinetic study in healthy Chinese volunteers.

2. Experimental

2.1. Materials

Perospirone hydrochloride standard reference (100.3%, lot no. 040910) and perospirone hydrochloride tablets (4 mg/Tab, lot no. 041003) were kindly provided by Qin Hua Yuan Xin Pharmaceutical Limited (Shengzheng, China). The internal standard (amlodipine benzenesulfonate, IS, Fig. 1B) was purchased from National Institute for the Control of Pharmaceutical and Biological Products (lot no. 100374-200301; NICBP, Beijing, China); HPLC grade methanol was purchased from Tedia company, Inc. (Fairfield, Ohio, USA). Water was deionized and purified using a Milli-Q system (Millipore, Bedford, MA, USA) and was used to prepare all aqueous solutions. Other chemicals and reagents were of analytical-grade. Drug-free and drug-containing plasma were taken from the volunteers. Plasma was stored at −40 °C until assayed.

2.2. Liquid chromatography–mass spectrometry

A Waters (Milford, MA, USA) Alliance 2690 liquid chromatographic system interfaced to a 2487 dual wavelength UV detector, a Micromass ZQ 2000 ESI mass spectrometer and a Masslynx™ 4.0 data system were equipped with a XTerra® MS C_{18} column (100 mm × 2.1 mm i.d., 3.5 μm, Waters, Ireland) at a column temperature of 25 °C. The mobile phase, methanol −10 mM ammonium acetate (84:16, v/v), was run at a flow rate 0.25 mL/min, and the injection volume was 40 μL. Separation was conducted under isocratic conditions and the total running time was greater than 7 min. The system autosampler was controlled at 4 °C. After establishing the final conditions for the chromatographic analysis of perospirone of the detector interface and mass spectrometer were systematically optimized to maximize the response for the perospirone $[M+H]^+$ ion with detection in the selected ion monitoring (SIM) mode, since a single-quadrupole mass spectrometer was being used. Electrospray ionization-mass spectrometry (ESI-MS) was performed in the positive mode: capillary and cone voltage were 2500 and 40 V, respectively; drying-gas (N_2) flow rate was 500 L/h; the ionization sources were worked at 120 °C. The desolvation temperature was 450 °C. The gas used was of high purity. Selected ion monitoring was used to quantify perospirone hydrochloride *m/z* 427.5 $[M+H]^+$, and amlodipine benzenesulfonate (IS) *m/z* 431.4 $[M+Na]^+$. The two ions were monitored simultaneously within the analytical procedure.

2.3. Preparation of calibration standards and quality control samples

All concentrations of perospirone and amlodipine refer to the free bases. Stock solutions of perospirone and amlodipine were prepared in methanol using their salts. All stock solutions were stored at 4 °C when not in use. The stock solutions were further individually diluted with methanol to give working standard solutions of perospirone and amlodipine. Calibration standards of perospirone (0.10–21.1 ng/mL) were prepared by spiking appropriate amount of the working standards solutions of perospirone in screw capped glass tubes, then, they were evaporated to dryness under a stream of nitrogen gas, respectively, and added 1.0 mL drug-free plasma obtained from healthy volunteers and well mixed. Quality control (QC) samples were prepared in drug-free plasma at concentrations of 0.32, 1.06 and 10.6 ng/mL for perospirone in the same manner as standard curves. Then, the Calibration standards and QC samples were treated following the sample preparation procedure, as indicated in Section 2.4.

2.4. Sample extraction

Frozen human plasma samples were thawed at ambient temperature and 1.0 mL aliquots of samples were placed in screw capped glass tubes. Fifty microliters of internal standard working solution (956 ng/mL) and 0.1 mL of 0.1 M NaOH were then added. After a thorough vortex mixing for 30 s, mixtures were extracted with 5 mL of *n*-hexane, vortex-mixed for 3 min, and centrifuged at 4000 rpm for 10 min. The 4 mL of organic layer was removed and evaporated under a stream of nitrogen gas at 50 °C until completely dry. The dried residue obtained was dissolved in 100 μL of mobile phase, and 40 μL of this solution was then injected into the LC–MS system.

2.5. Pharmacokinetic study design

The developed method was used to study the pharmacokinetic characteristics of perospirone hydrochloride tablets in healthy Chinese volunteers.

2.5.1. Subjects

The pharmacokinetic study protocol used was approved by the Stated Food and Drug Administration (SFDA, China). The volunteers had the following clinical characteristics (expressed as means ± S.D. [range]): age, 23.5 ± 1.6 years [21–25]; height,174.2 ± 3.5 cm [170.2–180.5]; body weight, 65.8 ± 7.0 kg [50–72]. Twelve healthy volunteers, six males and six females, were selected after passing a clinical screening procedure including a physical examination and laboratory tests, which included hematology, blood biochemistry, and urine analysis. No volunteers had a history or evidence of a renal, gastrointestinal, hepatic, or hematologic abnormality or any acute or chronic disease, or an allergy to any drugs. This was done to ensure that the existing degree of variation would not be due to an influence of illness or other medications. All volunteers avoided using other drugs for at least 2 weeks prior to the study and until after its completion. Each volunteer received an oral dose of 8 mg (two tablets) of perospirone hydrochloride. This study was performed according to the revised Declaration of Helsinki for biomedical research involving human subjects and the rules of Good Clinical Practice. The protocol of this study was approved by the Ethical Committee of School Of Pharmaceutical Sciences Central South University (Changsha, China). All participants signed a written informed consent after they had been informed of the nature and details of the study.

Volunteers were hospitalized at 9:00 p.m. 1 day before this study and fasted 10 h before each drug administration. At 8.00 a.m., they were administered a single dose of perospirone hydrochloride (8 mg) with 250 mL water. A standard lunch was served at 4 h, and an evening meal was provided 12 h after administration. During the 24 h period after drug administration, no strenuous physical or mental activity was permitted. No other food was permitted during the 'in-house' period but liquid consumption was allowed ad libitum after lunch (with the exception of alcohol, soda, and coffee drinks, as well juices).

Heparinized blood samples (5 mL) were collected from a suitable forearm vein using an indwelling catheter into heparin containing tubes before (0 h) and 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 13, 16 and 24 h after dosing. The blood samples were centrifuged at 3000 rpm for 10 min, and plasma samples were separated and stored at −40 °C until required for analysis.

2.5.2. Pharmacokinetic analysis

The data analysis of pharmacokinetic parameters was performed by using Drug and Statistics software (Version. 2.0, Chinese). Two analysis results of compartment and noncompartment were described. The types of the compartmental model were simulated by orally administrated open one- or two-compartmental model according to AIC method respectively. The peak perospirone concentrations (C_{max}) and the time to C_{max} (T_{max}) were determined by inspection of the individual plasma concentration-time profiles of the drug. The area under the plasma concentration–time curve from time zero to the last measurable concentration (AUC_{0-t}) was calculated using the linear trapezoidal rule and was extrapolated to infinity ($AUC_{0-\infty}$) according to the relationship: $AUC = (AUC_{0-t} + C_t)/k_e$. C_t is the last concentration evaluated in plasma greater than the limit of quantification (LOQ) and the elimination rate (k_e) was obtained as the slope of the linear regression of the log-transformed concentration–time curve data in the terminal phase. The half-life ($t_{1/2}$) and CL/F were calculated based on the following equations: $t_{1/2} = 0.693/k_e$; $CL/F = k_e V_c$. V_c was the apparent volume of distribution of the center compartment, which was estimated by the model after calculation. V/F was the apparent volume of distribution, MRT was mean residence time.

3. Results and discussion

3.1. Method development

Sample preparation is usually required for the determination of pharmaceuticals in biological samples owing to complex matrices in order to remove possibly interfering matrix components and increase the selectivity and sensitivity. Liquid–liquid extraction (LLE) was a widely adopted method and often achieved satisfactory extraction recoveries of analytes from biological samples. In that assay [5], the test compounds were extracts from 2 mL of plasma using chloroform-hexane (30:70, v/v) and the extract was injected into a column I for clean-up and column II for separation with different flow rates (from 1.2 to 0.6 mL/min) and mobile phases, respectively. The peak was detected using a fluorescence detector and the total time for a chromatographic separation was about 30 min.

In the present work, *n*-hexane was used for the extraction of the perospirone from human plasma, which produced a clean chromatogram for a drug-free plasma sample and offered satisfactory extraction recoveries for the analyte more than 85%.

A XTerra® MS C_{18} column (100 mm × 2.1 mm i.d., 3.5 μm, Waters, Ireland) was used for the chromatographic separation. For mobile phase, a mix of methanol and 10 mM ammonium acetate (84:16, v/v) was found to be optimal for the study, which provided symmetric peak shapes of the analytes and the internal standard as well as a short run time. For the selection of the internal standard, the similar extracted recovery and the retention time become the significant choice. Several compounds (i.e. zaleplon, finasteride) were tried and amlodipine benzenesulfonate was finally used as the internal standard in this work.

A preliminary series of experiments indicated that perospirone was very responsive to ESI/MS with positive ion detection. With appropriates election of the fragmentor voltage, the protonated molecule at m/z 427.5 appeared as the base peak in the ESI mass spectrum of the drug (Fig. 2), without significant fragmentation to lower mass ions. After establishing the final conditions for the chromatographic analysis of perospirone in human plasma, all operational parameters of the detector interface and mass spectrometer were systematically optimized to maximize the response for the perospirone $[M+H]^+$ ion with detection in the selected ion monitoring (SIM) mode, since

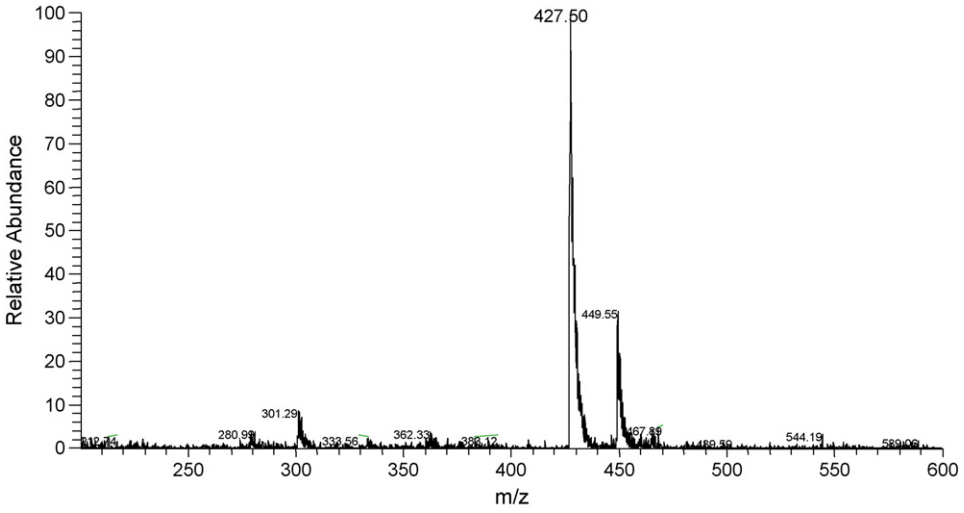

Fig. 2. Positive ion ESI mass spectrum acquired at the apex of the chromatographic peak for perospirone by continuous scanning over a mass range of 200–600 a.m.u. Aside from operating the mass spectrometer in the scanning mode, the interface and detector were operated at the settings that provided optimal response of the perospirone $[M+H]^+$ ion at *m/z* 427.5.

a single-quadrupole mass spectrometer was being used. The parameters examined included the nebulizer pressure, drying gas flow rate and temperature, capillary voltage, SIM ion, mass resolution, and fragmentor voltage. A solution of 20 ng/mL perospirone in methanol with an injection volume of 100 μL was used for the optimization. Using the optimal detection parameters, the base peak in the mass spectrum of the compound selected for use as the internal standard in the assay, amlodipine was the sodium adduct at *m/z* 431.4 (not shown).

Moreover, two detection channels, channel 1 (MSD1) for amlodipine (IS) and channel 2 (MSD2) for perospirone were adopted.

As electrospray gave good sensitivity, fragmentation, and linearity, we have not yet tested atmospheric pressure ionization.

3.2. Specificity and selectivity

The specificity and selectivity of the method were investigated by preparing and analyzing drug-free human plasma from six different batches of pooled human plasma. The product ion chromatograms extracted from plasma are depicted in Fig. 3. As shown, the retention times of perospirone and amlodipine (IS) using our system were 3.10 ± 0.01 min and 4.15 ± 0.2 min, respectively, which are greatly lower than those reported by Yasui-Furukoria et al. [5]. It showed that the method exhibited good specificity and selectivity and was applicable to clinical use.

3.3. Calibration curves

Validation runs were conducted on three separate days. Each validation run consisted of a set of the spiked calibration standards at seven concentrations over the concentration range ($n = 5$ at each concentration) and QC samples at three concentrations ($n = 5$ at each concentration). Calibration curves ($y = ax + b$) were represented by plotting the peak area ratios (y) of the perospirone to IS versus the concentrations (x) of the calibration standards. Calibration curves were obtained from weighted ($1/x^2$) least-squares linear regression analysis of the data. The linearity was also assessed for three consecutive days for the standard solutions of the same range of concentrations prepared from the stock solutions. The regression equations for calibration curves at the range 0.10–21.1 ng/mL were $y = 0.33573x + 0.02524$ for perospirone. The correlation coefficient was 0.9997, indicating a good linearity. Standards curves were prepared daily and were checked using the QC samples (Tables 1 and 2).

3.4. Lower limit of the quantification

The LOQ was defined as the lowest concentration on the standard calibration curves with acceptable repeatability and recovery. The precision of the analyte response at the LOQ should be less than 20%. For this method, the LOQ of perospirone was 0.10 ng/mL, R.S.D. = 12% (S/N = 10).

3.5. Precision and accuracy

The precision of the method obtained by QC samples was evaluated by the inter- and intra-day assays at three different

Table 1
Individual and mean values for slope, intercepts and correlation coefficients of five calibration curves for perospirone

Analyte	Curve	Slope	Intercept	r
Perospirone	1	0.34329	0.02169	0.9998
	2	0.31006	0.01626	0.9998
	3	0.34232	0.03086	0.9997
	4	0.34204	0.02754	0.9967
	5	0.34301	0.02954	0.9996
	Mean	0.33573	0.02524	0.9997
	S.D.	0.013	0.0055	

Table 2
Validation from QC samples of human plasma extracts ($n = 5$)

Added concentration (ng/mL)	Detected concentration (ng/mL)					Mean	±S.D.	R.S.D.%
0.3165	0.336	0.336	0.340	0.301	0.296	0.322	0.021	6.64
1.055	1.033	1.045	1.010	0.936	0.980	1.001	0.044	4.38
10.55	9.421	10.242	9.716	9.417	9.100	9.579	0.430	4.49

concentrations of perospirone in the range 0.32–10.6 ng/mL. Intra-day precision was determined by repeating the analysis of standards five times in a single day, and inter-day precision and accuracy were determined by repeating analysis on three consecutive days. Sample concentrations were determined using calibration standards prepared on the same day. Assay precision was defined as the relative standard deviation (S.D.) from the mean (M), as calculated using the equation R.S.D. % = (S.D./M) × 100. Accuracy was defined as the ratio of the mean computed value (E) to the true value (T)

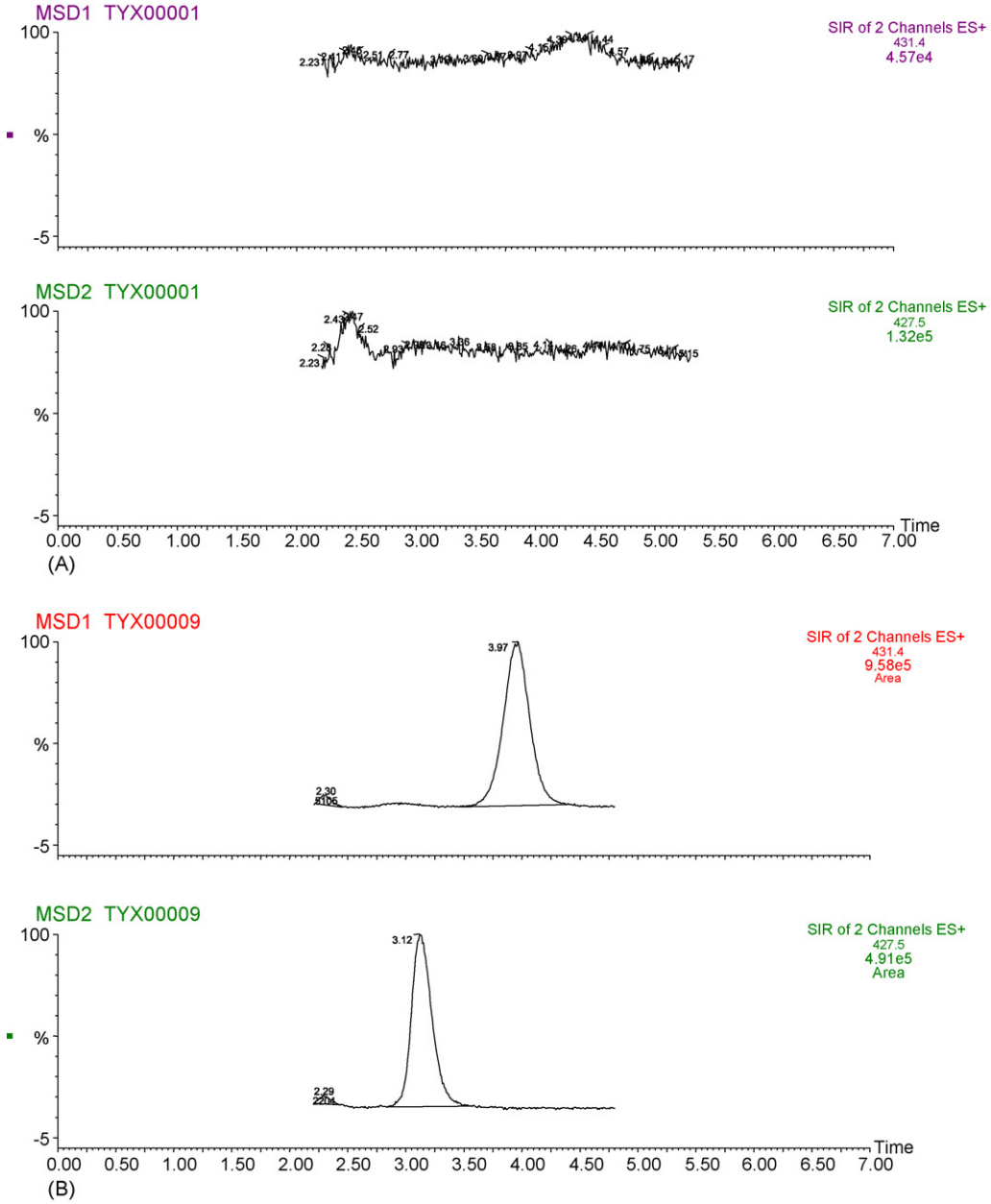

Fig. 3. LC–MS chromatograms of (A) drug-free human plasma, (B) a drug plasma spiked with perospirone (1.055 ng/ml)and amlodipine (0.956 μg/ml, IS); (C) a plasma sample from a volunteer orally administered 8 mg of perospirone hydrochloride after 3 h. Two channels were used for the quantitation, MSD1 for amlodipine (IS) and MSD2 for perospirone.

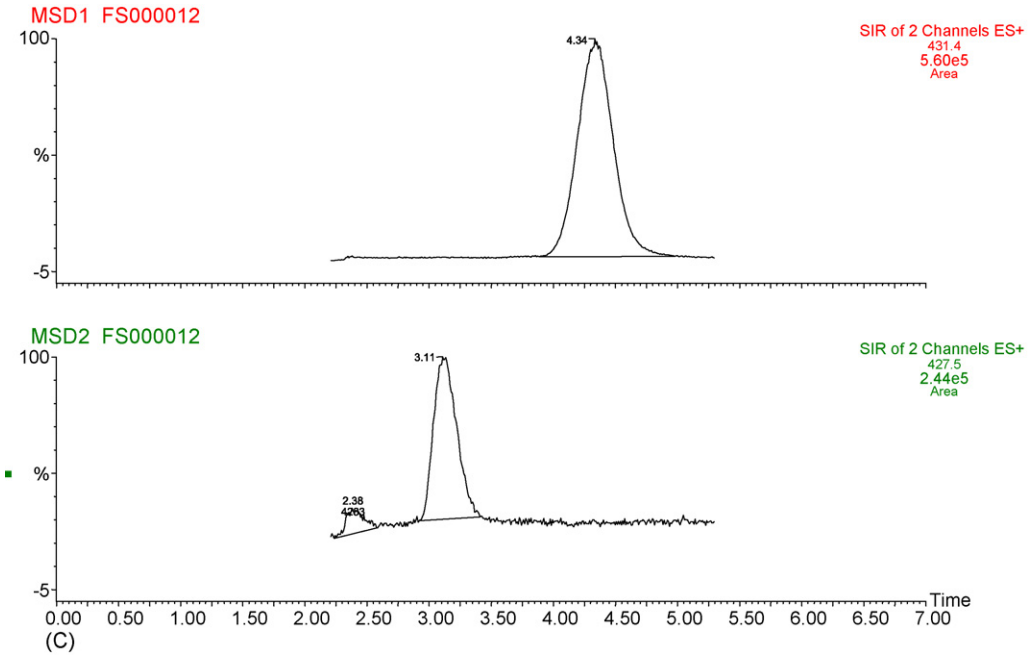

Fig. 3. (*Continued*).

expressed as a percentage (accuracy (%)). As a conclusion, the mean accuracy for perospirone was 90.8–101.7% at the concentrations at levels corresponding to the low (0.32 ng/mL), near the middle (1.06 ng/mL) and the high (10.6 ng/mL). The repeatability for intra- and inter-day was below 6.43% R.S.D., 11.9% R.S.D., respectively. As listed in Table 3, the precision and accuracy of the method met the acceptable criteria [6].

3.6. Extraction recovery

The extraction recoveries of perospirone were determined at low, medium and high concentrations by comparing the responses from QC samples spiked before extraction with standard solutions without extraction. The recovery is calculated by the formula: recovery (%) = (detector response of extracted analyte/detector response for non-extracted analyte) × 100, where detector response is the area of the chromatographic peak for extracted or non-extracted analyte divided by the area of the chromatographic peak for the internal standard added.

The extraction recoveries of perospirone from the human plasma were 85.6 ± 1.97%, 88.8 ± 0.86% and 85.5 ± 0.34% at concentration levels of 0.32, 1.06 and 10.6 ng/mL, the R.S.D. were 1.97, 0.86, 0.34% (n = 5), respectively.

Table 3
Intra- and inter-day precision and accuracy of the method for determination of perospirone in human plasma

Measurement	Added concentration (ng/mL)	Perospirone	
		Precision [a] R.S.D. (%)	Mean accuracy [b] (%) (n = 15)
Intra-day	0.3165	6.41	101.7
	1.055	6.43	94.9
	10.55	4.06	90.8
Inter-day	0.3165	11.9	96.8
	1.055	11.6	93.4
	10.55	9.20	100.4

[a] Expressed as relative standard derivation.
[b] Expressed as [(mean observed concentrations/nominal concentrations) × 100] (n = 5).

3.7. Stability

The stability experiments aimed at testing all possible conditions that the samples might be exposed to during sample shipping and handling. The stock solutions were investigated by storing under refrigeration at −40 °C and were discovered to be stable for at least 1 month with the R.S.D. below 2.0%. To evaluate perospirone stability in human plasma, drug-free plasma samples were spiked at 0.32, 1.06 and 10.6 ng/mL (QC). After extraction, samples were arranged in the autosampler at 4 °C and were analyzed. In the short-term stability study, the QC plasma samples were found to be stable for 24 h at 4 °C in the autosampler and room temperature. In the long-term stability study, the plasma samples spiked with the QC plasma samples also showed no loss of analytes when they were stored for 1 month at −40 °C. The final stability test was demonstrated after three freeze thaw cycles in 1 month. No significant deterioration of the analytes was observed under any of these conditions (Table 4).

3.8. Pharmacokinetic study

Yasui-Furukoria et al. [5] described the pharmacokinetic parameters in three schizophrenic patients receiving perospirone

Table 4
Stability data for perospirone ($n = 3$ per test and each concentration, ±S.D.)

	Added concentration (ng/mL)		
	0.3165	1.055	10.55
Long-term			
One month, −40 °C	95.5 ± 2.31	97.3 ± 2.1	96.3 ± 2.6
Short-term			
24 h, room temperature (%)	101.5 ± 1.34	102.4 ± 1.8	98.5 ± 1.5
24 h, 4 °C (%)	98.5 ± 0.78	101.6 ± 2.5	101.5 ± 1.9
Freeze/thaw stability (%)	97.4 ± 2.8	97.3 ± 2.7	102.3 ± 2.1

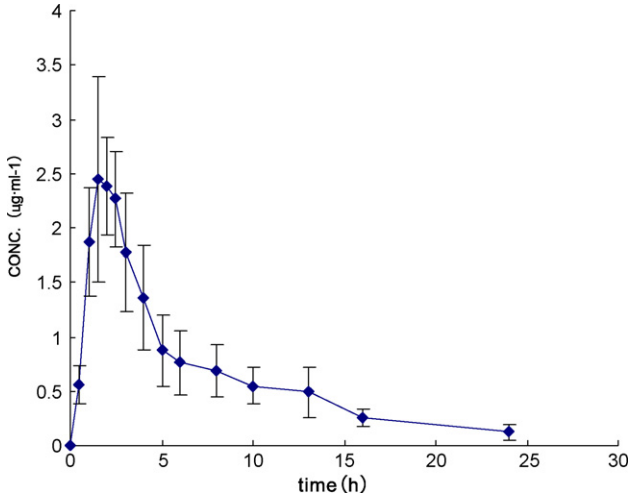

Fig. 4. Plasma concentration–time profile of perospirone hydrochloride after an oral administration of 8 mg perospirone hydrochloride to 12 healthy volunteers. Each point represents a mean ± S.D. ($n = 12$).

32 mg/day for 8 h. The developed method was successfully used for a pharmacokinetic study in which plasma concentration of perospirone in 12 healthy Chinese volunteers were determined up to 24 h after the oral administration of 8 mg perospirone hydrochloride. Plasma drug concentration/time curves are shown in Fig. 4.

By using Drug and Statistics software (Version 2.0, Chinese) analysis, the compartmental and noncompartmental analysis pharmacokinetic parameters were listed in Table 5, the pharmacokinetic characteristics of the healthy Chinese volunteers were fitted for two-compartmental mode, there are four data points

Table 5
Pharmacokinetic parameters of perospirone in 12 healthy Chinese volunteers

Compartmental parameters	Unit	Parameter value ± S.D.
$t_{1/2\beta}$	h	6.78 ± 1.38
T_{max}	h	1.79 ± 0.45
C_{max}	μg/L	2.79 ± 0.78
$V1/F$	L	4224.4 ± 2075.9
CL/F	L/h	422.99 ± 156.21
AUC_{0-24}	μg/L h	15.48 ± 4.23
$AUC_{0-\infty}$	μg/L h	17.889 ± 5.56
MRT_{0-24}	h	6.74 ± 0.81

to be used to determine terminal elimination half life and residual AUC. Moreover, the data of T_{max}, $t_{1/2\beta}$ and V/F illustrated that perospirone hydrochloride was rapidly absorbed, widely distributed and fast eliminated in healthy Chinese body.

4. Conclusions

The developed method adopted a simple preparation, offered sufficient sensitivity, satisfactory selectivity and good reproducibility and took short run time. In comparison with the reported method [5], the present LC–MS procedure not only reduced the volume of sample but also the run time and the volume of solvents, also, the internal standard is commercially available. So, it suits the pharmacokinetic study, therapeutic drug monitoring and drug abuse screening, especially in large amount samples. It was successfully applied to pharmacokinetic study of a perospirone hydrochloride tablet (8 mg) administered as a single oral dose in healthy Chinese volunteers.

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