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Quantitative determination of ondansetron in human plasma by enantioselective liquid chromatography-tandem mass spectrometry

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Abstract

A sensitive and enantioselective method was developed and validated for the determination of ondansetron enantiomers in human plasma using enantioselective liquid chromatography-tandem mass spectrometry. The enantiomers of ondansetron were extracted from plasma using ethyl acetate under alkaline conditions. HPLC separation was performed on an ovomucoid column using an isocratic mobile phase of methanol–5 mM ammonium acetate–acetic acid (20:80:0.02, v/v/v) at a flow rate of 0.40 mL/min. Acquisition of mass spectrometric data was performed in multiple reaction monitoring mode, using the transitions of *m/z* 294 → 170 for ondansetron enantiomers, and *m/z* 285 → 124 for tropisetron (internal standard). The method was linear in the concentration range of 0.10–40 ng/mL for each enantiomer using 200 μL of plasma. The lower limit of quantification (LLOQ) for each enantiomer was 0.10 ng/mL. The intra- and inter-assay precision was 3.7–11.6% and 5.6–12.3% for *R*-(−)-ondansetron and *S*-(+)-ondansetron, respectively. The accuracy was 100.4–107.1% for *R*-(−)-ondansetron and 103.3–104.9% for *S*-(+)-ondansetron. No chiral inversion was observed during the plasma storage, preparation and analysis. The method was successfully applied to characterize the pharmacokinetic profiles of ondansetron enantiomers in healthy volunteers after an intravenous infusion of 8 mg racemic ondansetron.

Keywords: Ondansetron; Enantiomers; Stereoselective pharmacokinetics; Enantioselective LC-MS/MS

1. Introduction

Ondansetron, (±)-9-methyl-3-[(2-methylimidazol-1-yl) methyl]-2,3-dihydro-1*H*-carbazol-4-one (Fig. 1A), is a highly selective and potent 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonist. It is effective in the treatment of nausea and vomiting during cancer chemotherapy and radiotherapy, and has reported anxiolytic and neuroleptic properties [1–4]. Ondansetron was the first member of 5-HT3 receptor antagonists to be marketed as a racemate mixture of the *R*-(−) and *S*-(+) enantiomers. Both enantiomers were approximately equipotent on rat vagus nerve. However, on the longitudinal smooth muscle of the Guinea-pig ileum, the potency of *R*-(−)-ondansetron was approximately eight-fold higher than that of *S*-(+)-ondansetron [5]. Also, administration of *R*-(−)-ondansetron can avoid adverse effects including headache, constipation and increases in transaminase levels, which are associated with the administration of racemic ondansetron [6].

A number of achiral methods for determination of ondansetron in biological matrix have been reported. For instance, a LC-MS/MS method was developed and validated for simultaneous determination of ondansetron and its hydroxylated metabolites in human serum [7]. Besides, several chiral methods have been reported for determination of *R*-(−)- and *S*-(+)-ondansetron in serum, including HPLC-UV using a Chiralcel OD column [8] or a Chiralcel OD-R column [9], high performance capillary electrophoresis with heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin as a mobile phase modifier [10]. Although these methods gave good chromatographic resolution of the enantiomers, they showed poor sensitivity with the lower limit of quantification (LLOQ) that ranged from 10 to 15 ng/mL. It was reported that plasma concentration of racemic ondansetron was less than 100 ng/mL after an i.v. infusion of 8 mg racemic ondansetron to healthy volunteers [11,12]. The methods mentioned above were inadequate for stereoselective pharmacokinetic study of ondansetron enantiomers.

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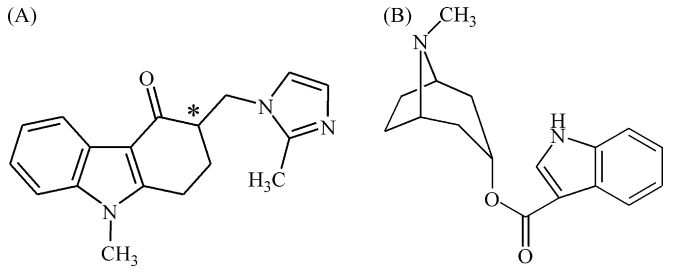

Fig. 1. Structures of ondansetron (A) and tropisetron (B). The asymmetric carbon is marked with asterisk.

To answer whether the enantiomers of ondansetron have different pharmacokinetic profiles, it is necessary to develop and validate a highly sensitive and enantioselective method for determination of the enantiomers in human plasma. In recent years, mass spectrometry as a sensitive and selective detector combined with enantioselective HPLC applications has been increasingly used in stereoselective pharmacokinetic studies [13–19]. We presented here an enantioselective LC-MS/MS method for the determination of ondansetron enantiomers and its application to a stereoselective pharmacokinetic study in humans.

2. Experimental

2.1. Chemicals and reagents

R-(−)-ondansetron hydrochloride (chemical purity 99.5%) and *S*-(+)-ondansetron hydrochloride (chemical purity 99.5%) were obtained from Hengrui Medicine Co. Ltd. (Jiangsu, China). Tropisetron hydrochloride (purity 99.9%) was obtained from Bestcomm Pharmaceutical R&D Co. Ltd. (Jinan, China). Methanol and acetonitrile of HPLC grade were purchased from Sigma (St. Louis, MO, USA). Ammonium acetate and acetic acid of HPLC grade were purchased from Tedia (Fairfeild, OH, USA). HPLC grade water was obtained from a Millipore Milli-Q Gradient Water Purification System (Molsheim, France).

2.2. Instrumentation and analytical conditions

The HPLC system consisted of a LC-20AD pump and a SIL-HT_A autosampler (Shimadzu, Kyoto, Japan). The chromatographic separation of enantiomers was performed on an Ultron ES-OVM column (150 mm × 4.6 mm, 5 μm) with an Ultron ES-OVM cartridge (10 mm × 4.0 mm, 5 μm) (Agilent, Wilmington, DE, USA). A mixture of methanol–5 mM ammonium–acetic acid (20:80:0.02, v/v/v) was used as mobile phase at a flow rate of 0.40 mL/min for isocratic elution. The column temperature was maintained at 20 °C.

Mass spectrometric detection was performed on an API 4000 triple quadrupole instrument (Applied Biosystems, Concord, Ontario, Canada) in multiple reaction monitoring (MRM) mode. A TurboIonSpray ionization (ESI) interface in positive ionization mode was used. Data processing was performed with Analyst 1.4.1 software (Applied Biosystems). For the optimization of MS/MS parameters, we made use of the auto-optimization feature of the software and standard solutions

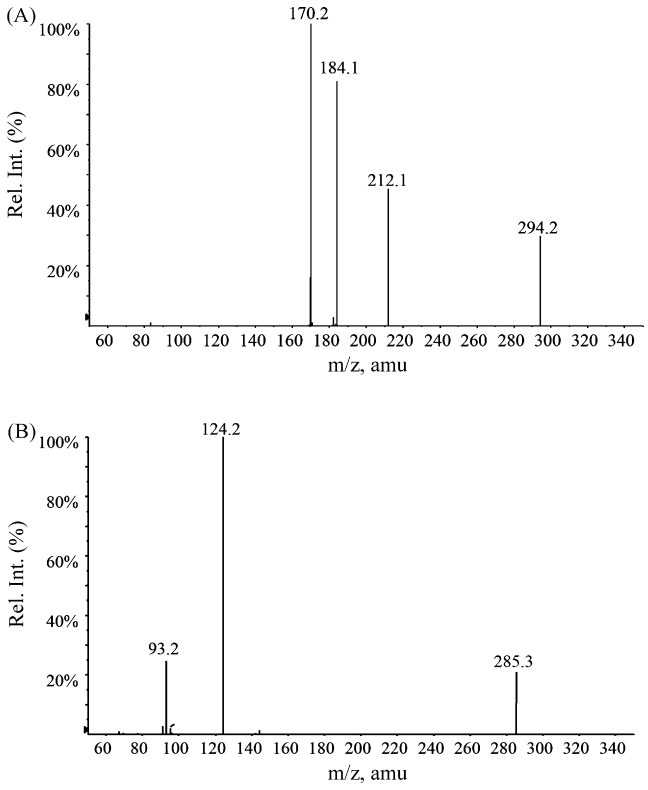

Fig. 2. Product ion spectra of $[M+H]^+$ of ondansetron (A) and tropisetron (B).

of ondansetron and tropisetron (IS) prepared in a mixture of methanol/water (50:50, v/v) were infused into the mobile phase (0.5 mL/min) at a flow rate of 20 μL/min using a syringe pump (Harvard Apparatus, Holliston, MA, USA). Finally, the instrument was operated with an ion spray voltage at +4.0 kV, heater gas temperature at 450 °C, nebulizer gas (Gas 1) of 50 psi, heater gas (Gas 2) of 60 psi, curtain gas of 10 psi and collision gas of 4 psi. Nitrogen was used as nebulizer, heater, curtain and collision activated dissociation (CAD) gas. Declustering potential (DP) was set at 70 V for both the analytes and IS. The optimized MRM fragmentation transitions (Fig. 2) were *m/z* 294 → *m/z* 170 with collision energy (CE) of 34 eV for ondansetron enantiomers, and *m/z* 285 → *m/z* 124 with CE of 34 eV for tropisetron (IS). The dwell time for each transition was 200 ms.

2.3. Preparation of calibration standards and quality control (QC) samples

Stock solutions of *R*-(−)-ondansetron or *S*-(+)-ondansetron at a concentration of 400 μg/mL were prepared by dissolving the accurately weighed reference substance of each enantiomer in methanol. A standard working stock solution containing 4.00 μg/mL of each enantiomer was prepared by appropriate mixing of the two 400 μg/mL stock solutions and then dilution with methanol. Standard working stock solution was then serially diluted with methanol/water (50:50, v/v) to give working solutions at the concentrations of 0.40, 1.2, 2.4, 8.0, 32.0, 80.0 and 160 ng/mL for each enantiomer. The quality control (QC) solutions were similarly prepared at concentrations of 0.30, 2.0 and 36 ng/mL, by separate weighing of the reference

substances. A 100 ng/mL solution of the IS was also prepared by diluting the 400 μg/mL stock solution of tropisetron with methanol/water (50:50, v/v). All the solutions were kept at 4 °C and were brought to room temperature before use. Both the calibration standard samples and the quality control samples were prepared by spiking 200 μL blank plasma with 50 μL working solutions correspondingly.

2.4. Sample preparation

A 50 μL aliquot of the IS solution (tropisetron, 100 ng/mL), 50 μL of methanol/water (50:50, v/v) and 100 μL of 0.1 M NaOH solution were added to 200 μL of plasma samples. The sample was vortex-mixed and extracted with 3 mL of ethyl acetate by shaking for 10 min. The organic and aqueous phases were separated by centrifugation at 2000 × *g* for 5 min. The upper organic phase was transferred to another tube and evaporated to dryness at 40 °C under a stream of nitrogen in the TurboVap evaporator (Zymark, Hopkinton, MA, USA). The residue was reconstituted in 150 μL of the mobile phase and vortex-mixed for 1 min. A 20 μL aliquot of the reconstituted extract was injected for the enantioselective LC-MS/MS analysis.

2.5. Method validation

To evaluate linearity, calibration curves with seven levels covering the range 0.10–40 ng/mL of each enantiomer were prepared and analyzed in duplicates on three consecutive days. The curves were fitted by a weighted ($1/x^2$) least squares linear regression method through the measurement of the peak-area ratio of each analyte to IS.

QC samples at three concentration levels (0.30, 2.00 and 36.0 ng/mL for each enantiomer) were analyzed to assess the accuracy and precision of the method. These samples were extracted in six replicates on three consecutive days. The accuracy and precision were calculated using one-way ANOVA. The accuracy was expressed by relative error (R.E.) and the precision by relative standard deviation (R.S.D.). The accuracy was required to be within ±15%, and the intra- and inter-day precisions not to exceed 15%.

To assess the accuracy and precision of the method to at various ondansetron enantiomeric ratios, ondansetron enantiomers were combined to obtain three mixtures of known enantiomeric ratios at 2:1, 3:1 and 1:2 (*R*/*S*), containing *R*-(−)-ondansetron and *S*-(+)-ondansetron at total concentration of 12.0 ng/mL. The mixed standard solutions were spiked to the blank plasma (total ondansetron plasma concentration of 3.00 ng/mL) and were analyzed with the enantioselective LC-MS/MS system in six replicates on three consecutive days.

The LLOQ defined as the lowest concentration at which both precision and accuracy were less than or equal to 20%, was evaluated by analyzing samples which were prepared in six replicates in three different batches.

The extraction recoveries of ondansetron enantiomers at three QC levels ($n = 6$) were determined by comparing peak-area ratios of the analytes to IS in samples that were spiked with the analytes prior to extraction with samples to which the analytes were added post-extraction. The IS was added to the two sets of samples post-extraction. The extraction recovery of the IS was determined in a similar way using the QC samples at medium concentration as a reference.

To evaluate the matrix effect, six different lots of blank plasma were extracted and then spiked with each enantiomer at 2.00 ng/mL. The corresponding peak areas of the analytes in spiked plasma post-extraction (*A*) were then compared to those of the solution standards in mobile phase (*B*) at equivalent concentrations. The ratio ($A/B \times 100$) is defined as the absolute matrix effect (ME). The assessment of the relative ME was made by a direct comparison of the analyte peak-area values between different lots of plasma. The variability in the values, expressed as R.S.D. (%), is a measure of the relative ME for the target analyte. The same evaluation was performed for the IS.

The stabilities of ondansetron enantiomers in human plasma were evaluated by analyzing replicates ($n = 3$) of plasma samples at the concentrations of 2.0 and 36 ng/mL (each enantiomer), which were exposed to different conditions (time and temperature). These results were compared with those obtained for freshly prepared plasma samples. The analytes were considered stable in the biological matrix when 85–115% of the initial concentrations were found. The short-term stability was determined after the exposure of the spiked samples at 24 °C for 2 h, and the ready-to-inject samples (after extraction) to the autosampler rack (24 °C) for 24 h. The freeze/thaw stability was evaluated after three complete freeze/thaw cycles on consecutive days. The long-term stability was assessed after storage of the standard spiked plasma samples at −20 °C for 60 days.

To evaluate the enantiometic stability of *R*-(−)-ondansetron or *S*-(+)-ondansetron in human plasma, plasma samples at concentration of 40.0 ng/mL (each enantiomer) were incubated in triplicate for 16 h at 37 °C, then extracted and analyzed as described.

2.6. Stereoselective pharmacokinetic studies

Four healthy male Chinese volunteers who provided written informed consent took part in the study. The study was approved by the Ethics Committee. Venous blood samples of about 5 mL were collected in heparin-containing tubes pre-dose (0 h) and 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 14 and 24 h after an i.v. infusion of 8 mg racemic ondansetron (Zofran®, GlaxoSmithKline S.p.A, Polo Di Torrile, Italy) in 50 mL of normal saline in 15 min. Plasma samples were obtained by centrifugation at 2000 × *g* for 10 min and were frozen at −20 °C until analysis.

3. Results and discussion

3.1. Enantioselective chromatographic conditions

To resolve ondansetron enantiomers, three types of chiral stationary phase columns were tried in the experiment, including Chirobiotic V2 250 mm × 4.6 mm, Chiral-AGP 150 mm × 4.0 mm and Ultron ES-OVM 150 mm × 4.6 mm. Poor resolution and long retention time (>25 min) for

Table 1
Effect of proportion of organic modifier acetonitrile in the mobile phase on chromatographic resolution of ondansetron enantiomers

Proportion of acetonitrile (%)	Flow rate (mL/min)	Resolution (R_s)	Retention time (min)
2.5	1.0	1.99	10.6, 12.7
5	1.0	1.61	7.8, 9.6
8	0.50	1.39	8.3, 9.5
10	0.30	1.10	10.2, 11.0

ondansetron enantiomers were observed on Chirobiotic V2 and Chiral-AGP Column, although a various percentage of acetonitrile, methanol, isopropanol and acid/base modifier were tested. Baseline separation of the two enantiomers within 20 min was only achieved on Ultron ES-OVM column, using a mobile phase of acetonitrile, water and acetic acid (2.5:97.5:0.0025, v/v/v). However, one problem when coupling protein-based columns to ESI-MS, is that the interface usually requires a high concentration of organic modifier to obtain a good spray which is associated with the sensitivity. The protein-based stationary phases, however, works best in an aqueous environment and can only tolerate moderate amounts of organics [13,19]. The optimized mobile phase for Ultron ES-OVM column was not suitable to LC-MS/MS due to the low proportion of organic phase. Therefore, further optimization for the mobile phase system was performed. Firstly, when the percentage of organic modifier acetonitrile remained unchanged at 2.5% and 5 mM ammonium acetate containing 0.025% acetic acid was used as aqueous phase instead of 0.0025% acetic acid water, resolution of ondansetron enantiomers was increased from 1.50 to 1.99. Consequently, ammonium acetate buffer can achieve better enantiomeric separation by increasing the peak efficiencies and was used preferably to acetic acid water in the subsequent experiment. In order to make the mobile phase suitable for LC-MS/MS, the possibility of using higher proportion of organic component acetonitrile was attempted. However, it was found that as the proportion of acetonitrile increased from 2.5% to 10%, the chromatographic separation (R_s) of the enantiomers significantly decreased from 1.99 to 1.10 (Table 1). Secondly, the organic modifier was changed from acetonitrile to methanol. Using 10% of methanol, resolution of the enantiomers was 1.87, with the retention time of 13.2 min for *R*-(−)-ondansetron and 15.5 min for *S*-(+)-ondansetron at the flow rate of 1.0 mL/min. Furthermore, it was attempted that the percentage of methanol was increased and the flow rate of the mobile phase was decreased, which was favorable to electrospray ionization MS/MS analysis. As the proportion of methanol was increased to 20%, an acceptable chromatographic separation (R_s = 1.37) of the enantiomers was achieved with the retention time of 8.1 min for *R*-(−)-ondansetron and 9.6 min for *S*-(+)-ondansetron at the flow rate of 0.40 mL/min. Finally, all the subsequent plasma analyses were thus run with the mobile phase consisting of methanol–5 mM ammonium acetate–acetic acid (20:80:0.02, v/v/v), among which a small amount of acetic acid in the mobile phase was necessary to separate ondansetron enantiomers and increase the sensitivity of ondansetron in MS/MS detector.

Tropisetron, an achiral analog of ondansetron, was chosen as the internal standard. It produced good peak shape and suitable retention time (4.9 min) on the Ultron ES-OVM column.

3.2. Method validation

3.2.1. Assay selectivity

Selectivity was assessed by comparing the chromatograms of six different batches of blank human plasma with the corresponding spiked plasma. Fig. 3 shows the typical chromatograms of a blank plasma sample, blank plasma sample spiked with *R*-(−)-ondansetron and *S*-(+)-ondansetron at the LLOQ and IS, and a plasma sample obtained 2 h after intravenous infusion of 8 mg racemic ondansetron to a healthy volunteer. No significant interference from endogenous substances was observed at the retention times of the analyte and IS.

3.2.2. Linearity and LLOQ

The calculated peak-area ratios of ondansetron enantiomers to the IS versus the concentrations displayed a good linear relationship over the concentration range from 0.10 to 40 ng/mL (each enantiomer) in human plasma. The mean (±S.D.) regression equation from replicate calibration curves on different days was:

$$R\text{-}(-)\text{ondansetron}: y = (0.0350 \pm 0.000656)x + (0.000228 \pm 0.000566)r = 0.9970$$

$$S\text{-}(+)\text{ondansetron}: y = (0.0357 \pm 0.00115)x - (0.000124 \pm 0.000620)r = 0.9973$$

where y represents the peak-area ratio of each analyte to IS and x represents the plasma concentration of each enantiomer.

The lower limit of quantification was 0.10 ng/mL for determination of ondansetron enantiomers in plasma. The intra- and inter-day precision and accuracy at the concentration of LLOQ are shown in Table 2. The precision and accuracy at this concentration level were acceptable, with R.S.D. values below 16.5% and R.E. values within ±5.4%.

3.2.3. Precision and accuracy

Table 2 also summarizes the intra- and inter-day precision and accuracy for ondansetron enantiomers from QC samples. The intra- and inter-day precision were <9.8% and <11.6%, for *R*-(−)-ondansetron, respectively; <6.3% and <12.3% for *S*-(+)-ondansetron, respectively. The accuracy ranged from 0.4% to 7.1% (R.E.) for *R*-(−)-ondansetron and from 3.3% to 4.9% for *S*-(+)-ondansetron.

The precision and accuracy for ondansetron enantiomeric ratios are presented in Table 3. The intra- and inter-day precision were <5.0% and 6.5%. The accuracy ranged from −0.5% to −3.5% (R.E.). Fig. 4 shows the typical chromatograms of *R*-(−)-ondansetron and S-(+)-ondansetron from different enantiomeric ratios QC samples at total ondansetron plasma concentration of 3.0 ng/mL.

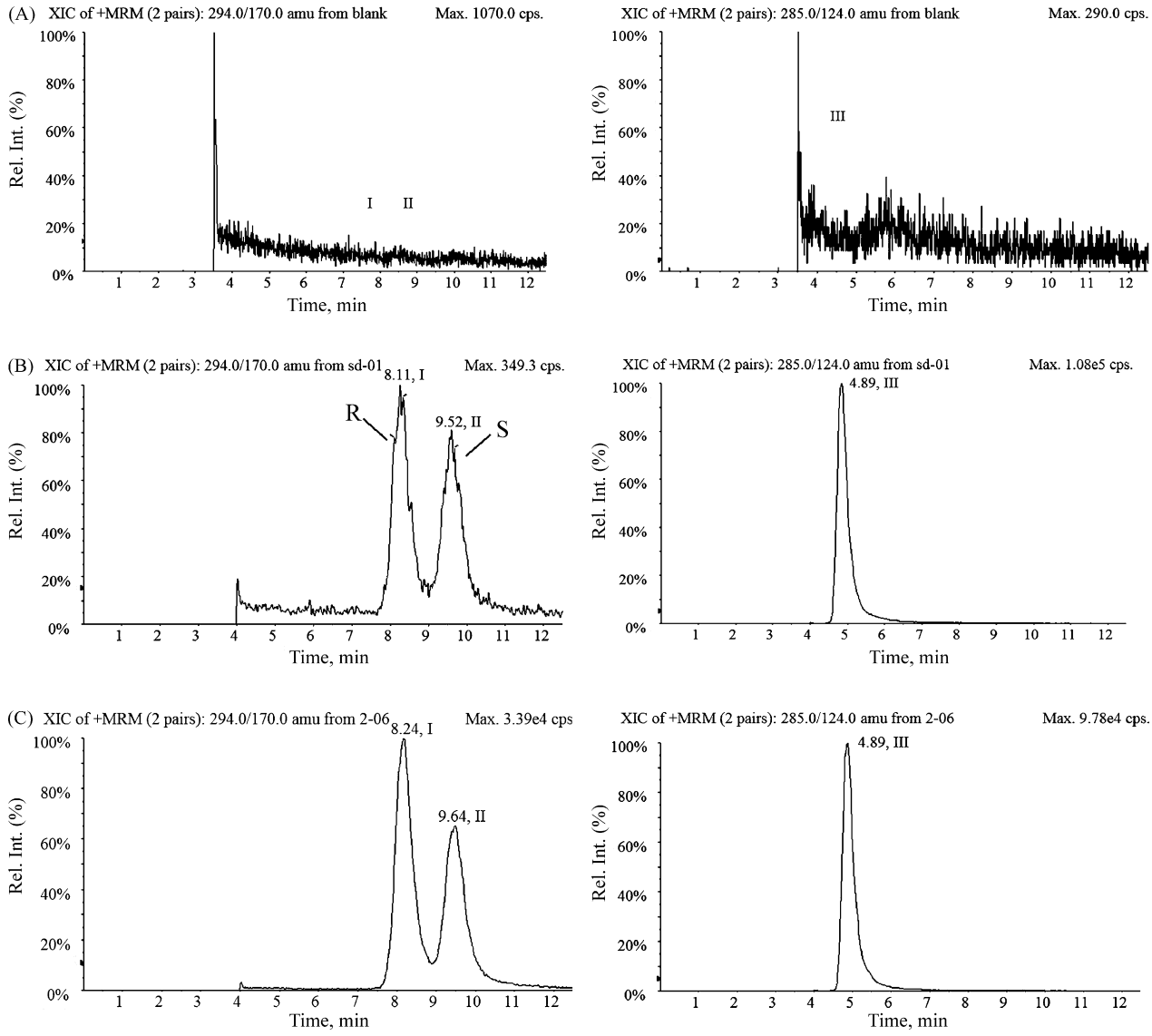

Fig. 3. Typical chromatograms of *R*-(−)-ondansetron, *S*-(+)-ondansetron and tropisetron (IS) in human plasma by multiple reaction monitoring scan mode. (A) Blank plasma sample, (B) plasma spiked with 0.1 ng/mL *R*-(−)-ondansetron, 0.1 ng/mL *S*-(+)-ondansetron and 25 ng/mL IS and (C) plasma sample 2 h after intravenous infusion of 8 mg racemic ondansetron to a healthy volunteer. Peaks I–III refer to *R*-(−)-ondansetron, *S*-(+)-ondansetron and IS, respectively.

Table 2
Precision and accuracy of the chiral LC-MS/MS method to determine ondansetron enantiomers in human plasma (in pre-study validation, $n = 3$ days, six replicates per day)

Analyte	Concentration (ng/mL)		R.S.D. (%)		Relative error (%)
	Added	Found	Intra-day	Inter-day	
R-(−)-ondansetron	0.100 (LLOQ)	0.0946	8.0	16.5	−5.4
	0.300 (L)	0.321	6.3	8.9	7.1
	2.00 (M)	2.11	3.7	11.6	5.4
	36.0 (H)	36.1	9.8	9.3	0.4
S-(+)-ondansetron	0.100 (LLOQ)	0.0981	5.4	11.4	−2.0
	0.300 (L)	0.315	5.6	11.7	4.9
	2.00 (M)	2.07	6.3	12.3	3.3
	36.0 (H)	37.6	6.0	11.6	4.5

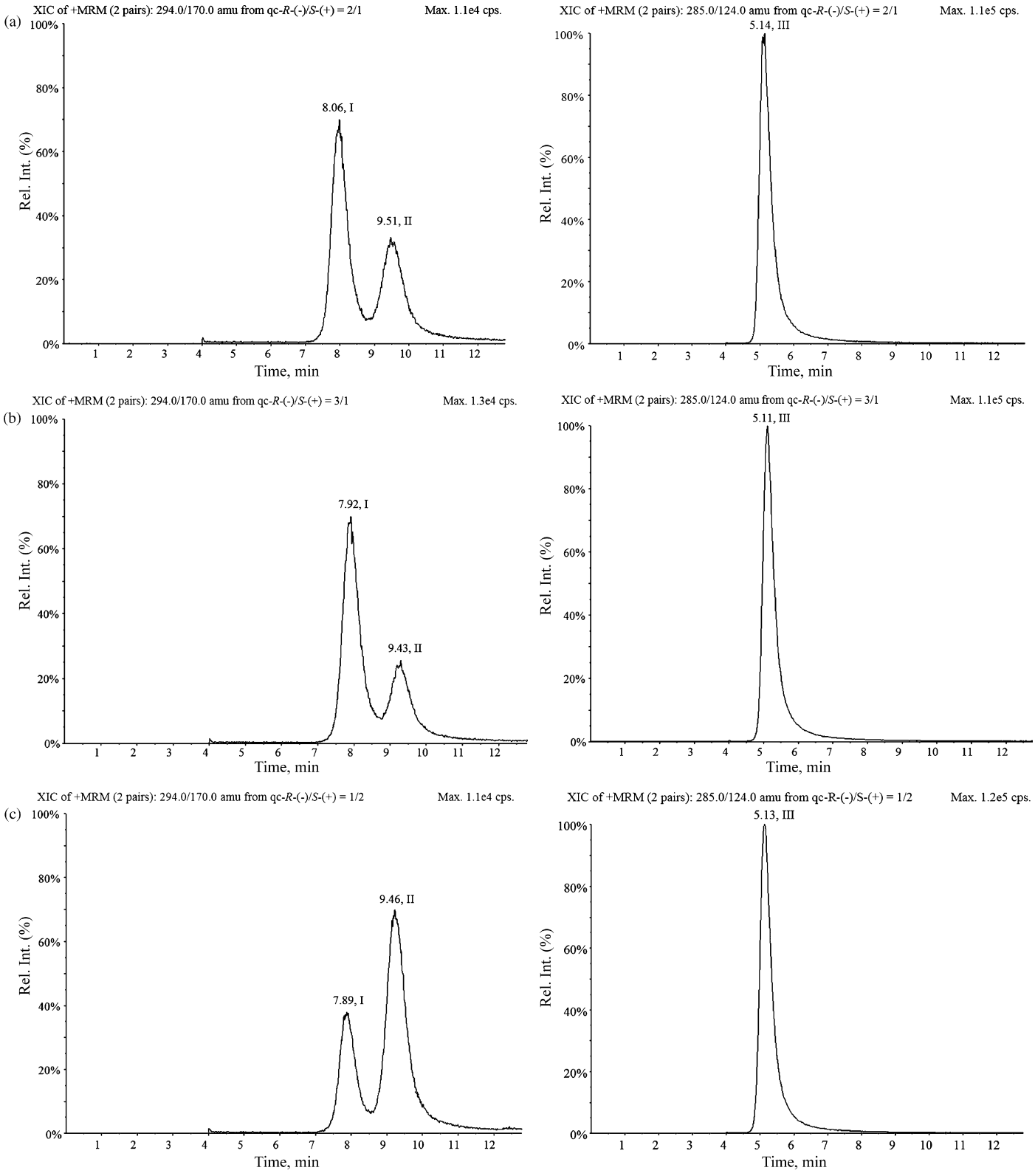

Fig. 4. Typical chromatograms of *R*-(−)-ondansetron and S-(+)-ondansetron from different enantiomeric ratios. (A) *R*-(−)/*S*-(+) = 2/1, (B) *R*-(−)/*S*-(+) = 3/1 and (C) *R*-(−)/*S*-(+) = 1/2. Peaks I–III refer to *R*-(−)-ondansetron, *S*-(+)-ondansetron and IS, respectively.

3.2.4. Extraction recovery and matrix effect

Mean extraction recoveries of *R*-(−)-ondansetron were 81.6 ± 2.8%, 80.3 ± 4.9% and 82.7% ± 3.6% at the concentrations of 0.30, 2.00 and 36.0 ng/mL, respectively. The recoveries of *S*-(+)-ondansetron were 83.1 ± 5.4%, 78.4% ± 4.1% and 84.5 ± 3.3% at the concentrations of 0.30, 2.00 and 36.0 ng/mL, respectively. The recovery of IS (25 ng/mL) was 82.5% ± 5.7%. Matrix effect of *R*-(−)-ondansetron and *S*-(+)-ondansetron at

Table 3
Precision and accuracy of the chiral LC-MS/MS method to determine ondansetron enantiomeric ratios in human plasma (total plasma concentration at 3.00 ng/mL, $n = 3$ days, six replicates per day)

R-(−)/*S*-(+) ratios		R.S.D. (%)		Relative error (%)
Added	Found	Intra-day	Inter-day	
2.00	1.96	4.8	4.6	−2.2
3.00	2.89	5.0	6.5	−3.5
0.500	0.498	3.4	4.1	−0.5

2.0 ng/mL was 98.3% and 103.3%, respectively. The relative matrix effect of *R*-(−)-ondansetron and *S*-(+)-ondansetron at 2.0 ng/mL was 8.9% and 12.3%, respectively. Obviously, ion suppression or enhancement from plasma matrix was negligible in present conditions.

3.2.5. Stability

The enantiomers were found to be stable in following conditions: in plasma at 24 °C for 2 h, in the mobile phase at 24 °C for 24 h, three freeze/thaw cycles, or in plasma at −20 °C for 60 days. All R.E. values between post-storage and initial QC samples were within ±15%. The peak of another enantiomer was not observed after incubation of plasma samples containing one enantiomer at 37 °C for 16 h, which is shown in Fig. 5. As a result, no chiral inversion was observed between *R*-(−)-ondansetron and *S*-(+)-ondansetron during the storage, processing and analysis.

3.3. Method application

Due to the poor sensitivity of the existing analytical methods [8–10], there was no report on the stereoselective pharmacokinetics study of ondansetron enantiomers in humans. The present enantioselective LC-MS/MS method provided the LLOQ down to 0.10 ng/mL for each enantiomer which satisfied the demand of evaluating stereoselective pharmacokinetics of ondansetron. Under the present LLOQ, the ondansetron enantiomers concentration could be determined in plasma samples up to 24 h after a single intravenous infusion of 8 mg racemic ondansetron. After an i.v. administration of 8 mg racemic ondansetron to four healthy male volunteers, profiles of the mean plasma concentration of ondansetron enantiomers versus time are shown in Fig. 6. The concentrations of *R*-(−)-ondansetron were higher than those of *S*-(+)-ondansetron at all complying times, with a mean ratio of *R*-(−)- to *S*-(+)-ondansetron of 1.19.

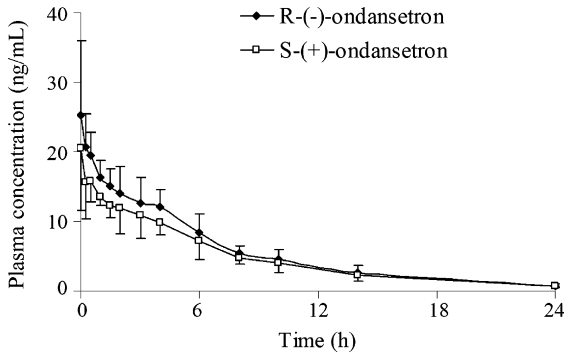

Fig. 6. Mean plasma concentration curve of *R*-(−)-ondansetron and *S*-(+)-ondansetron after intravenous infusion of 8 mg racemic ondansetron to four healthy volunteers.

4. Conclusions

A highly sensitive and enantioselective method was developed and validated to determine ondansetron enantiomers in human plasma by combining separation via a chiral stationary phase column with tandem mass spectrometry. The lower limit of quantification was 0.10 ng/mL for *R*-(−)-ondansetron and *S*-(+)-ondansetron using a 0.2 mL aliquot of the plasma sample. This method was successfully applied to characterize the pharmacokinetic profiles of ondansetron enantiomers in healthy volunteers after an intravenous infusion of 8 mg racemic ondansetron. It was found that the concentration of *R*-(−)-ondansetron was higher than that of *S*-(+)-ondansetron at all time

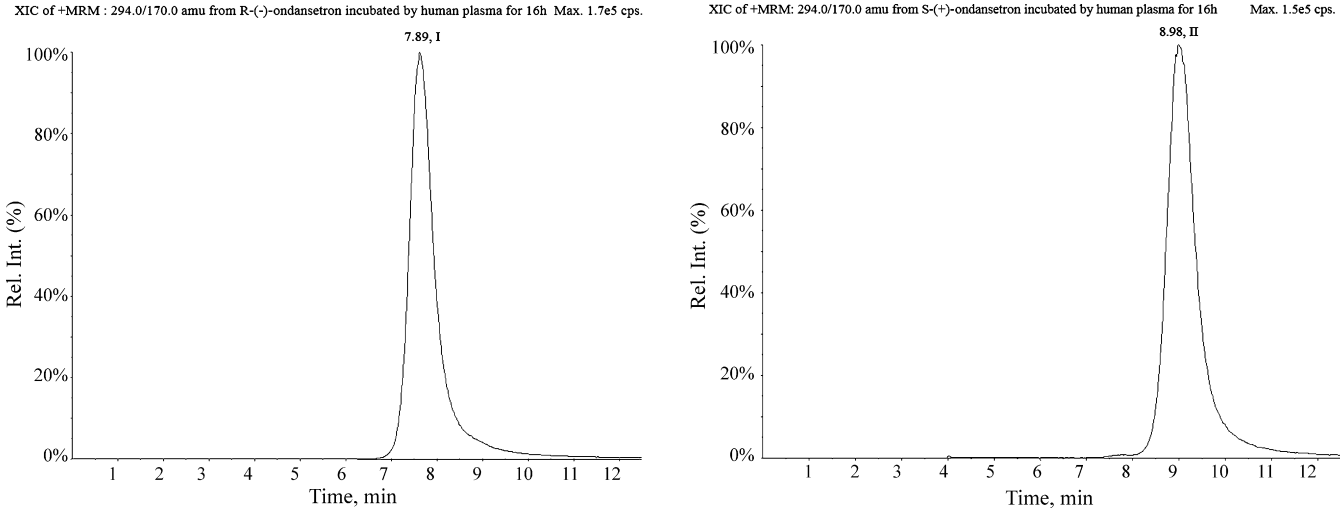

Fig. 5. Typical chromatograms of *R*-(−)-ondansetron and *S*-(+)-ondansetron in human plasma incubated at 37 °C for 16 h at plasma concentration of 40.0 ng/mL. Peaks I and II refer to *R*-(−)-ondansetron and *S*-(+)-ondansetron, respectively.

points, implying the stereoselective disposition of ondansetron enantiomers.

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