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ORIGINAL RESEARCH

Rapid quantification of lisinopril in human plasma by liquid chromatography/tandem mass spectrometry

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ABSTRACT: An assay based on protein precipitation and liquid chromatography/tandem mass spectrometry (LC-MS/MS) has been developed and validated for the quantitative analysis of lisinopril in human plasma. After the addition of enalaprilat as internal standard (IS), plasma samples were prepared by one-step protein precipitation using perchloric acid followed by an isocratic elution with 10 mM ammonium acetate buffer (pH adjusted to 5.0 with acetic acid)–methanol (70:30, v/v) on a Phenomenex Luna 5μC_{18} (2) column. Detection was performed on a triple-quadrupole mass spectrometer utilizing an electrospray ionization (ESI) interface operating in positive ion and selected reaction monitoring (SRM) mode with the precursor to product ion transitions m/z 406→246 for lisinopril and m/z 349→206 for enalaprilat. Calibration curves of lisinopril in human plasma were linear (r = 0.9973–0.9998) over the concentration range 2–200 ng/mL with acceptable accuracy and precision. The limit of detection and lower limit of quantification in human plasma were 1 and 2 ng/mL, respectively. The validated LC-MS/MS method has been successfully applied to a preliminary pharmacokinetic study of lisinopril in Chinese healthy male volunteers. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: lisinopril; LC-MS/MS; pharmacokinetics

INTRODUCTION

Lisinopril, Fig. 1 (A), a long-acting angiotensin-converting enzyme inhibitor, is an effective treatment with hypertension, congestive heart failure and acute myocardial infarction and has shown promising benefits in patients with diabetic nephropathy (Langtry and Markham, 1997). Following oral administration, lisinopril is absorbed by the gut and eliminated primarily by the kidneys without metabolism. Thus its bioavailability shows large inter-subject variability and therapeutic doses effective in lowering blood pressure range from 10 to 80 mg per day (Noble and Murray, 1988). Therefore, in order to lower the risks of dosage-related side effects, dosages usually need to be adjusted in elderly patients or in patients with significant renal impairment (Langtry and Markham, 1997). For this reason a simple and sensitive method for the rapid determination of plasma concentration of lisinopril for therapeutic drug monitoring (TDM) may be useful in assessing compliance and evaluating risks of toxicity.

Different methods have been reported for the quantification of lisinopril in biological fluids. These methods are based on high-performance liquid chromatography (HPLC) with ultraviolet (UV) or fluorescence (F) or mass spectrometric (MS) detection; and gas chromatography (GC) with mass spectrometric (MS) detection. The HPLC-UV (Wong and Charles, 1995) method is unsuitable for the measurement of lisinopril in plasma where the drug concentrations are rather low. The HPLC-F (Sagirli and Ersoy, 2004; El-Amam *et al.*, 2004) and GC-MS (Leis *et al.*, 1998, 1999) methods require derivatization of lisinopril to produce a chromophore detectable by fluorescence or to covert the thermo labile and ionic lisinopril into a derivative that is suitable for gas chromatography analysis. Although the HPLC-MS (Tsakalof *et al.*, 2003) was successfully applied to the determination of lisinopril in human plasma, the lower limit of quantification (LLOQ) in plasma of the method was 6 ng/mL, which was insufficiently sensitive to enable full pharmacokinetic profiling of lisinopril in low dosages.

Nowadays, LC-MS/MS becomes more and more common in quantification of drug in biological matrices

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Abbreviations used: ESI, electrospray ionization; IS, internal standard; PPT, protein precipitation; TDM, therapeutic drug monitoring.

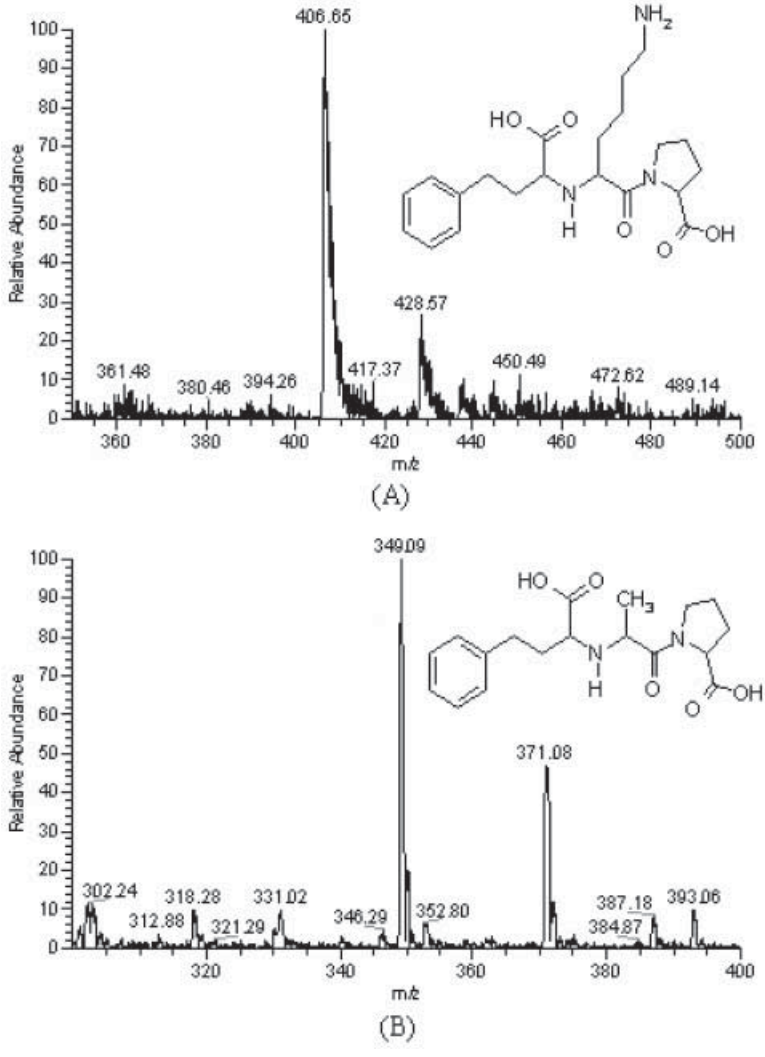

Figure 1. Full-scan ESI (+) precursor ion mass spectra of (A) lisinopril and (B) the IS and their chemical structures.

owing to its high sensitivity and selectivity. Padua *et al.* (2004) reported an LC-MS/MS method for the quantification of lisinopril in human plasma using solid-phase extraction (SPE) in sample preparation, which requires considerable time and work. Kousoulos *et al.* (2005) improved their method by utilizing 96-well format solid-phase extraction protocol to save time. However, this does not mean that the sample preparation procedure of this method is automated because samples need to be pretreated initially with manual processes that include tedious steps of precipitation, evaporation and reconstitution. Recently, based on laborious liquid–liquid extraction, Huang *et al.* (2006) developed an LC-MS/MS method for the quantification of lisinopril in human plasma employing pseudoephedrine hydrochloride as internal standard (IS).

The proposed assay focuses on exploring the high selectivity and sensitivity of triple quadrupole MS system with an electrospray interface for the development and validation of a robust reversed phase LC-MS/MS method in SRM mode for the quantification of lisinopril in human plasma employing its structural analog, enalaprilat [Fig. 1(B)], as internal standard. The sample preparation of this method involved a simple protein precipitation without time-consuming steps of derivatization and evaporation–concentration. In short, simplicity, rapidity, selectivity and sensitivity, the main advantages of the validated method presented in this paper, make it an attractive procedure in high-throughput bioanalysis of lisinopril.

EXPERIMENTAL

Chemicals. Lisinopril reference standard (batch no. 5122-03-001, 99.6% purity) and lisinopril tablets (batch no. 051013) were obtained from Jiangsu Enhua Saide Pharmaceutical Co. Ltd (Jiangsu, China). Enalaprilat reference standard (IS,

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99.1% purity) was supplied by Jiangsu Institute for Drug Control (Nanjing, China). Methanol (HPLC grade) was purchased from VWR International Company (Darmstadt, Germany). Acetic acid and ammonium acetate (analytical reagent) were purchased from Nanjing Chemical Reagent No. 1 Factory. Perchloric acid (analytical reagent) was purchased from Jinlu Chemical Reagent Co. Ltd. Other chemicals were all of analytical grade. Water was distillated twice before use.

Preparation of stock and working solutions. Standard stock solutions of lisinopril (1 mg/mL) and enalaprilat (IS, 1 mg/mL) were prepared separately by dissolving appropriate amounts in 10 mL water–methanol (70:30, v/v), respectively. Working solutions of lisinopril for calibration and quality control (QC) were prepared by appropriate dilution in water–methanol (70:30, v/v) to the final concentrations of 0.1, 1 and 10 μg/mL. The stock solution of enalaprilat was further diluted with water–methanol (70:30, v/v) to prepare the working internal standard solution containing 1 μg/mL of enalaprilat. Working solutions were prepared daily and stock solutions were stored at 4°C.

LC-MS/MS conditions. Liquid chromatographic separation and mass spectrometric detection were achieved by employing the Finnigan™ TSQ Quantum Discovery MAX™ LC-MS/MS system consisted of a Finnigan Surveyor LC pump, a Finnigan Surveyor auto-sampler and combined with a triple quadrupole TSQ Quantum mass spectrometer (Thermo Electron Corporation). The chromatography was on a Phenomenex Luna 5μC_{18} (2) (150 × 4.6 mm, 5 μm) analytical column at 40°C. The isocratic mobile phase composition was a mixture of 10 mM ammonium acetate buffer (pH adjusted to 5.0 with acetic acid)–methanol (70:30, v/v), which was pumped at a flow rate of 1.0 mL/min with a split ratio of 1:5.

The tandem MS system is equipped with an ESI source, and run with the Xcalibur 2.0 software (Thermo Electron Corporation). Tuning of the instrument was done by continuous infusion of lisinopril (1 μg/mL) with a TSQ Quantum electronically controlled integrated syringe and the TSQ Quantum Tune program. The mass spectrometer was operated in positive ion and SRM mode with precursor to product qualifier transition *m*/*z* 406→246 for lisinopril and *m*/*z* 349→206 for enalaprilat. Spray voltage was optimized at 4000 V, transfer capillary temperature at 300°C, sheath gas and auxiliary gas (nitrogen) pressure at 30 and 5 arbitrary unites (set by the LCQ software, Thermo Electron Corporation) respectively. Argon was used as collision gas at a pressure of 1.0 mTorr and collision energy was 20 V for both lisinopril and enalaprilat. The scan width for SRM was 0.01 *m*/*z* and scan time was 0.3 s. The peak width settings (FWHM) for both Q1 and Q3 were 0.7 *m*/*z*.

Sample preparation. Sample preparation involved a single step of protein precipitation with 10% perchloric acid aqueous solution. Aliquots (500 μL) of human plasma were pipetted into 5 mL plastics centrifuge tubes with addition of IS working solution (5 μL × 1 μg/mL) and 200 μL 10% perchloric acid aqueous solution. The samples were vortex mixed for 2 min and centrifuged at 1300***g*** for 10 min. The upper layer was transferred into 1.5 mL plastics centrifuge tubes and centrifuged at 13,800***g*** for 8 min. Only 10 μL aliquots of the supernatant were injected into the LC-MS/MS system.

Bioanalytical method validation. The method validation assays were carried out according to the United States Food and Drug Administration (FDA) bioanalytical method validation guidance (Food and Drug Administration, 2001).

Calibration curves were prepared on five different days by spiking blank plasma with proper volume of one of the working solutions mentioned above to produce the standard curve points equivalent to 2, 5, 10, 20, 50, 100 and 200 ng/mL of lisinopril. The following assay procedures were the same as that described above. In each run, a blank plasma sample (processed without the IS) was analyzed to confirm absence of interferences but not used to construct the calibration function. Calibration curves were generated by using the ratios of the analyte peak area to the IS peak area vs concentration and were fitted to the equation $y = bx + a$ by weighted least-squares linearity regression. Quality control (QC) samples were prepared by spiking blank plasma with proper volume of one of the working solution mentioned above to produce a final concentration equivalent to 5 ng/mL (low level), 20 ng/mL (medium level) and 100 ng/mL (high level) of lisinopril. The following procedures were the same as that described above. The limit of detection (LOD) and the lower limit of quantification (LLOQ) were determined as the concentrations with a signal-to-noise ratio of 3 and 10, respectively. Each back-calculated concentration standard should meet the following acceptable criteria: no more than 20% deviation at LLOQ and no more than 15% deviation above LLOQ.

Blank plasma samples of healthy human used for testing the specificity of the method were obtained from six different sources. The visible interferences were tested with blank plasma samples and plasma samples with lisinopril concentrations close to the lower limit of quantification (LLOQ). The potential matrix effect on the ionization of the analyte was evaluated by comparing the peak area of the analyte dissolved in the supernatant of the processed blank plasma with that of standard solutions at the same concentration. Three different concentration levels of lisinopril (5, 20 and 100 ng/mL) were evaluated by analyzing five samples at each set. The matrix effect of internal standard (10 ng/mL in plasma) was evaluated using the same method.

The intra-batch precision and accuracy was determined by analyzing five sets of spiked plasma samples of lisinopril at each QC level (5, 20 and 100 ng/mL) in a batch. The inter-batch precision and accuracy was determined by analyzing five sets of spiked plasma samples of lisinopril at each QC level (5, 20 and 100 ng/mL) in three consecutive batches. The concentration of each sample was calculated using standard curve prepared and analyzed on the same day.

The absolute extraction recovery of lisinopril was assessed by comparing lisinopril to the IS peak area ratios obtained from extracted plasma samples with those from the standard solutions at the same concentration. This procedure was repeated ($n = 5$) at each QC level (5, 20 and 100 ng/mL). Similarly, the absolute recovery of the IS was assessed by comparing the IS mean peak areas obtained from extracted QC plasma samples ($n = 5$) with those from the standard solutions at the concentration of 10 ng/mL.

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The short-term stability of lisinopril was assessed by determining QC plasma samples kept at room temperature for 6 h, which exceeded the routine preparation time of samples. The long-term stability was evaluated by determining QC plasma samples kept at low temperature (–20°C) for 15 days. The post-preparative stability was measured by determining QC samples kept under the auto-sampler conditions (4°C) for 6 h. The freeze and thaw stability was tested by analyzing QC plasma samples undergoing three freeze (–20°C) and thaw (room temperature) cycles on consecutive days. The stock solution stabilities of lisinopril and the IS were evaluated by analyzing their working solutions (concentration in three QC levels for lisinopril and 10 ng/mL for the IS) kept at room temperature for 6 h, respectively.

RESULTS AND DISCUSSION

Selection of IS

It is necessary to use an internal standard to achieve high accuracy when HPLC is equipped with a tandem mass spectrometer. Enalaprilat, from which lisinopril was derived, was adopted as the internal standard because its structure, retention action and ionization as well as extraction efficiency are similar to those of lisinopril. The structures of lisinopril and enalaprilat are shown in Fig. 1.

Sample preparation

Owing to the inherent high selectivity and sensitivity of the LC-MS/MS technique, protein precipitation (PPT) has become one of the most widely used biological sample pretreatment methods for its simple and time-saving procedure (Chen *et al.*, 2006; Ramakrishna *et al.*, 2006; Medvedovici *et al.*, 2005). To obtain a clean chromatogram and achieve a sufficient extraction recovery, three types of precipitation reagents (methanol, acetonitrile and perchloric acid) were investigated during the experiment. Perchloric acid was eventually proved to be the best among the three reagents in terms of the higher extraction recovery and absences of endogenous interference at the retention time of lisinopril and the IS in the chromatogram.

LC-MS/MS conditions

Even though lisinopril is an amphoteric compound that can produce both negative and positive ions, electrospray in negative ion mode [ESI (–)] was less sensitive than the positive mode [ESI (+)]. Full-scan ESI (+) mass spectra of lisinopril and the IS and their structure are shown in Fig. 1. According to the scan mass spectra, the protonated molecule ion $\{[M+H]^+\}$ m/z 406 for lisinopril and $[M+H]^+$ m/z 349 for enalaprilat were selected as the precursor ions to obtain the product ion. The most sensitive mass transitions from the precursor ion to the product ion were m/z 406→246 for lisinopril and m/z 349→206 for the IS, respectively. The proposed fragmentation patterns are shown in Fig. 2.

To achieve good resolution, symmetric peak shape as well as a short run time for the analysis of lisinopril and the IS, the chromatographic conditions were optimized through trials. It was found that the acetic acid was not only necessary to lower the pH to enhance sensitivity by improving protonation of the analyte in the ESI source but also important to the peak shape of the IS and the retention of the analyte. Based on 10 mM ammonium acetate buffer–methanol (70:30, v/v), pH adjusted to 5.0 and 3.5 with acetic acid was investigated and pH 5.0 was adopted finally for it improved retention of the analyte and symmetrical peak shape of the IS while pH 3.5 split the IS peak. Under the condition of 30% methanol and pH adjusted with acetic acid, water (pH 5.0) and two concentration levels (10 and 50 mM) of ammonium acetate buffer (pH 5.0) were tested. The condition of 10 mM ammonium acetate buffer (pH 5.0) was accepted eventually because chromatographic peak of the IS become much broader under the condition of water (pH 5.0) and the suppression of the analyte signal was the greatest under the condition of 50 mM ammonium acetate buffer (pH 5.0). The adopted mobile phase, a mixture of 10 mM ammonium acetate buffer (pH adjusted to 5.0 with acetic acid)–methanol (70:30, v/v), well balancing the chromatographic separation efficiency and MS/MS sensitivity, successfully separated the analyte and the IS at retention times of 3.5 and 4.3 min, respectively, which avoided the interference of ionisation between them. The total LC-MS/MS analysis time was 5 min per sample.

Specificity and linearity

No visible interferences were observed. Blank plasma samples showed signal-to-noise ratios <3 at the retention times of lisinopril (3.5 min) and the IS (4.3 min) [shown in Fig. 3(A)]. Ion chromatograms from plasma samples with lisinopril concentrations at the lower limit of quantification (LLOQ) gave a signal-to-noise ratio of 12 and ion chromatograms from plasma samples with lisinopril concentrations at 1 ng/mL gave a signal-to-noise ratio of 4. Therefore, the LLOQ for lisinopril was proved to be 2 ng/mL in human plasma [shown in Fig. 3(B)] and the LOD was 1 ng/mL. All the ratios of the peak area of the analytes dissolved in the supernatant of the processed blank plasmas compared with that of standard solutions at the same concentration were between 85 and 115%, which meant that no significant matrix effect for lisinopril and the IS was implied in the method.

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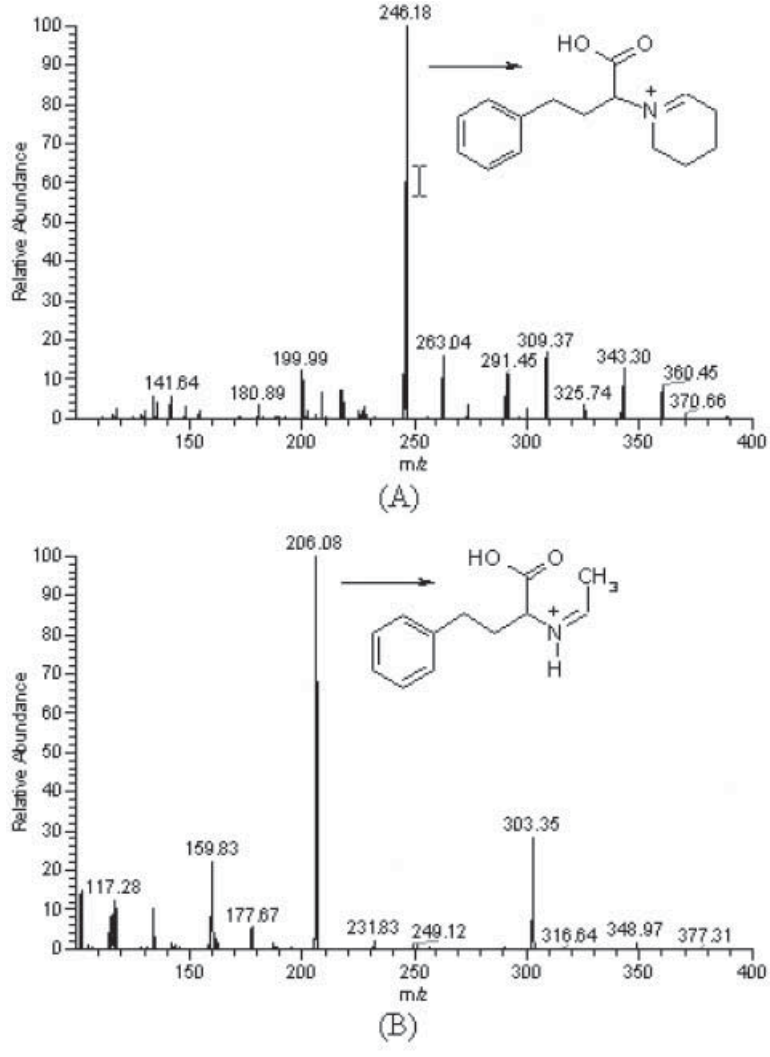

Figure 2. Full scan ESI (+) product ion mass spectra of (A) lisinopril and (B) the IS and their proposed fragmentation patterns.

The method exhibited excellent linear response over the selected concentration range of 2–200 ng/mL by weighted ($1/x$) least-squares linear regression analysis. The mean standard curve was typically described by the equation: $y = 0.0086x + 0.0012$, $r = 0.9996$, where y corresponds to the peak area ratio of lisinopril to the IS and x refers to the concentration of lisinopril added to plasma. The results of five representative standard curves for LC-MS/MS determination of lisinopril are given in Table 1.

Precision and accuracy

Data for intra-batch and inter-batch precision and accuracy of the method for lisinopril are presented in Table 2. The precision deviation values for intra-batch and inter-batch are all within 15% of the relative standard deviation (RSD) at each QC level. The intra-batch and inter-batch accuracy values were all within (100 ± 15)% of the actual values at each QC level. The results revealed good precision and accuracy.

Extraction efficiency

The data of extraction efficiency measured for lisinopril and the IS in human plasma were consistent, precise and reproducible. The mean absolute extraction recoveries of lisinopril at each QC level (5, 20 and 100 ng/mL) were 57.2 ± 6.5, 55.1 ± 4.7 and 58.6 ± 2.4%, respectively, and the mean absolute extraction recovery of the IS was 66.8 ± 5.3% at the concentration used in the assay (10 ng/mL).

Stability

Table 3 summarizes the results of the short-term stability, long-term stability, post-preparative stability and freeze and thaw stability of lisinopril. The data show

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Table 1. The results of five calibration curves for determining lisinopril in human plasma

Concentration added (ng/mL)	Assay	2	5	10	20	50	100	200
Concentration found	1	2.3	4.6	9.4	19.9	50.4	98.3	202.0
(ng/mL)	2	2.1	4.5	10.5	21.4	51.4	95.1	192.7
	3	1.8	5.3	10.6	22.1	45.8	92.0	207.6
	4	1.9	4.9	10.7	21.0	47.4	95.3	205.2
	5	1.9	4.9	10.3	21.0	48.7	99.6	200.4
Mean (ng/mL)		2.0	4.8	10.3	21.1	48.7	96.1	201.6
SD (ng/mL)		0.2	0.3	0.5	0.8	2.2	3.0	5.7
Precision (%)		9.3	6.8	5.1	3.8	4.6	3.1	2.8
Accuracy (%)		99.8	96.9	103.1	105.4	97.5	96.1	100.8

Table 2. The precision and accuracy of the method for determining lisinopril in human plasma

	Intra-batch (n = 5)			Inter-batch (n = 3)		
Concentration added (ng/mL)	Concentration found (mean ± SD, ng/mL)	Accuracy (%)	Precision (%)	Concentration found (mean ± SD, ng/mL)	Accuracy (%)	Precision (%)
5	5.4 ± 0.6	107.5	10.6	4.9 ± 0.6	98.8	12.4
20	20.7 ± 1.3	103.8	6.3	19.5 ± 1.6	97.7	8.0
100	103.5 ± 4.1	103.5	4.0	102.5 ± 5.4	102.5	5.3

Table 3. The stability of lisinopril in human plasma under tested conditions

	Accuracy (mean ± SD%)		
Concentration added (ng/mL)	5 (ng/mL)	20 (ng/mL)	100 (ng/mL)
Short-term stability (6 h, room temperature, n = 5)	93.4 ± 4.6	95.3 ± 5.2	104.6 ± 3.2
Long-term stability (15 days, –20°C, n = 5)	103.3 ± 7.0	105.8 ± 4.9	96.5 ± 3.7
Post-preparative stability (6 h, 4°C, n = 5)	92.7 ± 5.1	106.2 ± 2.5	97.4 ± 2.8
Freeze and thaw stability (3 cycles, –20°C, room temperature, n = 5)	94.8 ± 7.4	97.4 ± 5.5	106.0 ± 3.8

the reliable stability behavior of lisinopril under the condition tested. Based on the data obtained, the working solutions of lisinopril and the IS were intact within 6 h.

Application

The validated method was successfully used to quantify lisinopril concentration in a preliminary pharmacokinetic study, the clinical protocol of which was approved by Institute of Dermatology, Chinese Academy of Medical Sciences and Peking Union Medical College. Four Chinese healthy male volunteers participated in the preliminary pharmacokinetic study. After fasting overnight, four volunteers were administred a lisinopril tablet (10 mg). Blood samples (3 mL) were sampled before intake and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 24 and 36 h after oral administration. They were put into lithium heparin tubes and were immediately centrifuged at 1600***g*** for 10 min. The plasma obtained was frozen at –20°C in coded polypropylene tubs until analysis. A representative chromatogram of a plasma sample obtained at 6.0 h from a subject who received a single oral dose (10 mg) of lisinopril is shown in Fig. 3(C). The pharmacokinetic profiles of lisinopril from the four subjects after oral administration are shown in Fig. 4.

CONCLUSIONS

The present paper describes a rapid, selective and sensitive LC–MS/MS method using an ESI source in SRM mode for the determination of lisinopril in human plasma after a simple sample preparation without time-consuming solid-phase extraction or liquid–liquid extraction step needed by other LC–MS/MS methods. We consider these advantages of the method would make it efficient in analyzing large numbers of plasma samples obtain from pharmacokinetic, bioavailability or bioequivalence studies of lisinopril in human.

REFERENCES

Chen Z, Zhang J, Yu J, Cao G, Wu X and Shi Y. Selective method for the determination of cefdinir in human plasma using liquid chromatography electrospray ionization tandam mass spectrometry. *Journal of Chromatography B* 2006; **834**: 163.

DOI: 10.1002/bmc

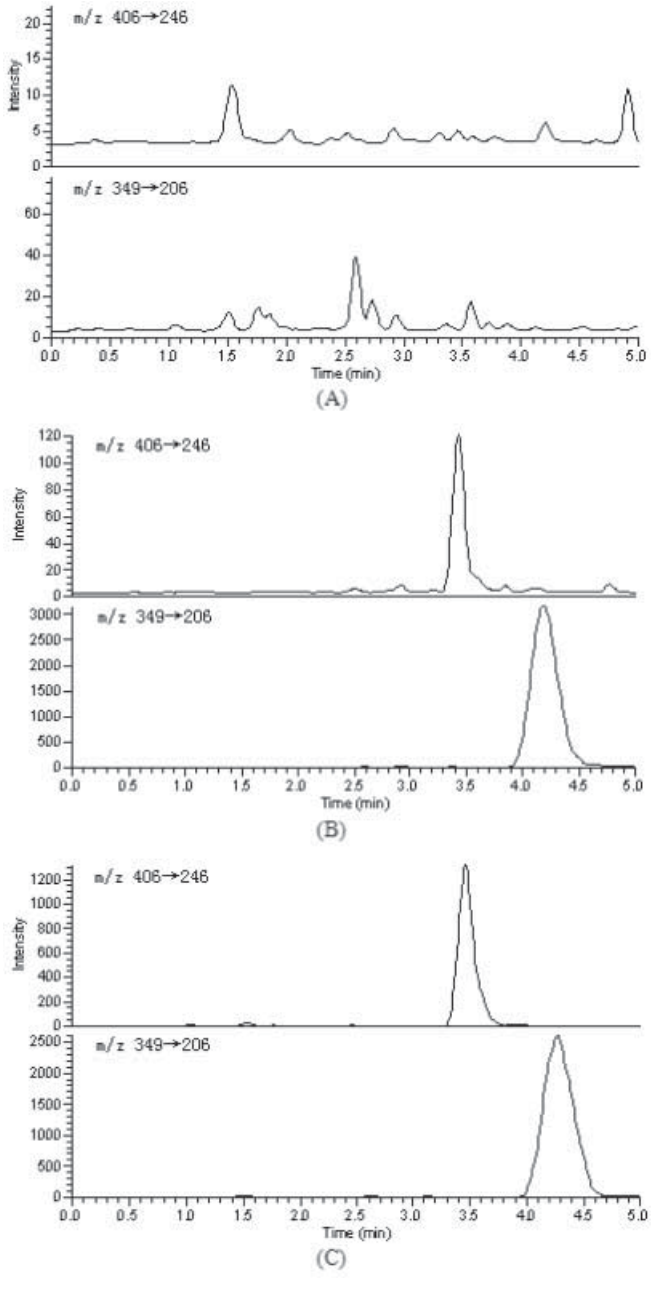

Figure 3. Representative SRM chromatograms for lisinopril and the IS resulting from analysis of (A) blank plasma (drug and IS free); (B) 2 ng/mL (LLOQ) of lisinopril in human plasma spiked with the IS; (C) a plasma sample obtained at 6.0 h from a subject after a single oral dose (10 mg) of lisinopril and the sample concentration was determined to be 32.02 ng/mL for lisinopril.

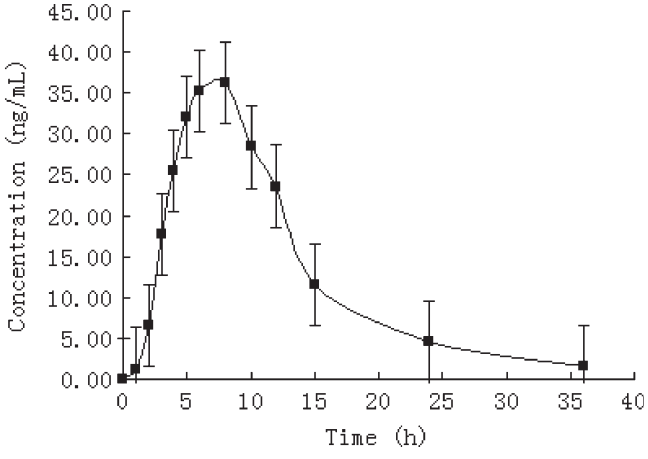

Figure 4. Mean drug plasma concentration–time curve of lisinopril from the four subjects after oral administration.

El-Amam AA, Hansen SH, Moustafa MA, El-Ashry SM and El-Sherbiny DT. Determination of lisinopril in dosage forms and spiked human plasma through derivatization with 7-chloro-4-nitrobenzo-2-oxa-1, 3-diazole (NBD-Cl) followed by spectrophotometry or HPLC with fluorimetric detection. *Journal of Pharmaceutical and Biomedical Analysis* 2004; **34**: 35.

Food and Drug Administration. *Center for Drug Evaluation and Research (CDER) Guidance for Industry, Bioanalytical Method Validation*. US Department of Health and Human Services, May 2001.

Huang J, Xu Y, Liu F, Gao S and Guo Q. Development of a rapid liquid chromatography tandem mass spectrometry assay for the quantification of lisinopril in human plasma. *Rapid Communication in Mass Spectrometry* 2006; **20**: 248.

Kousoulos C, Tsatsou G, Dotsikas Y and Loukas YL. Development of a rapid liquid chromatography tandem mass spectrometry method for the determination of lisinopril, applicable for a bioequivalence study, employing a 96-well format solid phase extraction protocol. *Analytica Chimica Acta* 2005; **551**: 177.

Langtry HD and Markham A. Lisinopril. A review of its pharmacology and clinical efficacy in elderly patients. *Drugs and Aging* 1997; **10**: 131.

Leis HJ, Fauler G, Raspotnig G and Windischhofer W. Quantitative determination of the angiotensin-converting enzyme inhibitor lisinopril in human plasma by stable isotope dilution gas chromatography/negative ion chemical ionization mass spectrometry. *Rapid Communications in Mass Spectrometry* 1998; **12**: 1591.

Leis HJ, Fauler G, Raspotnig G and Windischhofer W. An improved method for the measurement of the angiotensin-converting enzyme inhibitor lisinopril in human plasma by stable isotope dilution gas chromatography/negative ion chemical ionization mass spectrometry. *Rapid Communications in Mass Spectrometry* 1999; **13**: 650.

Medvedovici A, Albu F, Georgita C and David V. Non-extractive procedure followed by LC/APCI MS/MS analysis of trimetazidine in plasma samples for assessing bioequivalence of immediate/modified release formulations. *Biomedical Chromatography* 2005; **19**: 549.

Noble TA and Murray KM. Lisinopril: a nonsulfhydryl angiotensin-converting enzyme inhibitor. *Clinical Pharmacy* 1988; **7**: 659.

Padua AAF, Barrientos-Astigarraga RE, Rezende VM, Mendes GD and De Nucci G. Lisinopril quantification in human plasma by liquid chromatography–electrospray tandem mass spectrometry. *Journal of Chromatography B* 2004; **809**: 211.

Ramakrishna NVS, Vishwottam KN, Koteshwara M, Manoj S, Santosh M, Chidambara J, Sumatha B and Varma DP. Rapid quantification of gabapentin in human plasma by liquid chromatography/tandem mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis* 2006; **40**: 360.

Sagirli O and Ersoy L. An HPLC method for the determination of lisinopril in human plasma and urine with fluorescence detection. *Journal of Chromatography B* 2004; **809**: 159.

Tsakalof A, Bairachtari K and Georgarakis M. Lisinopril quantification in human plasma by liquid chromatography–electrospray tandem mass spectrometry. *Journal of Chromatograhpy B* 2003; **783**: 425.

Wong Y and Charles BG. Determination of the angiotensin-converting enzyme inhibitor lisinopril in urine using solid-phase extraction and reversed-phase high-performance liquid chromatography. *Journal of Chromatography B* 1995; **673**: 306.