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Simultaneous determination of loratadine and pseudoephedrine sulfate in human plasma by liquid chromatography–electrospray mass spectrometry for pharmacokinetic studies

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Abstract

To support the pharmacokinetic and bioavailability study of an extended-release loratadine (LOR)/pseudoephedrine sulfate (PES) tablet, a high performance liquid chromatographic-electrospray ionisation–mass spectrometric method (LC–MS) was developed for the simultaneous determination of LOR and PES in human plasma. Diazepam (DP) and phenylpropanolamine (PPA) were used as internal standards for LOR and PES, respectively. Analytes were extracted from alkalized human plasma by liquid/liquid extraction using ethyl ether. Chromatographic separation was performed on an ODS column at flow rate of 0.2 ml/min. The total chromatographic run time was 10.5 min with the retention time of 7.1 min and 6.2 min for LOR and DP, respectively, and 2.2 min for both of PES and PPA. The LOQ was 10 pg/ml and 50 pg/ml for LOR and PES, respectively. The method is accurate and precise enough for its intended purpose.

Keywords: Loratadine; Pseudoephedrine sulfate; Pharmacokinetics; LC–MS

1. Introduction

Loratadine (LOR) and pseudoephedrine sulfate (PES) are two common components of many preparations used for the relief of symptoms associated with allergic rhinitis. LOR (4-(8-chloro-5,6-dihydro-11*H*-benzo[5,6]-cycloheptal[1,2-*b*]-pyridin-11-ylidine)-1-piperidinecarboxylic acid ethyl ester) is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonist activity that is used for relief of symptoms of seasonal allergies and skin rash. Among the second-generation antihistamines, LOR is free from sedation at recommended dosages [1]. PES (benzenemethanol,α-[1-(methylamino)ethyl]-,[*S*-(R^*,R^*)]sulfate) is the synthetic salt of one of the naturally occurring dextrorotatory diastereomers of ephedrine and is classified as an indirect and direct-acting sympathomimetic amine.

Extended-release LOR/PES twice- or once-daily tablet formulations have been marketed in the United States since 1993 and have been shown to be safe and effective for the relief of symptoms associated with allergic rhinitis. The twice-daily tablet consists of loratadine 5 mg in an immediate-release coating and pseudoephedrine sulfate 120 mg, of which 60 mg is in an immediate-release coating and 60 mg is in a barrier-protected core. Different formulations based on the same mechanism as the extended-release formulation have been developed recently. To study the bioavailability and bioequivalence of these formulations, both PES and LOR must be measured in plasma of participants. Various analytical procedures have been reported for separate quantitative determination of loratadine or pseudoephedrine sulfate in dosage forms and in biological fluids. These include high performance liquid chromatography with ultraviolet detection (HPLC-UV) for PES [2] and LOR [3,4], HPLC with fluorescence detection for LOR [5], capillary electrophoresis (CE) for LOR [6] and PES [7], and LC–MS

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for LOR [8,9]. Sutherland et al. [10] and Weng et al. [11] described different methods for the simultaneous detection of LOR and its metabolite descarboethoxy-loratadine (DCL) using liquid chromatography–tandem mass spectrometry (LC–MS/MS).

Due to the differences in the pK_a values and polarities, it is difficult and time consuming to chromatograph both LOR and PES in a single chromatographic run by isocratic mobile phase when biological samples are involved. Few researches have addressed the simultaneous detection of LOR and PES in plasma. Feyyaz et al. [12] described a method of simultaneous determination of PES, LOR and other compounds in formulations by first-derivative spectrophotometry and ratio-spectra derivative spectrophotometry, as well as HPLC to separate PES and dexbrompheniramine maleate. The method was only suitable for the analysis of drugs in formulations, and not applicable to pharmacokinetic studies due to endogenous interferences and low sensitivity. Since both LOR and PES have basic functional groups, they can be extracted from alkalized human plasma using liquid/liquid extraction. A simple one-step liquid/liquid extraction of LOR and PES from alkalized plasma was developed. With the selectivity provided by mass spectrometry, determination can be optimized by gradient elution. To support the bioequivalence study of extended-release LOR/PES tablet, we developed a sensitive method for simultaneous determination of LOR and PES in human plasma using a gradient elution mode.

2. Experimental

2.1. Chemicals and reagents

LOR (purity 99.90%), PES (purity 99.98%) DP (purity 99.80%), PPA (purity 99.70%), descarboethoxy-loratadine (DCL, purity 99.80%) were supplied by Jiangsu Institute for the Control of Pharmaceutical Products (Nanjing, China). HPLC grade acetonitrile (ACN) and methanol were obtained from Fisher Scientific (St. Louis, MO, USA). Milli-Q water was generated by passing distilled water through a Quantum EX ultrapure organex cartridge (Cat No. QTUM 000EX, Millipore S.A. 67120, Molshem, France). Blank plasma was obtained from the Blood Supply Center (Nanjing, China) and was stored in a freezer at −/20 °C. Sodium heparin used as an anticoagulant, was obtained from Huixing Biochemistry Co. Ltd. (Shanghai, China). Ethyl ether was obtained from Nanjing Chemical Reagent No. 1 Factory (Nanjing, China).

2.2. LC–mass spectrometry (LC–MS)

The LC–MS system consisted of a Shimadzu 10ADvp Pump, DGU-14AM degasser, SIL-HTC Autoinjector and LCMS2010A mass spectrometer with an electrospray ionization source (Shimadzu, Kyoto, Japan). A Shimadzu LCMass Solution Version 2.04 on a Windows 2000 operating system was used for data analysis.

The analysis was carried out on an ODS column (Shim-pack, 5 μm, 2.1 mm × 150 mm i.d., Shimadzu, Japan) equipped with an ODS guard column (Security Guard, Phenomenex, USA). Mobile phases of acetonitrile–water (35:65), containing 0.1% of glacial acetic acid (v/v) (A) and acetonitrile–water (80:20), containing 0.1% of glacial acetic acid (v/v) (B) were used. The column was equilibrated with mobile phase A before injection. After the injection was initiated, the mobile phase was changed immediately to mobile phase B. PES and internal standard PPA were eluted within 3 min and LOR and DP were eluted within 8 min. The column was equilibrated with mobile phase A for 3 min before the second injection was initiated. The total period for one sample was about 11 min (see Fig. 1).

2.3. Standard solutions and sample preparation

LOR, DCL, PES, DP (internal standard 1, IS-1) and PPA (internal standard 2, IS-2) stock solutions were prepared by weighing out the reference standards, which were dissolved in methanol. Intermediate stock solutions were prepared by diluting the stock solution with methanol. Standard solutions for preparing calibration curve and quality control (QC) samples were obtained by serial dilutions of intermediate stock solutions with water, except for DP which was diluted with methanol.

Volumes (1.0 ml) of QC and blank plasma samples were transferred into glass tubes. Twenty microliters of IS-1 solution (500 ng/ml of DP in methanol) and IS-2 solution (20 μg/ml of PPA in water) were added to all tubes except blank plasma samples. After 30 s vortex-mixing, 100 μl of 0.1 mol/l sodium hydroxide solution was added to each tube and samples were vortex-mixed for another 30 s. Ethyl ether (6 ml) was added to each tube and the samples were vortex-mixed for 3 min. The tubes were then centrifuged at 1200 × *g* for 10 min at room temperature using a Centrifuge (Model 0412-1, Shanghai Surgical Instruments Factory, Shanghai). The upper organic layer was transferred into a glass tube and the lower aqueous layer was discarded. The organic solvent was evaporated to dryness under nitrogen in thermostatic water bath at 45 °C. The samples were reconstituted with 200 μl of acetonitrile by vortex-mixing for 60 s. After further centrifuging at 21 000 × *g* for 10 min at 4 °C (Micromax RF, Thermo IEC, USA), the supernatant was transferred to 1.5 ml autosampler vial. A 5 μl volume of the supernatant was used for analysis.

2.4. Calibration standard samples and quality control (QC)

During validation and batch analysis of plasma samples, calibration standard samples were prepared freshly by adding aliquot of LOR and of PES calibration solutions into glass tubes containing 1.0 ml of blank plasma to obtain serial concentrations of 0.05/5.0, 0.10/10.0, 0.25/25.0, 0.50/50.0, 1.00/100.0, 2.50/250.0, 5.00/500.0, 10.00/1000.0 ng/ml for

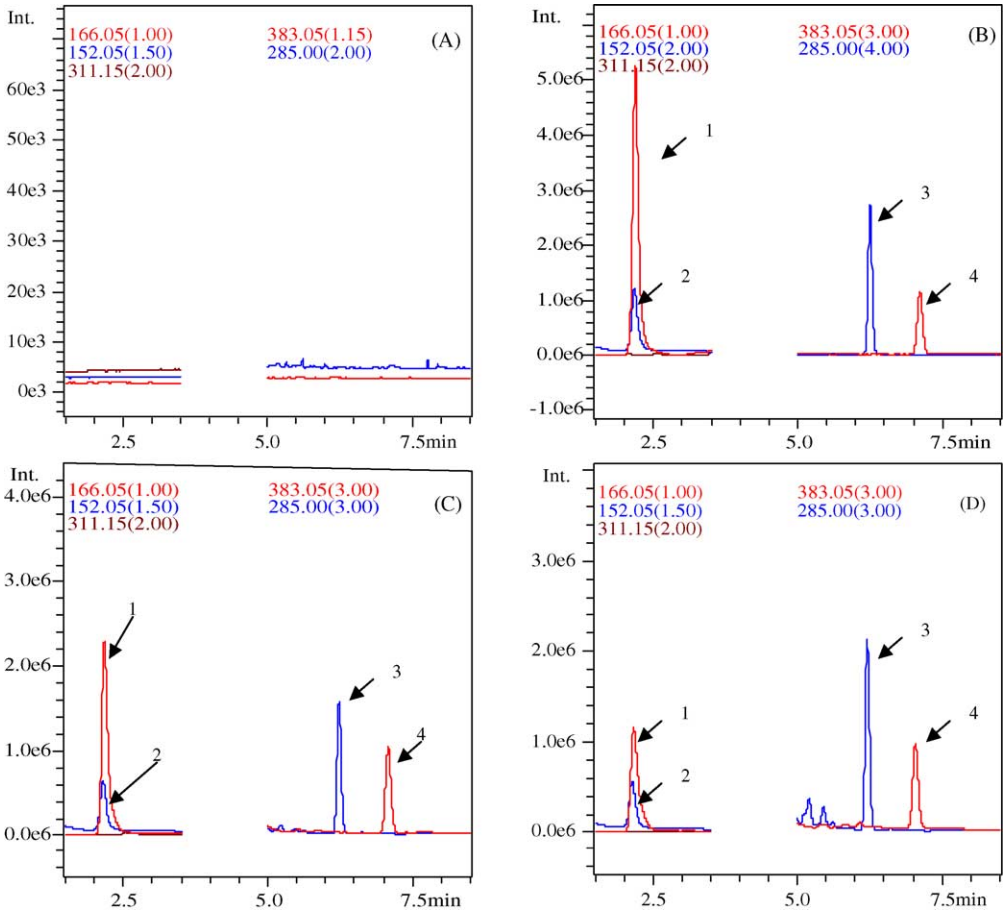

Fig. 1. LC–MS chromatograms of LOR, PES, DCL, PPA and DP: (A) blank human plasma; (B) LOR (500 ng/ml) PES (10ng/ml) and internal standards PPA and DP in acetonitrile; (C) blank human plasma spiked with LOR (500 ng/ml) PES (10ng/ml) and internal standards PPA and DP; (D) human plasma sample 2 h after oral administration of one tablet of CLARITIN-D® 12 h (Schering); *m/z* 166.05, 152.05, 311.15, 383.05, 285.00 for PES (1), PPA (2), DCL, LOR (3), DP (4), respectively. The numbers in the parentheses represent ratio of the displayed peak to the original peak.

LOR/PES. Calibration curves were constructed using linear regression (peak area ratio of the analyte of interest versus the IS against the concentrations). QC samples at levels of 0.25/25.0, 2.50/250.0, 10.0/1000.0 ng/ml for LOR/PES, were prepared by adding appropriate amounts of LOR and PES working solutions to blank human plasma. The amount of methanol in QC samples was always less than 0.2% (v/v). All QC samples were sub-divided and stored frozen at −20 °C.

2.5. Validation

The developed method was validated for the simultaneous determination of LOR and PES according to specificity, linearity, precision and accuracy. The linearity of the method was verified by analyzing calibration standard samples five times at eight levels of (0.05/5.0, 0.10/10.0, 0.25/25.0, 1.00/100.0, 2.50/250.0, 5.00/500.0, 10.00/1000.0 ng/ml for LOR/PES). The precision (CV%) and accuracy (% nominal)

Table 1
Absolute recoveries of PES and LOR spiked in human plasma ($n = 5$)

Spiked concentration (ng/ml)	Recovery (mean ± S.D.) (%)
PES	
10.0	79.9 ± 4.0
100.0	79.2 ± 2.3
1000.0	80.7 ± 1.6
LOR	
0.10	93.3 ± 6.8
1.00	83.1 ± 2.1
10.00	90.0 ± 4.2

Table 2
Intra-day assay precision and accuracy ($n = 5$)

Nominal concentration (ng/ml)	Mean concentration found (ng/ml)	CV (%)	Nominal (%)
PES			
10.0	11.1	10.4	111.1
100.0	89.5	6.0	89.5
1000.0	994.1	1.1	99.4
LOR			
0.10	0.094	14.2	94.3
1.00	0.98	6.5	98.0
10.0	10.04	5.1	100.4

Table 3
Inter-day assay precision and accuracy ($n = 5$)

Nominal concentration (ng/ml)	Mean concentration found (ng/ml)	CV (%)	Nominal (%)
PES			
10.0	11.2	13.7	112.4
100.0	108.0	11.5	107.9
1000.0	1052.0	7.2	105.2
LOR			
0.10	0.101	14.9	100.6
1.00	1.02	11.3	102.3
10.0	11.05	9.4	110.5

Table 4
The freeze–thaw stabilities of LOR and PES in human plasma after stored at −20 °C for 2 weeks ($n = 5$)

Nominal concentration (ng/ml)	Mean concentration found (ng/ml)	CV (%)	Nominal (%)
PES			
25.0	23.4	11.6	93.7
250.0	259.4	7.9	103.8
1000.0	1034.9	2.7	103.5
LOR			
0.25	0.25	12.6	98.2
2.50	2.54	5.4	101.4
10.0	9.88	2.4	98.8

were determined in five separate runs and five-fold analysis in one run by analysis of quality control samples at three different independent levels, i.e. 10.0/0.10, 100.0/1.00, 1000.0/10.0 ng/ml for PES and LOR ($n = 5$), respectively. Absolute recoveries of the analytes from human plasma were determined in quintuplicate at three different independent concentrations by extracting drug free plasma samples spiked with PES and LOR and internal standards. Recoveries were calculated by comparison of the peak areas of the extracted analytes with those of the reconstituted blank plasma extracts spiked with PES and LOR. Blank human plasma samples were spiked with standard solutions to obtain freeze–thaw stability study samples at levels of 0.25/25.0, 2.50/250.0, 10.0/1000.0 ng/ml for LOR and PES ($n = 5$), respectively. PPA and DP were used as internal standards for quantitation of the co-formulated drugs.

3. Results and discussion

3.1. Specificity, linearity, precision and accuracy

In this study, complete separation and resolution of LOR, PES and internal standards with good peak shapes and without any apparent shoulders confirmed specificity of the method (see Fig. 1). No interfering substances were found at the same retention times of the analytes of interest. Retention times were 7.0 and 2.0 min for LOR and PES, respectively, and 6.2 and 2.1 min for the internal standards DP and PPA, respectively. Analysis could be achieved within 11 min for a total chromatography run, which made it possible to analyze batches of up to 120 samples per day. Six blank plasma samples from different people were used to test the specificity of the method, by comparison with the retention

Table 5
Quality control results of intra-day study and within batch study ($n = 5$)

Nominal concentration (ng/ml)	PES			LOR		
	25.0	100.0	500.0	0.25	1.0	5.0
Intra-day						
Mean	23.5	94.8	482.5	0.24	1.01	5.06
CV (%)	11.5	5.8	3.2	16.7	6.9	6.9
% of nominal	94.0	94.8	96.5	96.0	101.0	101.2
Intra-batch						
Batch 1						
Mean	22.5	92.1	518.9	0.23	1.08	5.51
CV (%)	15.1	12.8	9.4	13.0	10.2	7.6
% of nominal	90.0	92.1	103.8	92.0	108.0	110.2
Batch 2						
Mean	26.0	88.1	482.4	0.21	0.87	4.2
CV (%)	7.3	7.2	5.2	4.8	5.7	3.8
% of nominal	104.0	88.1	96.5	84.0	87.0	84.0
Batch 3						
Mean	22.5	89.4	428	0.23	0.91	4.85
CV (%)	16.4	10.0	3.8	8.7	5.5	14.6
% of nominal	90.0	89.4	85.6	92.0	91.0	97.0
Batch 4						
Mean	24.7	104.0	550.1	0.26	0.96	4.92
CV (%)	7.7	8.5	6.5	7.7	12.5	5.5
% of nominal	98.8	104.0	110.0	104.0	96.0	98.4

Each batch lasted for 5 days.

times for standard samples. Calibration curves were drawn in the concentration range of 5.0/0.05 to 1000.0/10.0 ng/ml for LOR/PES by linear regression: the ratio (f_1) of LOR peak area to that of internal standard 1 (IS-1) was plotted vs. the concentration of LOR in plasma, and the ratio (f_2) of PES peak area to that of internal standard 2 (IS-2) was plotted versus the concentration of PES in plasma. The mean equation of the calibration curve ($n = 5$) obtained from eight points was $f_1 = 0.0873\ (\pm 0.0042)C + 0.0009(\pm 0.0026)$ (correlation coefficient $r = 0.9999$) for LOR and $f_2 = 0.006(\pm 0.0001)C - 0.0269(\pm 0.0941)$ ($r = 0.9998$) for PES.

The mean absolute recovery from human plasma at high, medium and low concentrations was ca. 70% and 100% for PES and LOR, respectively (see Table 1).

The accuracy and precision data for the LC–MS analysis of blank human plasma spiked with LOR and PES are presented in Tables 2 and 3. The coefficient of variance (CV%) values ranged from 1.1 to 10.4% and 5.14 to 14.2% for PES and LOR, respectively. Percentage recoveries ranging from 89.5 to 112.4% and 94.3 to 110.5% were obtained for PES and LOR, respectively

3.2. Freeze–thaw stability

Stabilities of LOR and PE were demonstrated for spiked human plasma samples stored at −20 °C for 2 weeks (see Table 4). On-instrument stability was inferred from special stability samples, which were prepared and included in the validation batch. No significant degradation could be detected in the cooled samples (4 °C) left on the autosampler for at least 24 h (data not shown).

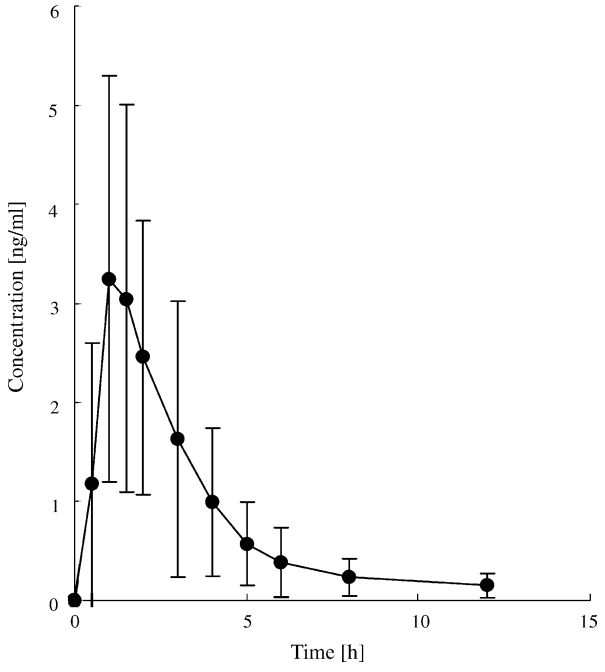

Fig. 2. Plasma concentration–time profile (mean ± S.D.) for LOR following a single oral administration of one tablet of CLARITIN-D® 12 h (Schering) to 20 healthy Asian volunteers.

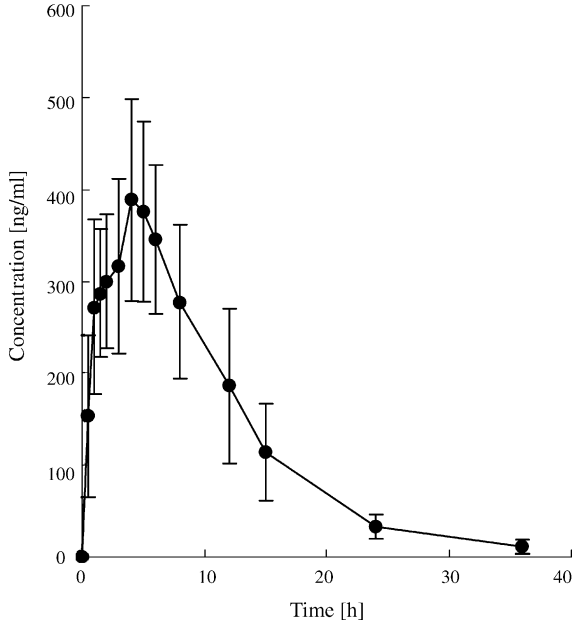

Fig. 3. Plasma concentration-time profile (mean ± S.D.) for PES following a single oral administration of one tablet of CLARITIN-D® 12 h (Schering) to 20 healthy Asian volunteers.

3.3. Quality control

The quality control (QC) samples were prepared according to the concentration of standard curve and the quantity of the total samples. QC samples were arranged evenly in each analysis batch. Data were obtained through linear regression analysis of peak area ratios of PES or LOR/internal standard (y) versus PES or LOR concentrations (ng/ml) in spiked plasma samples (x). The respective data are given in Table 5.

3.4. Pharmacokinetic research

The validated LC–MS assay was successfully applied to a bioavailability and bioequivalence study in 20 healthy Asian volunteers. The study was approved by the Helsinki Committee of the Clinical Research Center of Jiangsu People's Hospital. All volunteers provided informed written consent before participating in the study. Subjects who

Table 6
The pharmacokinetic parameters of LOR and PES in Asian volunteers after oral administration of one tablet of CLARITIN-D® 12 h (Schering) ($n = 20$)

Parameters	LOR	PES
C_{max} (ng/ml)	3.75 ± 1.97	418.9 ± 86.2
T_{max} (h)	1.35 ± 0.52	4.52 ± 1.29
$t_{1/2}$ (h)	2.93 ± 0.67	5.97 ± 1.54
MRT (h)	4.45 ± 2.45	10.02 ± 1.39
AUC_{0-12} (h ng/ml)	10.37 ± 6.03	4759.7 ± 1223.2
$AUC_{0-\infty}$ (h ng/ml)	11.05 ± 6.36	4869.5 ± 1213.2

had no clinically relevant abnormalities on their physical examination, initial medical history, laboratory tests, or electrocardiographic (ECG) evaluation were enrolled. Venous blood samples were periodically collected up to 36 h after oral administration of one tablet of CLARITIN-D® 12 h (Schering). The blood samples (3–4 ml) were collected into heparinized tubes. Following centrifugation at 1200 × *g* for 10 min, resultant plasma was separated and stored at −20 °C until analysis. Plasma (1 ml) was extracted and analyzed by the same procedure as that of calibration samples. The maximum concentrations of LOR and PES were 3.75 ± 1.97, and 418.9 ± 86.2 ng/ml, respectively (see Figs. 2 and 3, and Table 6). No significant difference was found among the pharmacokinetic parameters, such as AUC and $t_{1/2}$ between the data from our study in Asian people and those from research in Caucasian subjects [13]. But results showed that C_{max}

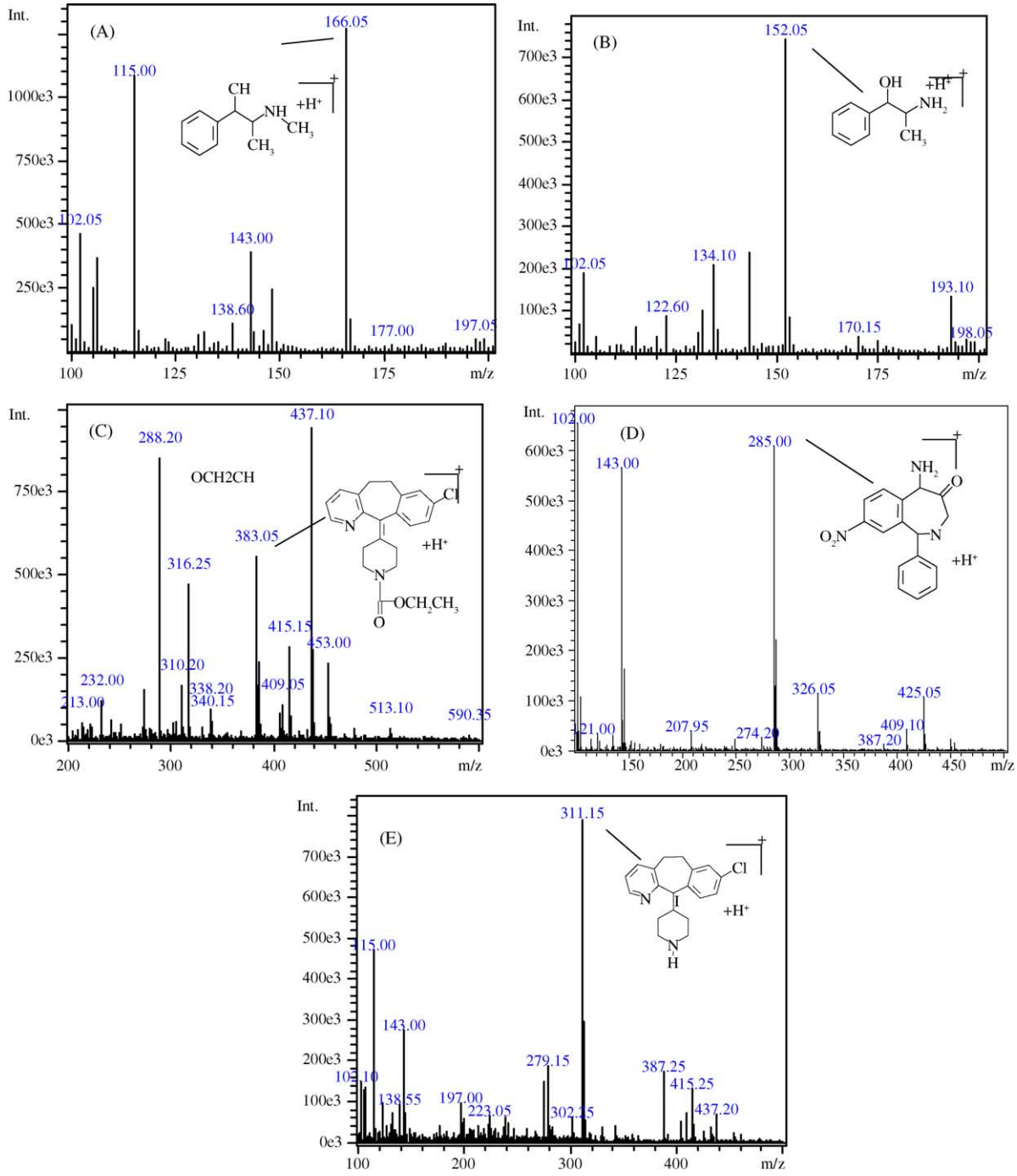

Fig. 4. Positive scan mass spectra of PES (A), PPA (B), LOR (C), DP (D) and DCL (E). Mass condition: CDL voltage, probe high voltage, Q-array voltage were all fixed as in tuning, scan interval set at 1 s (see Section 3.5).

values of both LOR and PES were higher in Asian people than that in Caucasian subjects. The method we set up could be used for bioequivalence and pharmacokinetics studies of PES and LOR.

3.5. Opitimization of MS parameters

In this paper, a simultaneous detection of LOR and PES, as well as the internal standards in human plasma by LC–MS method using ODS column was presented. The MS condition was optimized by scanning PES, LOR, DCL, PPA and DP in positive mode using different mobile phases. Both of LOR and PES were best ionized by protonated mode $[M+H]^+$ when the ratio of water in the mobile phase was high enough. The acidic mobile phase enhanced protonation and in turn improved sensitivity of the basic analytes PES and LOR (see Fig. 4).

Since C_{max} is about 400 ng/ml of PES after a single dose of 120 mg of PES, the detector gain was set at 1.35 kV during the period of 1.5–3.5 min post-injection, and at 1.6 kV during the period of 5.0–8.5 min to prevent saturation of the signal for PES. The MS detector was set to standby mode from 3.5 to 5 min. DCL could be detected at the same time but with low sensitivity that did not cause any interference to PES and PPA. Other mass spectrometer parameters were optimized to obtain maximum sensitivity, which were as follow: curve dissolution line (CDL) voltage −25 kV, probe high voltage −4.5 kV, Q-array voltage of direct current (DC) 0 V and radiation frequency (RF) +150 for LOR and DP, and +115 for PES and PPA. Mass spectra were obtained at a dwell time of 0.2 s in SIM mode and 1 s in scan mode. Liquid nitrogen (99.995%, from Gas Supplier Center of Nanjing University, China) was used as the nebulizer and curtain gas at 1.5 and 2.0 l/min, respectively.

3.6. Signal suppression and optimization of the mobile phase

Due to the rapid elution of PES, there might be some effects on the ionization of PES from the co-elution of endogenous components in biological fluids. To compensate for any potentially inconsistent response due to matrix effects, IS should have a similar structure to the analyte and elute close to the said analyte. PPA is an analogue of PES and they eluted from the column at the same time. Although the application of internal standards is a highly effective approach for addressing quantitative issues associated with signal suppression, it cannot be used to compensate for reductions in sensitivity. At certain concentrations, mobile phase additives or buffers can improve overall LC–MS signal sensitivity. However, to improve signal reproducibility between matrix and standard sample analyses, the concentrations of buffer or additives are required at a level where the overall sensitivity is significantly reduced [14]. During the optimization procedure, different concentrations of ammonium formate, ammonium acetate, formic acid and acetic acid were tested. With the increasing of ammonium acetate, the peak shapes of PES and PPA became sharper but the sensitivity of LOR was suppressed significantly. With the addition of formic acid, ammonium formate, ammonium acetate and acetic acid to the mobile phase, the elution time of LOR and DP changed significantly. With the addition of formic acid or ammonium formate, LOR was eluted faster than DP and the peak became broader. When using acetic acid, the LOR was eluted slower than DP but with good peak shape, as well as acceptable sensitivity. After consideration of benefits from the additives in the mobile phase, acetic acid at a concentration of 0.1% (v/v) in the water phase was chosen. This mobile phase turned out to be stable and suitable for the determination of PES and LOR by LC–MS.

No apparent signal suppression was observed for PES, PPA and LOR. The peak area of DP extracted from plasma samples was about 70% of that from standard samples, which indicates slight signal suppression from co-eluting matrix.

4. Conclusion

A sensitive and reliable LC–MS method for the simultaneous measurement of LOR and PES in human plasma has been developed and validated. Two internal standards were used to improve the robustness of the method. A simple liquid/liquid extraction procedure was used to extract analytes from plasma samples. The LOQ was 10 pg/ml for LOR and 50 pg/ml for PES. The analytical run time was 10.5 min per sample.

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