Available online at www.sciencedirect.com
SCIENCE DIRECT®
Journal of Pharmaceutical and Biomedical Analysis
34 (2004) 141–151
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Determination of loratadine in human plasma by liquid chromatography electrospray ionization ion-trap tandem mass spectrometry

Isam Ismail Salem*, Jafer Idrees, Jaafar I. Al Tamimi

ACDIMA Center for Bioequivalence and Pharmaceutical Studies, P.O. Box 925161, Amman 11190, Jordan

Received 10 April 2003; received in revised form 29 July 2003; accepted 31 July 2003

Abstract

A sensitive and specific liquid chromatography electrospray ionization ion-trap mass spectrometry (LC–ESI-IT-MS/MS) method has been developed and validated for the identification and quantitation of loratadine in human plasma. After the addition of the internal standard (IS), plasma samples were extracted using isooctane:isoamyl alcohol mixture. The compounds were separated on a prepacked Zorbax phenyl column using a mixture of acetonitrile, 0.20% formic acid as mobile phase. A Finnigan LCQ^{DUO} ion-trap mass spectrometer connected to a Waters Alliance high performance liquid chromatography (HPLC) was used to develop and validate the method. The results were within the accepted criteria as stated in the FDA bioanalytical method validation guidance. The method was proved to be sensitive and specific by testing six different plasma batches. Linearity was established for the range of concentrations 0.10–10.0 ng/ml with a coefficient of determination (r^2) of 0.9998. Accuracy for loratadine ranged from 105.00 to 109.50% at low, mid and high levels. The intra-day precision was better than 10.86%. The lower limit of quantitation (LLOQ) was identifiable and reproducible at 0.10 ng/ml with a precision of 9.84%. The proposed method enables the unambiguous identification and quantitation of loratadine for pharmacokinetic, bioavailability or bioequivalence studies.

Keywords: Loratadine; HPLC; MS/MS; Human plasma; Method validation

1. Introduction

Loratadine, ethyl-4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-*b*]pyridin-11-ylidene)-1-piperidinecarboxylate (Fig. 1) a white to off-white powder not soluble in water, but soluble in acetone, alcohol, and chloroform [1], is a long-acting tricyclic antihistamine with selective peripheral histamine H_1-receptor antagonist activity. Following an oral administration of 10 mg tablet, loratadine is rapidly absorbed and reaches peak concentration (T_{max}) at 1.3 h [2,3].

Different methods (radioimmunoassay, gas chromatography, high performance liquid chromatography (HPLC)-UV) have been used for the determination of loratadine and its metabolite in plasma [2,4,5]. Generally, these published methods are tedious and time

* Corresponding author. Tel.: +962-6-5821618; fax: +962-6-5821649.
E-mail address: dr.salem@acdima.com (I.I. Salem).

0731-7085/$ – see front matter © 2003 Elsevier B.V. All rights reserved.
doi:10.1016/j.japna.2003.07.001

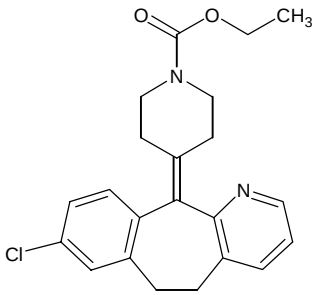

Fig. 1. Chemical structure of loratadine.

consuming. A recently published HPLC method for loratadine quantitation reported the use of a four-step liquid–liquid extraction technique, where, the internal standard (IS), itraconazole, was added in the third extraction step [6]. The authors used a triple quadrupole mass spectrometer for analytes identification and quantitation. In a different interesting study [7], loratadine was used as an analyte to evaluate the advantages/disadvantages of triple quadrupole MS/MS methods in enhanced resolution mode in comparison with unit mass resolution techniques. Among other parameters, the paper reported effects on selectivity and sensitivity. Naidong et al. [8], reported a simultaneous multiple triple quadrupole LC–MS/MS methods for the determination of loratadine along with five other drugs at the same time. The paper describes the use of gradient elution methods on reversed-phase and normal phase silica columns. On the other hand, a triple quadrupole mass spectrometer was evaluated for the simultaneous validation of LC–MS/MS methods for the quantitation of loratadine in four different animals biological matrixes using a 96-well solid-phase extraction technique [9]. It is worthwhile to comment that a one common issue in the above-mentioned methods of analysis was the use of a triple quadrupole mass detector for the assay development. Some of these methods were somewhat accessible and exciting techniques regardless of their possible/feasible application in a practicable way for a daily use.

As an effort to reduce the time required for drugs testing in biological fluids, our laboratories are continually investigating new strategies for improving sample preparation, chromatography, and mass spectrometric detection. The aim of the present study was to combine a fast high performance liquid chromatography technique with MS/MS spectrometry in order to validate a robust and reproducible reversed-phase LC–MS/MS method for loratadine determination in human plasma and to increase dramatically sample throughput. Our interest was to establish a simple single step extraction technique and, at the same time, to employ the price affordable ion-trap mass detector, comparable to a triple-stage quadrupole MS system. This method was to be validated to ensure the proper quantification of loratadine in human plasma down to the concentration limit of 0.10 ng/ml. At the same time, it was expected that this method would be efficient in analyzing large number of plasma samples supporting pharmacokinetic, bioavailability or bioequivalence studies after therapeutic doses of loratadine.

2. Experimental

2.1. Reagents

The following chemicals and reagents were used: acetonitrile and methanol (HPLC grade, Acros, Belgium), ammonia and formic acid (Panreac, Spain), ammonium chloride, dichloromethane and isoamyl alcohol (BDH laboratories, England), isooctane (Scharlau, Spain). A Milli-Q® (Millipore, France) water purification system was used to obtain the purified water for the HPLC analysis. Lithium heparin plasma (six different batches) of healthy volunteers was obtained from Jordan University Hospital (Jordan).

2.2. Preparation of stock solutions

Primary stock solutions of loratadine for preparation of standards and quality controls (QC) were prepared from separate weighing. The primary stock solutions were prepared in methanol (2.0 mg/ml) and stored at −20 °C. This primary stock solution was diluted in methanol to produce a final concentration of 10 μg/ml.

The internal standard stock solution was prepared by dissolving 15.0 mg of itraconazole in 25 ml solvent (dichloromethane:methanol, 4:96, v/v) producing a concentration of 0.6 mg/ml. This solution was stored at −20 °C.

Working solutions of loratadine were prepared daily in methanol by appropriate dilution at: 5.0, 25.0, 50.0, 100.0, 150.0, 300.0 and 500.0 ng/ml.

2.3. Calibration curves

Calibration curves were prepared by spiking different samples of 1 ml plasma each with 20 μl of one of the above-mentioned working solutions to produce the calibration curve points equivalent to 0.10, 0.50, 1.0, 2.0, 3.0, 6.0 and 10.0 ng/ml of loratadine. Each sample also contained 150.0 ng/ml of the internal standard. Zero plasma samples used in each run were prepared containing 150.0 ng/ml of internal standard only. In each run, a plasma blank sample (no IS) was also analyzed.

2.4. Quality control samples

Quality control samples were prepared at three different levels, low limit (three times the lower limit of quantitation, LLOQ), middle level and a high level (80% of the upper limit of quantitation limit, ULOQ). QC samples were prepared daily by spiking different samples of 1 ml plasma each with 20 μl of the corresponding standard solution to produce a final concentration equivalent to 0.30, 5.0, and 8.0 ng/ml of loratadine and 150.0 ng/ml of internal standard.

2.5. Extraction

QC, calibration curve and blank plasma samples were extracted employing a liquid–liquid extraction technique. To each tube containing 1 ml plasma, 100 μl of 1.25 M ammonium chloride buffer/ammonia 25% at pH 10.5, and 3 ml isooctane:isoamyl alcohol (95:5, v/v) were added and later vortexed for 2 min. Afterwards, samples were centrifuged for 5 min at 3200 × *g* (Eppendorf 5810R, Germany). The organic layer was evaporated under a stream of nitrogen at 50 °C. Samples were reconstituted with 50 μl of methanol:0.2% formic acid (50:50, v/v), of which 25 μl were injected into the HPLC column.

2.6. HPLC conditions

Chromatography for separation and determination of the drug was carried out by applying the samples to a prepacked narrow-bore Zorbax SB-phenyl, 5 μm, 150 mm × 2.1 mm column (Agilent, USA), using a 2690 Alliance high performance liquid chromatograph (Waters, Milford, MA, USA). The analytical column was protected by a Phenomenex C_{18} guard column (4 mm × 2.0 mm i.d.). The combination of the mobile phase, prepared by mixing acetonitrile:0.20% formic acid in the ratio of 68:32 (v/v) and a flow rate of 0.20 ml/min was found to be adequate for the samples analysis. Separations were performed at room temperature.

2.7. LC–MS/MS conditions

Drug monitoring and quantitation were done using a Finnigan LCQ^{DUO} quadrupole ion-trap mass spectrometer (Finnigan ThermoQuest, USA) equipped with an electrospray ionization (ESI) source (Finnigan) run by XCALIBUR 1.2 software.

Operating conditions for the ESI source, used in the positive ionization mode, were optimized by constantly adding loratadine in methanol (0.10 mg/ml) to the HPLC flow by a syringe pump via a T-connector in the infusion mode. The signal was optimized on the total ion current in MS mode, producing a transfer capillary temperature of 210 °C, a spray voltage of 7.2 kV, and a sheath gas flow of 70 units (units refer to arbitrary values set by the LCQ software). At the same time, the selection of ions and the collision voltages were optimized using LCQ software. In the MS/MS experiments, the protonated precursor molecular ions $[MH]^+$ of loratadine ($m/z = 383$) and the IS ($m/z = 705$) were selected and fragmented by helium gas collision in the ion trap at a relative collision energy of 35%. The mass spectra resulting from these fragmentations were acquired in the SRM mode at $m/z = 337$ for loratadine and $m/z = 432$ for IS. These product ions, $m/z = 337$ for loratadine and $m/z = 432$ for the IS, were extracted for quantification.

Although the detection in MS/MS technique is highly specific and sensitive, nevertheless, endogenous substances can exist in much higher concentration than the analytes of interest and may co-elute with those affecting the ionization of the analytes leading to high imprecision and loss of sensitivity. In order to determine ion suppression matrix effect profiles, analytes were infused into the mobile phase through a T-connection between the column and the interface while injecting the extracted blank plasma samples. The purpose of this post-column infusion

with the analytes is to raise the background level, so the suppression matrix will appear as negative peaks.

2.8. Data treatment

The linearity of loratadine method determination in human plasma was tested for the range of concentrations 0.10–10.0 ng/ml. Calibration curves were prepared by determining the best-fit of peak area ratios (peak area analyte/peak area internal standard) versus concentration, and fitted to the equation $y = bx + a$ by unweighted least-squares regression.

2.9. Method validation

In our laboratory, samples analysis is always carried out in a GLP-compliant manner and therefore the LC–MS/MS methods need to be validated according to currently accepted US Food and Drug Administration (FDA) bioanalytical method validation guidance [10]. The following parameters were considered.

The method's specificity was tested by screening six different batches of healthy human plasma. Each blank sample was tested for interference using the proposed extraction procedure and chromatographic/spectroscopic conditions and compared with those obtained with an aqueous solution of the analyte at a concentration near to the LLOQ.

Linearity was tested for the range of concentrations 0.10–10.0 ng/ml. For the determination of linearity, standard calibration curves of at least seven points (non-zero standards) were used. In addition, a blank and zero plasma samples were also analyzed to confirm absence of interferences, these two samples were not used to construct the calibration function. Four out of seven none zero standards including LLOQ and ULOQ were to meet the following acceptance criteria: no more than 20% deviation at LLOQ and no more than 15% deviation for standards above the LLOQ. The acceptance criteria for correlation coefficient was 0.998 or more, otherwise the calibration curve should be rejected. Six replicate analyses were done.

The intra-day precision and accuracy of the assay was measured by analyzing five spiked samples of loratadine at each QC level (0.30, 5.0 and 8.0 ng/ml). The inter-day precision and accuracy was determined over three days by analyzing 45 QC samples. The acceptance criteria for precision and accuracy deviation values should be within 15% of the actual values.

The absolute recoveries were calculated for both loratadine and IS by comparing peak areas of the extracted samples with the unextracted pure authentic standard solutions peak areas at three QC levels (0.30, 5.0 and 8.0 ng/ml).

In order to test the possible matrix effects, five different (1 ml) blank plasma samples were extracted and processed as mentioned above. Afterwards, each one of the dried samples was spiked with loratadine at the medium QC level (5.0 ng/ml). The samples were vortexed and 25 μl were injected into the HPLC column. The matrix effect was calculated by comparing peak areas obtained for these samples with the unextracted pure authentic standard solution peak areas at the medium QC level (5.0 ng/ml).

For sensitivity determination, the lowest standard concentration in the calibration curve was considered as the lower limit of quantitation, and was to meet the following criteria: LLOQ response should be five times the response of the blank and the LLOQ response should be identifiable, discrete and reproducible with precision of 20% and accuracy of 80–120%. The 0.10 ng/ml concentration was investigated as the lower limit of quantitation. Reproducibility and precision were determined.

Short-term stability: Stored plasma aliquots were thawed and kept at room temperature for a period of time exceeded that expected to be encountered during the routine sample preparation (around 6 h). Samples were analyzed as mentioned above.

Post-preparative stability: The autosampler stability was conducted reanalyzing extracted QC samples kept under the autosampler conditions (4 °C) for 24 h.

Freeze and thaw stability: QC plasma samples containing loratadine were tested after three freeze (−20 °C) and thaw (room temperature) cycles.

Long-term stability of loratadine in human plasma was studied for a period of 8 weeks employing QC samples at three different levels. If after the stability study the analyte was found to be unstable at −20 °C, then it should be stored at −70 °C.

The stability of loratadine and internal standard working solutions were evaluated by testing their validity for 6 h at room temperature. Stability of working solutions was expressed as percentage recovery.

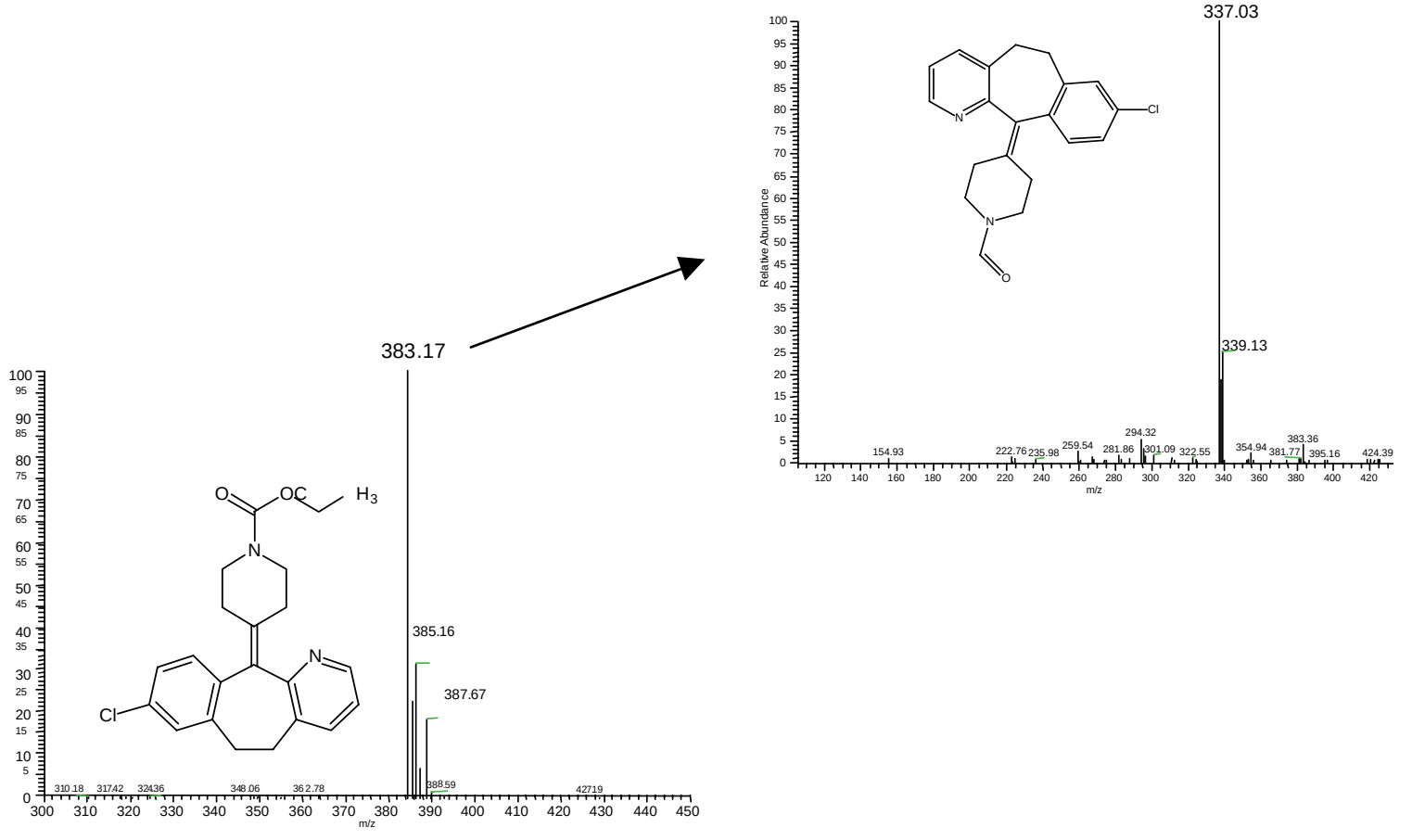

Fig. 2. Positive ion electrospray mass spectrum (bottom) and full scan product ion mass spectrum (top) used in SRM for loratadine determination.

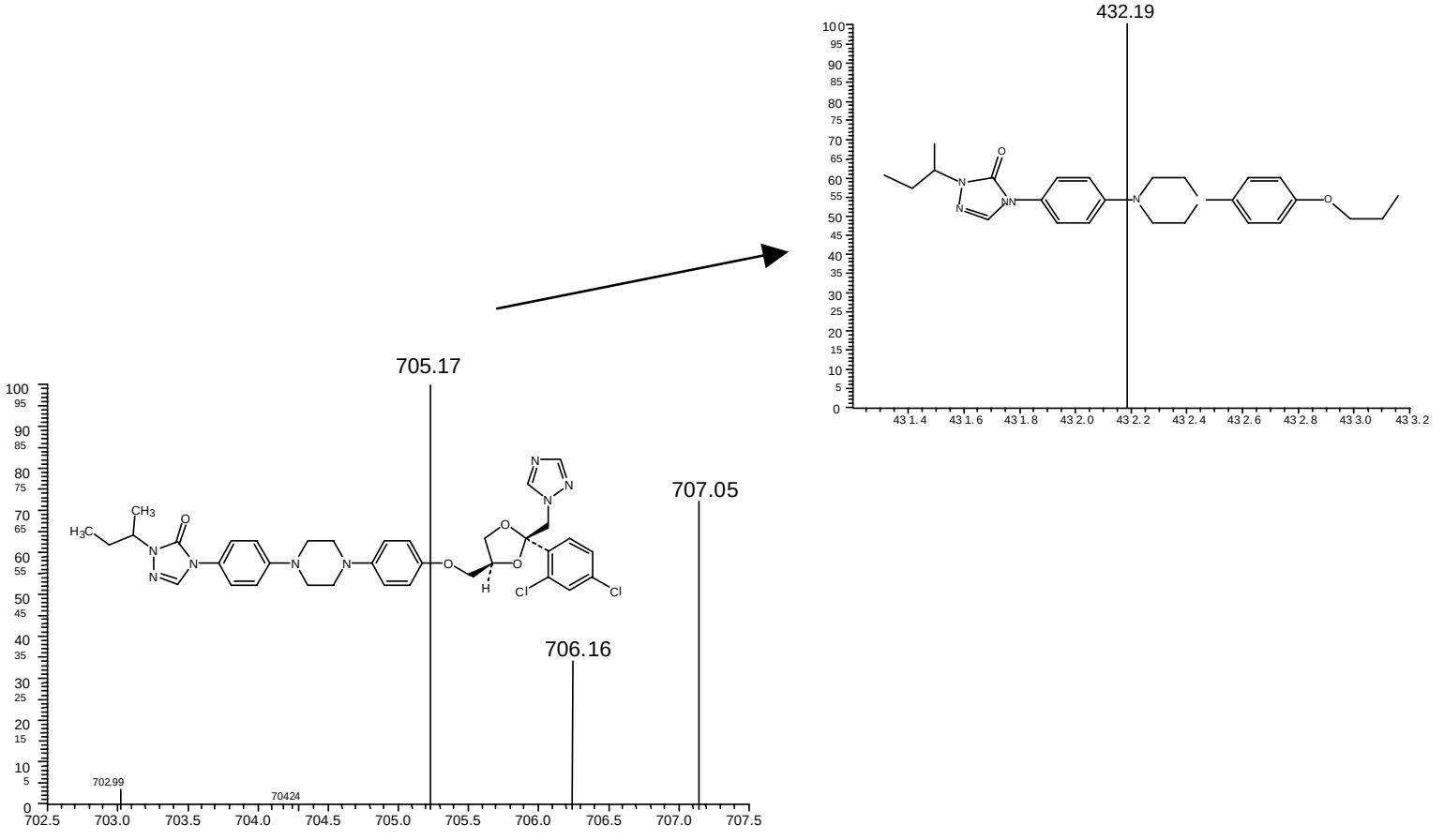

Fig. 3. Positive ion electrospray mass spectrum (bottom) and product ion mass spectrum (top) used in SRM for itraconazole (internal standard) determination.

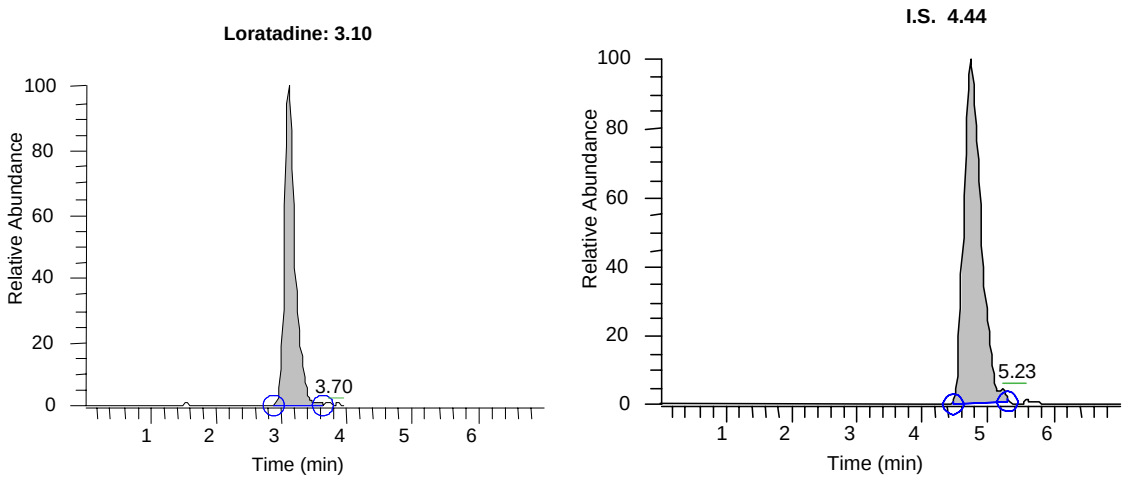

Fig. 4. LC–MS/MS chromatograms showing human plasma sample containing 0.10 ng/ml loratadine (left) and 150.0 ng/ml itraconazole (internal standard).

3. Results and discussion

3.1. Separation and specificity

Loratadine and IS gave protonated precursor molecular ions $[MH]^+$ in the MS mode. The major ions observed were $m/z = 383$ for loratadine (Fig. 2) and $m/z = 705$ for the IS (Fig. 3). The most intense product ions observed in the MS/MS spectra were $m/z = 337$ for loratadine and $m/z = 432$ for the IS. The corresponding single reaction monitoring (SRM) ion spectra of loratadine and the IS are shown in Figs. 2 and 3, respectively.

The product ion chromatograms extracted from supplemented plasma are depicted in Fig. 4. As shown, the retention times of loratadine and the IS were 3.1 and 4.4 min, respectively.

The total HPLC–MS/MS analysis time was 7 min per sample. No ion suppression effects were observed. No interferences of the analytes were observed because of the high selectivity of the MS/MS technique. Fig. 5 shows an HPLC chromatogram for a blank

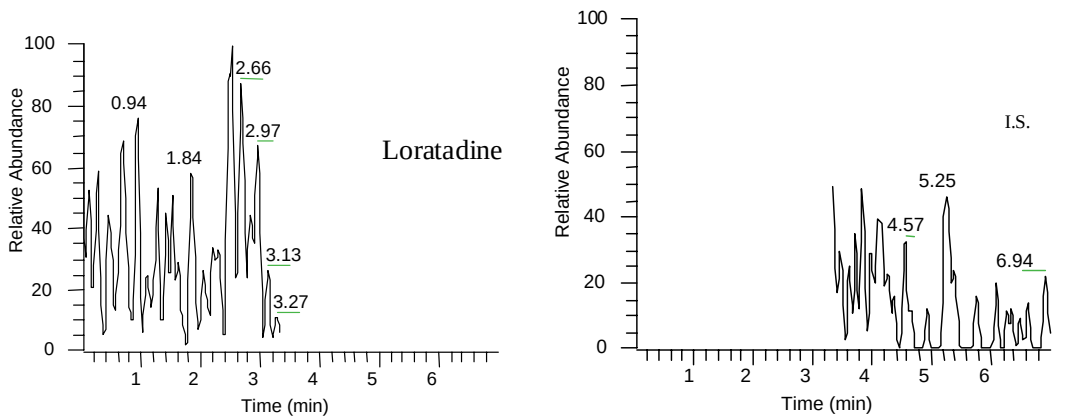

Fig. 5. LC–MS/MS chromatograms of a blank human plasma sample.

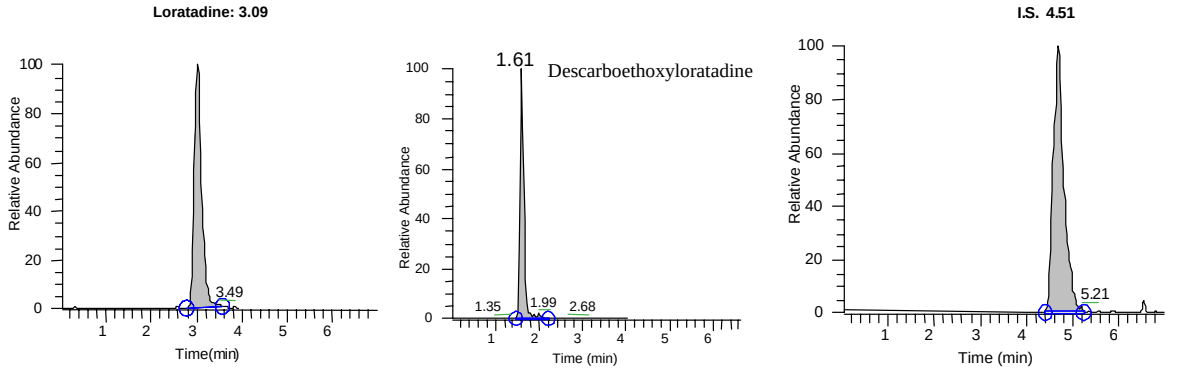

Fig. 6. LC–MS/MS chromatograms showing volunteer's plasma sample after the administration of an oral single dose of 20 mg (2 × 10 mg) tablets of loratadine. The sample's concentration was 5.20 ng/ml. Loratadine (left), metabolite (center) and IS (right).

plasma sample indicating no endogenous peaks at the retention times (t_R) of loratadine or internal standard (itraconazole).

The product ion chromatograms obtained from an extracted plasma sample of a healthy volunteer who participated in a bioequivalence study conducted on 24 persons, is depicted in Fig. 6. Loratadine was unambiguously identified and was quantified as 5.20 ng/ml.

Although the loratadine metabolite (descarboethoxyloratadine) was not quantified according to the FDA guidance for bioavailability and bioequivalence studies [11], nevertheless, the metabolite was monitored to assure absence of interferences with the parent drug or the IS. The metabolite monitoring was accomplished at the molecular ion $m/z = 311$ and MS/MS (daughter) at $m/z = 259$. Fig. 6 shows the metabolite's LC–MS/MS chromatogram of the same volunteer after the oral administration of the drug.

The purpose of these investigations was to develop a specific and sensitive assay for the determination of loratadine used as an antihistaminic drug. HPLC–ESI-MS/MS has several advantages for the analysis of loratadine. The combination of HPLC (under the isocratic conditions described) with ESI-MS/MS leads to short retention times and yields both high selectivity and sensitivity. ESI is a "gentle" ionization technique that produces high mass-to-charge $[M + 1]^+$ precursor ions with minimal fragmentation of the analyte.

3.2. Method validation

The method exhibited a good linear response for the range of concentrations from 0.10 to 10.0 ng/ml. Results of six representative calibration curves for loratadine HPLC determination are given in Table 1. The table also shows the back-calculated concentrations for each point and the mean recovery.

Intra-day accuracy of the method for loratadine as determined from the QC samples run, ranged from 105.00 to 109.50%, while the intra-day precision (CV) ranged from 6.44 to 10.86% at the concentrations of 0.30, 5.0 and 8.0 ng/ml.

Data for the inter-day precision and accuracy are presented in Table 2. The results were within the acceptance criteria for precision and accuracy which establish the deviation values should be within 15% of the actual values.

The absolute recovery determined for loratadine was shown to be consistent, precise and reproducible. Results ranged from 73.75% (CV 7.06%) to 83.03% (CV 5.91%) at the three QC levels (0.30, 5.0 and 8.0 ng/ml). Absolute analytical recovery of internal standard (itraconazole) at 150.0 ng/ml was 82.91% (CV 3.69%). On the other hand, the recovery for those samples tested for matrix effects at medium QC level was 79.54% (CV 5.23%). Compared to the absolute recovery at the same medium QC level (5.0 ng/ml), the results revealed 5.79% matrix effect.

The lower limit of quantitation for loratadine was proved to be 0.10 ng/ml, with a precision of

Table 1
Back-calculated concentrations of loratadine calibration standards and statistics for precision and accuracy from six representative calibration curves

Calibration curves	Concentration of standards (ng/ml)							Parameters of calibration curve		
	0.1	0.5	1.0	2.0	3.0	6.0	10.0	*a*	*b*	*r*
First	0.112	0.521	1.135	1.903	2.889	5.987	10.033	9.29E−02	2.15E−01	9.9973E−01
Second	0.086	0.513	1.095	1.956	2.923	5.994	10.011	8.74E−02	2.39E−01	9.9989E−01
Third	0.081	0.462	1.043	2.075	3.048	5.844	10.091	8.30E−02	1.86E−01	9.9972E−01
Fourth	0.100	0.553	0.875	1.917	3.123	6.090	9.922	7.67E−02	2.14E−01	9.9965E−01
Fifth	0.083	0.492	0.947	2.023	3.053	6.018	9.957	6.85E−02	1.98E−01	9.9995E−01
Sixth	0.115	0.523	0.908	2.018	3.000	6.110	9.963	7.80E−02	2.18E−01	9.9985E−01
Mean	0.096	0.511	1.001	1.982	3.006	6.007	9.996	8.11E−02	2.12E−01	9.9980E−01
Mean recovery (%)	94.19	101.85	99.13	99.02	100.13	100.10	99.96			
CV (%)	15.53	6.01	10.57	3.41	2.91	1.58	0.61	10.61	8.52	0.01

9.84%. Data for LLOQ are presented in Table 3. Fig. 4 shows the chromatogram of an extracted sample that contained 0.10 ng/ml of loratadine (LLOQ).

Table 2
Inter-day accuracy, precision for loratadine determination in spiked plasma samples

Day of analysis	Loratadine concentration in human plasma		
	Low QC, 0.30 ng/ml	Medium QC, 5.0 ng/ml	High QC, 8.0 ng/ml
Day 1	0.344	4.795	8.501
	0.312	5.734	7.776
	0.337	5.402	9.027
	0.325	5.719	8.952
	0.258	5.726	8.067
Day 2	0.272	5.408	9.101
	0.325	4.972	8.652
	0.287	5.083	9.135
	0.312	5.586	8.529
	0.338	5.269	9.126
Day 3	0.297	5.617	8.868
	0.333	4.715	7.642
	0.290	5.686	8.366
	0.302	5.013	8.923
	0.279	4.903	8.957
Mean	0.307	5.309	8.641
S.D.	0.026	0.367	0.489
Precision as CV (%)	8.62	6.92	5.66
Accuracy (%)	102.33	106.18	108.01

Table 3
Lower limit of quantitation

Actual concentration (ng/ml)	Accuracy (%)	R.E. (%)
0.087	87.00	13.00
0.106	106.00	6.00
0.086	86.00	14.00
0.103	103.00	3.00
0.102	102.00	2.00

Concentration = 0.10 ng/ml; mean = 0.097 ng/ml; CV = 9.84%.

3.3. Stability

Short-term stability indicated reliable stability behavior under the experimental conditions of the regular runs. Results are given below in Table 4.

Table 4
Data showing short-term stability of loratadine in human plasma at different QC levels

	QC recovery (%)		
	Low	Medium	High
Run #1	91.86	97.61	102.79
Run #2	94.77	94.49	97.90
Run #3	95.50	104.44	98.97
Run #4	95.32	99.87	93.38
Run #5	92.97	94.72	90.08
Mean	94.08	98.23	96.63
S.D.	1.595	4.120	4.964
CV (%)	1.70	4.19	5.14

Table 5
Data showing freeze and thaw stability of loratadine in human plasma at different QC levels

	QC recovery (%)		
	Low	Medium	High
Run #1	100.00	99.09	105.16
Run #2	86.60	101.40	98.22
Run #3	80.48	101.86	96.67
Run #4	98.54	103.49	79.91
Run #5	86.26	93.28	80.46
Mean	90.38	99.82	92.08
S.D.	8.490	3.985	11.324
CV (%)	9.39	3.99	12.30

Table 6
Data showing long-term stability of loratadine in human plasma at different QC levels

	QC recovery (%)		
	Low	Medium	High
Run #1	93.02	89.55	84.78
Run #2	86.86	92.30	86.84
Run #3	81.07	86.78	90.19
Run #4	92.79	87.79	87.36
Run #5	84.17	86.77	93.36
Mean	87.58	88.64	88.51
S.D.	5.27	2.34	3.33
CV (%)	6.02	2.64	3.76

The post-preparative stability of QC samples kept at 4 °C in the autosampler for 24 h, was also assessed. The mean recoveries of the low, mid and high QC levels were 98.91, 103.65 and 94.94%, respectively, whereas the precision (CV) were 7.50, 10.86 and 6.37%, respectively.

The data that represent the stability of loratadine plasma samples over three cycles of freeze and thawing are given in Table 5. The results indicated that the analyte is stable in human plasma for three cycles of freeze and thaw, when stored at −20 °C and thawed to room temperature.

Table 6 summarizes the long-term stability data of loratadine in plasma samples stored for a period of 8 weeks at −20 °C.

The stability study of loratadine in human plasma showed reliable stability behavior as the mean of the results of the tested samples were within the acceptance criteria of ±15% of the initial values of the controls. These findings indicated that storage of loratadine's plasma samples at −20 °C is adequate when stored for 8 weeks, and no stability-related problems would be expected during the samples routine

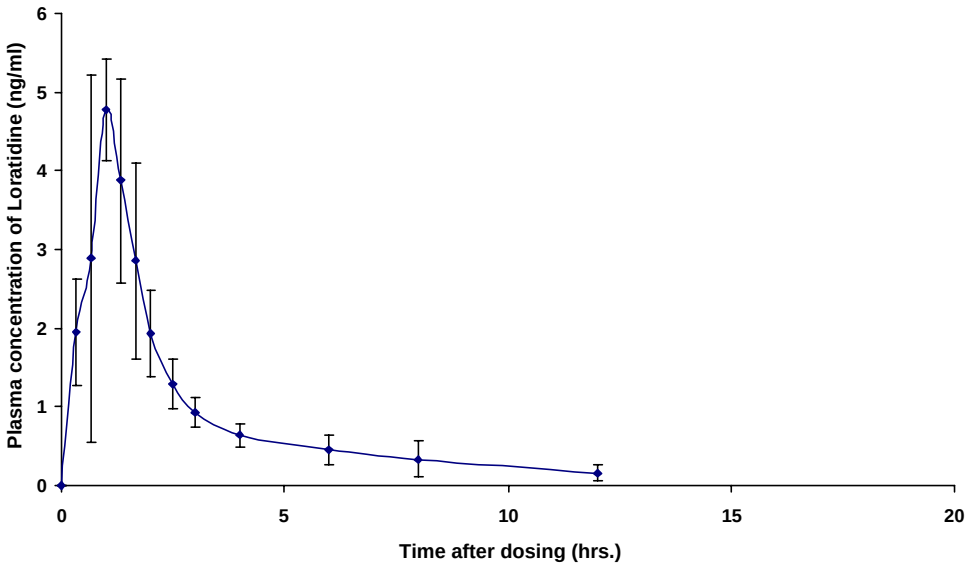

Fig. 7. Representative data showing mean plasma concentration-time profiles of four healthy volunteers after the administration of an oral single dose of 20 mg (2 × 10 mg) tablets of loratadine. The error bars represents ±standard deviation.

Table 7
Data showing working solutions stability

	Recovery (%)	
	Internal standard	Loratadine
Run #1	90.86	89.01
Run #2	86.55	89.14
Run #3	90.68	80.30
Mean	89.36	86.15
S.D.	2.44	5.07
CV (%)	2.73	5.89

analysis for the pharmacokinetic, bioavailability or bioequivalence studies.

The stability of working solutions was tested and established at room temperature for 6 h. Based on the obtained results, working solutions were prepared freshly just before spiking samples for the calibration curve and the QC's. These working solutions were not allowed to stand for a period of time more than needed to complete spiking of plasma samples. Data representing loratadine and internal standard working solutions stability is given in Table 7.

4. Application

The method was applied to analyze plasma samples obtained after the administration of a single dose of 20 mg (2 × 10 mg) loratadine tablets to healthy volunteers participating in bioequivalence studies. The analyses were accomplished in accordance with the FDA bioanalytical method validation guidance [10]. The mean plasma concentration–time profiles of four volunteers is represented in Fig. 7.

5. Conclusions

The proposed method of analysis provided a sensitive and specific assay for loratadine determination in human plasma. It was shown that this method is suitable for the analysis of loratadine in human plasma samples collected for pharmacokinetic, bioavailability or bioequivalence studies in humans.

References

[1] Physicians' Desk Reference (PDR), 55th edition, Medical Economics, Inc., Montvale, NJ, USA, 2001, pp. 2884–2890.
[2] J. Hilbert, E. Radwanski, R. Weglein, V. Luc, G. Perentesis, S. Symchowicz, N. Zampaglione, J. Clin. Pharmacol. 27 (1987) 694–698.
[3] K. Parfitt (Ed.), The Complete Drug Reference, 32nd edition, Pharmaceutical Press, Martindale, 1999, p. 413.
[4] J. Martens, J. Chromatogr. B 673 (1995) 183–188.
[5] P.K. Kunicki, J. Chromatogr. B 755 (2001) 331–335.
[6] F.C.W. Sutherland, A.D. de Jager, D. Badenhorst, T. Scanes, H.K. Hundt, K.J. Swart, A.F. Hundt, J. Chromatogr. A 914 (2001) 37–43.
[7] L. Yang, M. Amad, W.M. Winnik, A.E. Schoen, H. Schweingruber, I. Mylchreest, P.J. Rudewicz, Rapid Commun. Mass Spectrom. 16 (2002) 2060–2066.
[8] W. Naidong, H. Bu, Y.L. Chen, W.Z. Shou, X. Jiang, T.D. Halls, J. Pharm. Biomed. Anal. 28 (2002) 1115–1126.
[9] L. Yang, T.D. Mann, D. Little, N. Wu, R.P. Clement, P.J. Rudewicz, Anal. Chem. 73 (2001) 1740–1747.
[10] Guidance for Industry, Bioanalytical Method Validation, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), May 2001.
[11] Guidance for industry. Bioavailability and Bioequivalence Studies for Orally Administered Drug Products: General Considerations, US Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), March 2003.