

# Determination of Loratadine in Human Plasma by Liquid Chromatography Tandem Mass Spectrometry (LC/MS/MS) and its Pharmacokinetic Application

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## Abstract

**Background:** Development of simple, rapid, and sensitive assay for the determination of loratadine in order to investigate its pharmacokinetic parameters in human plasma and its application in bioequivalence study of Loratadine 10mg Oral Disintegrated Tablets manufactured locally (test) and originally (Reference).

**Methods:** After extraction of loratadine from human plasma, it was chromatographed with mobile phase consisting of 0.5% formic acid: Acetonitrile (10:90 V/V) at flow rate 0.6ml/min, ESI positive mode, and m/z 383→337 for Loratadine. The bioequivalence study was conducted in a Two-Way Open-Label, Crossover design involving 24 volunteers. The criteria used to assess bioequivalence of the two products were  $AUC_{0-4}$ ,  $AUC_{0-inP}$ ,  $C_{max}$ , and  $T_{max}$ .

**Results:** the described method of analysis showed that the average recovery of Loratadine from human plasma was 102.685%. The limit of Quantitation was 0.05ng/ml, and the correlation coefficient ( $r^2$ ) was equal to 0.999893.

Statistical analysis (ANOVA) of the measured parameters showed that there was no significant difference between the two products.

**Conclusion:** The LC/MS/MS method presented is direct, simple, reproducible, sensitive, and linear for the determination of Loratadine in human plasma, and is adequate for clinical pharmacokinetic studies, besides the test product was found to be bioequivalent to the reference and both products can be considered interchangeable in medical practice.

## Introduction

Loratadine is a second-generation H1 histamine antagonist drug used to treat allergies [1], it is closely related to tricyclic antidepressants [2]. In studies exploring physiological indices of CNS functioning, such as EEG-evoked potentials, and sleep latency tests, loratadine has been shown to be free of CNS effects [3].

Loratadine is available as a generic drug and is marketed for its non-sedating properties and is indicated for the relief of nasal and non-nasal symptoms of seasonal allergic rhinitis and for the treatment of chronic idiopathic urticaria [4].

Besides, loratadine is available in the market in several dosage forms, namely, tablets, syrup, and rapidly desintegrating tablets [5]. It is contraindicated in patients who are hypersensitive to this medication or to any of its ingredients. Patients with liver impairment or renal insufficiency (GFR < 30 mL/min) should be given a lower initial dose (10 mg every other day) [6].

Oral disintegrating tablets (ODT) is defined as a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue [7] The significance of these dosage forms is highlighted by the adoption of the term, "Orodispersible Tablet", by the European Pharmacopoeia which describes it as a tablet that can be placed in oral cavity where it disperses rapidly before swallowing [8].

The most frequent symptoms for respiratory conditions are throat soreness and cough; therefore, a new formulation combining loratadine and ambroxol hydrochloride was designed to treat these 2 major symptoms [9].

It worthy to mention that, different analytical methods used for

## Publication History:

Received: May 04, 2014

Accepted: June 04, 2014

Published: June 06, 2014

## Keywords:

Loratadine, Oral disintegrated Tablets, Determination in human plasma, Pharmacokinetics, Tandem Mass Spectrometry.

determination of loratadine in biological samples using HPLC-UV methods shows poor quantitation limits LLOQ above 33ng/ml [10]. Analytical method using HPLC coupled with fluorescence detector showed enhanced sensitivity with LLOQ of 0.5ng/ml after extraction of loratadine with organic solvent followed by back extraction with diluted phosphoric acid [11].

Moreover, for more sensitive determination, LC/MS/MS is used for determination of loratadine in human plasma by protein precipitation of human plasma samples, the detection of loratadine and internal standard was in MRM mode using an ion trap mass spectrometer with electrospray positive ionisation. The ion transitions monitored were 383→337 for loratadine, and 300→226.8 for internal standard [12].

Besides, a sensitive and selective liquid chromatography coupled with atmospheric pressure chemical ionization-mass spectrometry (APCI-LC-MS) method for quantification of loratadine (L) and its active metabolite descarboethoxylopratadine (DCL) in human serum was validated. The detection with m/z 383 for L, and 311 for DCL.

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**Citation:** Nagwa AS, Eslam MS, Erini SH, Sarah HA (2014) Determination of Loratadine in Human Plasma by Liquid Chromatography Tandem Mass Spectrometry (LC/MS/MS) and its Pharmacokinetic Application. Int J Pharm Sci Res 1: 102. doi: <http://dx.doi.org/10.15344/2394-1502/2014/102>

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The limits of quantification were established at 0.1 ng/mL of L and 0.2 ng/mL of DCL, respectively, with an accuracy and precision less than 9%. Recoveries of both analytes were around 80% [13].

For the best sensitive assay and better sample clean up, attaining quantitation limit of 10pg/ml. The tandem mass spectrometric detection was by monitoring singly charged precursor product ion transitions: 383→337(m/z) for loratadine, 388→342(m/z) for LOR-d(3). The low limit of quantitation (LLOQ) was 10 pg/ml [14].

This study was performed to investigate the bioequivalence of loratadine between a generic product of 10mg oral disintegrated Tablets and Reference Product. The study protocol called for 24 healthy volunteers [15]. The bioanalysis of clinical plasma samples was accomplished through development of an LC/MS/MS method, which was validated in accordance with the international guidelines [16]. Pharmacokinetic parameters, determined by standard non-compartmental methods, and analysis of variance (ANOVA) statistics was calculated. The significance of a sequence effect was tested using the subjects nested in sequence as the error term. The 90% confidence intervals for the ratio (or difference) between the test and reference product pharmacokinetic parameters of  $AUC_{0-t}$  and  $AUC_{0-inf}$  and  $C_{max}$  were calculated [17].

## Materials and Methods

### Chemicals and reagents

- Water of HPLC grade.
- Human plasma (Vacsera Blood Bank).
- Methanol HPLC Grade (Scharlau, Spain).
- Acetonitrile of HPLC Grade (Scharlau, Spain).
- Diethyl ether (MTEDA, U.S.A.).
- Dichloromethane. (MTEDA, U.S.A.).
- Sodium Hydroxide (Scharlau, Spain).
- Formic acid of Reagent Grade (SIGMA-ALDRICH, Germany).

### Equipment

- Adjustable Pippettes (P200, P1000 and P10000).
- Disposable plastic pipettes tips - Labtip Yellow (range 5 - 200 µL) & Labtip Blue (range 200 - 1000µL).
- Disposable Glass test tubes 120 x 12 mm.
- Vortex mixer (Boeco, Germany).
- Vacuum pump (Boeco, Germany).
- PH-meters (Boeco, Germany).
- Water purifier (Purelab option- R7ELGA, U. K.).
- Sonicator (Crest, U.S.A.).
- Analytical balance (Sartorius, U.S.A.).
- Concentrator Plus/Vacufuge® plus (Eppendorf, Germany).

### LC-MS/MS Components

- Quaternary pump: Agilent 1200 series, U.S.A.
- Degasser: Agilent 1200 series, U.S.A.
- Autosampler: Agilent 1200 series, U.S.A.
- Mass Detector: Agilent 6410B Triple Quad, U.S.A.
- Data system: Mass Hunter, Agilent.
- A C8 reversed phase column, Thermo Hypersil Gold C8, 4.6 x 50 mm I.D, 5.0 micron.
- Guard column Thermo hypersil Gold C8, 4 x 3 mm I.D.

## Methods

### LC/MS/MS assay

**Chromatographic conditions:** In house developed chromatographic

conditions was used. Mobile phase composition is 0.5% formic acid: Acetonitrile (10:90 V/V). The flow rate was set at 0.6ml/min. Injection volume was set at 2 µl. MS/MS 6410B detector was operated at ESI positive mode, m/z was 383→337 for Loratadine, and 705.2→392.2 (Internal standard) Itraconazole. Fragmentor energy was set at 135 and 90 for Loratadine, and (internal standard) Itraconazole. Collision energy was set at 20 for both Loratadine, and internal standard.

**Preparation of stock and working solutions:** Accurately weigh 10mg of LORATADINE standard. Transfer into a 100ml volumetric flask. Add about 80ml Methanol. Sonicate for 10 minutes. Complete to volume with Methanol. This solution contains 100ug/ml LORATADINE "Solution A". Transfer quantitatively 0.1ml of Solution A into a 100ml volumetric flask and complete to volume with water to obtain 100ng/ml "Solution B".

**From "Solution B" the following were prepared:**

Master Solution used	Mililitres taken	Final concentration obtained (ng/ml)	Final volume (ml)
"Solution B"	0.05	0.5	10
"Solution B"	0.1	1	10
"Solution B"	0.2	2	10
"Solution B"	0.4	4	10
"Solution B"	0.5	5	10
"Solution B"	2	20	10
"Solution B"	4	40	10

**Itraconazole (Internal Standard) standard solution:** Accurately weigh 10mg of Itraconazole Standard. Transfer into a 100ml volumetric flask. Add about 80ml of Methanol. Sonicate for 10 minutes. Complete to volume with Methanol. This solution contains 100ug/ml Itraconazole. Transfer quantitatively 2ml of prepared solution into a 100ml volumetric flask and complete to volume with water to obtain 2000ng/ml Itraconazole.

**Preparation of Loratadine Standard concentrations in human plasma:** The standard samples in human plasma were prepared by transferring a 50 µl aliquot of the working standard solutions of loratadine at concentrations ranging from 0.5 to 100 ng/ml to a centrifuge tubes containing 0.5 ml of blank human plasma.

**Sample preparation:** Volunteers human plasma samples, standard samples (500ul) were transferred into appropriate centrifuge test tubes 50ul of the internal standard (Itraconazole working solution 2000ng/ml) were added. Then samples were Vortex-mixed for approximately 1 minute. 50ul of 0.25M (NaOH) were added. Then samples were Vortex-mixed for approximately 1 minute. 3ml of [Diethyl ether: Dichloromethane (70:30) v/v] were added and Vortex-mix was done for approximately 1 to 2 minutes. Centrifugation of samples was done at 4000rpm for 5 minutes; clear organic supernatant layer were transferred to clean test tube and evaporated till dryness. The remaining residue was reconstituted with 200ul mobile phase and transferred to insert vial for injection and quantitation on LC/MS/MS.

**Quantitation:** The unknown sample concentration of volunteer human plasma was calculated from the following formula:  $Y = aX + b$ . Where Y is the peak area ratio, X is the unknown Concentration of loratadine

in human plasma samples,  $a$  is the slope of the calibration curve,  $b$  is the Y-Intercept.

All the previously mentioned procedure was performed stepwise by means of LC-MS/MS instrument using Mass Hunter Quantitative Analysis software, where it substitutes the obtained peak area ratio in the equation and calculates the concentration which is added in the printed output of the LC-MS/MS device for each chromatogram.

### Bioequivalence study

**Subjects:** Twenty-four healthy adult, male volunteers participated in this study were subjected to complete physical examination and neurological assessment, urine analysis and blood (hematology, biochemistry, and serology). None of the volunteers had any history of drug or alcohol abuse, nor did they have any acute or chronic gastrointestinal, cardiac, vascular, hepatic, or renal disease. No concurrent medication was allowed during the course of the study. Subjects did not receive any meals for four hours after study dose administration, neither any beverages drink, nor coffee or tea. At 1:00 p.m. they received a standard meal, and at 6:00 p.m. another meal. The written informed consent for the intended study were reviewed, discussed and then signed by the participant and clinical investigator before the beginning of screening procedure without any obligation on the volunteers to continue if they didn't want to.

**Study design:** This study was a single-center, open-label, randomized, single-dose study with Two-way crossover design to compare the bioavailability of loratadine between two products, in 24 healthy adult, male volunteers under fasting conditions with a washout period fourteen days between dosing. The number and disposition of the blood collections as well as the washout period were designed with respect to pharmacokinetic parameters of loratadine.

**Sample collection:** The number of blood collections for drug analysis was 17 samples in each study period. The volume of blood taken for the determination of Loratadine in plasma was 5ml per sample. The following blood samples for the analysis of Loratadine in plasma were collected at the following intervals: 0 (directly prior to dosing), 10min, 20min, 30min, 45min, 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 9.0, 12.0, 24.0, 48.0 and 72.0 hours after the administration. Blood samples were collected into tubes containing EDTA disodium as an anticoagulant slightly shaken, and centrifuged at approximately 4000 r.p.m. for 10 minutes. After centrifugation, plasma samples were transferred directly into a 5ml-plastic tube. These samples were immediately stored at the study site in a freezer at a nominal temperature  $-80^{\circ}\text{C}$  until analysis. The label of the collecting tubes had the study's code number, subject number, study period, and the designated sample number. The total amount of blood loss during the whole study did not exceed 170ml.

**Analysis of plasma samples:** A high-performance liquid chromatography coupled with Triple Quad Mass Detector LC-MS/MS was used for the determination of loratadine in human plasma. Samples from 24 subjects (who completed both periods of the study) were analyzed. The bioanalytical method was validated according to the international guidelines.

**Pharmacokinetic calculations:** The following Pharmacokinetic parameters (variables) of Loratadine were assessed; Maximum plasma concentration ( $C_{\text{max}}$ ), Time point of maximum plasma concentration ( $T_{\text{max}}$ ), Half-life of drug elimination during the terminal phase ( $t_{1/2\text{e}}$ ), and terminal rate of elimination ( $K_e$ ),

area under plasma concentration-time curve from zero to the last quantifiable concentration estimate ( $AUC_{0-t}$ ), Mean Residence Time (MRT), Area under plasma concentration-time curve from zero to infinity ( $AUC_{0-\infty}$ ), Assessment of drug absorption rate ( $C_{\text{max}} / AUC_{0-\infty}$ ), Percent of the area measured by  $AUC_{0-t}$  relative to the extrapolated total  $AUC_{0-\infty}$  [ $(AUC_{0-t} / AUC_{0-\infty}) \times 100$ ].

**Statistical analysis of data:** Statistical analysis of the determined pharmacokinetic data was performed using statistical computerized program M-Stat software for determination of analysis of variance (ANOVA). Bioequivalence could be demonstrated for loratadine within the prescribed 90% confidence interval of 80.00% to 125.00% for  $AUC_{0-t}$ ,  $AUC_{0-\infty}$  and  $C_{\text{max}}$  with respect to the parametric method on Ln-transformed data.

### Results and Discussion

#### HPLC Assay Analytical procedure validation

**Chromatogram of loratadine:** Loratadine was well separated and its retention time was 1.37 min. sharp, and symmetrical peaks were obtained with good baseline resolution and minimum tailing, thus facilitating the accurate measurement of the peak area. The in house developed chromatographic conditions, was nearly in accordance to published literature [12,14,18] with modifications.

**Linearity and quantitation:** Peak area ratios of varying amounts of loratadine in human plasma (Ranging from 0.05 to 10 ng/ml) was highly linear ( $r^2$  was equal to 0.999893). The results of three replicate analysis of loratadine at three different days over one week period were obtained, where the average correlation coefficient was 0.9907, which is in accordance with the latest FDA Guidelines [16], and so it could be used for pharmacokinetic and bioavailability studies of Loratadine.

**Precision and accuracy:** To assess the precision and accuracy of the developed analytical method, three distinct concentrations in the range of expected concentrations where evaluated. Precision and accuracy was assessed at within-day basis, which defines those parameters during a single analytical run; and at between-day basis, which measure the between day variability, possibly involving different analysts, reagents, etc. The results of within day accuracy of loratadine showed an average recovery percentage of 98.254%. The results of between days accuracy of loratadine showed an average recovery percentage of 100.8315%, with an average CV% of 13.027%. The results of freeze-thaw stability, short term stability, and long term stability of loratadine in human plasma showed that the average recovery of loratadine was greater than 96% providing that loratadine is stable in the studied condition.

The method used for sample preparation is in accordance with published literature [12,18] which applies alkalization of plasma followed by liquid- liquid extraction technique for sample preparation.

#### Bioequivalence study

**Clinical observation:** All the participating volunteers well tolerated the drug and the procedure adopted in the study. Every sample from the 24 volunteers during each phase was obtained at the proper. No serious adverse event, or unexpected adverse drug reaction occurred during the study. No adverse events were observed in either period.

**Pharmacokinetic data and assessment of bioequivalence:** The assessment of bioequivalence, as a measure of efficacy, was based on

pharmacokinetic parameters derived individually for each participant from the loratadine concentration in plasma.

The mean Maximum plasma concentration ( $C_{max}$ ) was  $5.8215 \pm 2.0128$  ng/ml and  $5.3907 \pm 2.0484$  ng/ml, Time point of maximum plasma concentration ( $T_{max}$ )  $1.2778 \pm 0.8794$  hr and  $1.4236 \pm 0.8098$  hr, Half-life of drug elimination during the terminal phase ( $t_{1/2e}$ )  $19.8722 \pm 3.3993$  hr and  $20.5016 \pm 3.8831$  hr (Table 1), Area under plasma concentration-time curve from zero to the last quantifiable concentration estimate ( $AUC_{0-t}$ )  $48.9551 \pm 21.9226$  ng.hr/ml and  $46.2835 \pm 20.6650$  ng.hr/ml, Mean Residence Time (MRT)  $30.6343 \pm 6.2843$  hr and  $29.6545 \pm 7.1982$  hr (Figure 1).

Pharmacokinetic Parameter	Treatment (Mean $\pm$ SD)	
	Test product	Reference product
$C_{max}$ (ng/ml)	$5.8215 \pm 2.0128$	$5.3907 \pm 2.0484$
$T_{max}$ (hr)	$1.2778 \pm 0.8794$	$1.4236 \pm 0.8098$
$AUC_{0-t}$ (ng. hr/ml)	$48.9551 \pm 21.9226$	$46.2835 \pm 20.6650$
$AUC_{0-inf}$ (ng. hr/ml)	$54.3295 \pm 22.3423$	$51.3693 \pm 22.1563$
Ke ( $hr^{-1}$ )	$0.0360 \pm 0.0073$	$0.0349 \pm 0.0061$
$t_{(1/2)e}$ (hr)	$19.8722 \pm 3.3993$	$20.5016 \pm 3.8831$
MRT	$30.6343 \pm 6.2843$	$29.6545 \pm 7.1982$

Table 1: Pharmacokinetic parameters for Loratadine oral disintegrated tablets of Test and Reference Products.

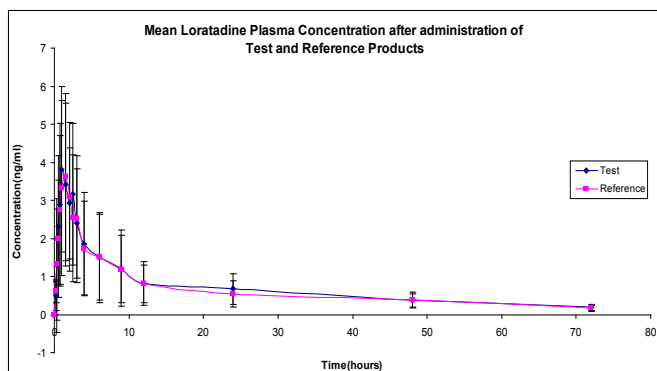


Figure 1: Mean Plasma concentration of Loratadine following single dose administration of loratadine Oral disintegrated tablet test and reference products.

Area under plasma concentration-time curve from zero to infinity ( $AUC_{0-\infty}$ )  $54.3295 \pm 22.3423$  ng.hr/ml and  $51.3693 \pm 22.1563$  ng.hr/ml for test and reference products respectively (Figure 2-3). The results of loratadine pharmacokinetic parameters obtained was nearly in accordance with reported literature [19] which stated that  $T_{max}$  for loratadine were found to be 1.5hr (range 0.5 to 4.5hr),  $C_{max}$   $3.65 \pm 2.82$  ng/ml, and reported literature [5] which stated that  $T_{1/2}$  ranges from 3 to 20 hours (Table 2).

Pharmacokinetic Parameter	90% Confidence intervals of parametric means		
	Point estimate (%)	Lower limit (%)	Upper limit (%)
$C_{max}$	109.601	101.597	118.235
$AUC_{0-t}$	105.393	93.6556	118.602
$AUC_{0-inf}$	106.212	94.5184	119.352

Table 2: 90 % C.I for Loratadine oral disintegrated tablets Test and reference Products.

**Statistical analysis:** The data obtained from measurements of plasma concentration was transformed prior to analysis using natural Ln transformation. Pharmacokinetic parameters, e.g:  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-inf}$  were analyzed using two way ANOVA procedure to rule out the possibility of a significant carryover effect. Also 90% confidence interval of 80.00% to 125.00% for  $AUC_{0-t}$ ,  $AUC_{0-inf}$  and  $C_{max}$  with respect to the parametric method on Ln-transformed data should be fulfilled. The results of 2 way ANOVA on  $C_{max}$ ,  $T_{max}$ ,  $AUC_{0-t}$ , and  $AUC_{0-inf}$  for loratadine showed that there was no significant difference between test and reference product (Table 3 & 4, Figure 4).

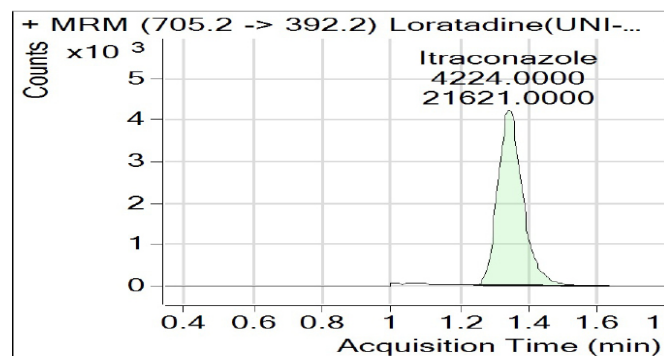
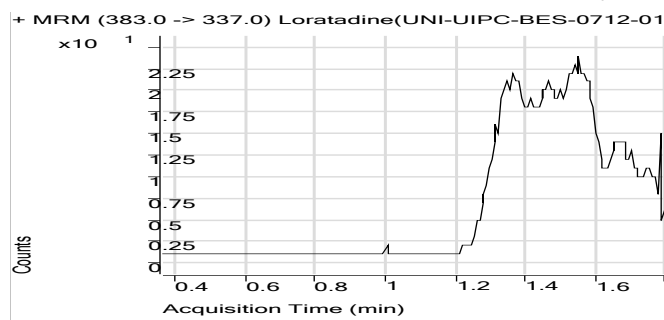


Figure 2: Sample chromatogram representing an MRM data of blank human plasma sample spiked with internal standard itraconazole.

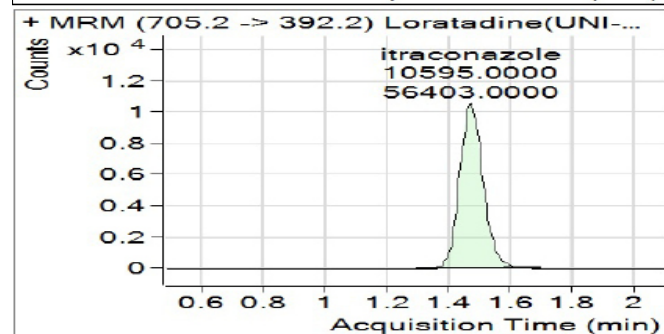
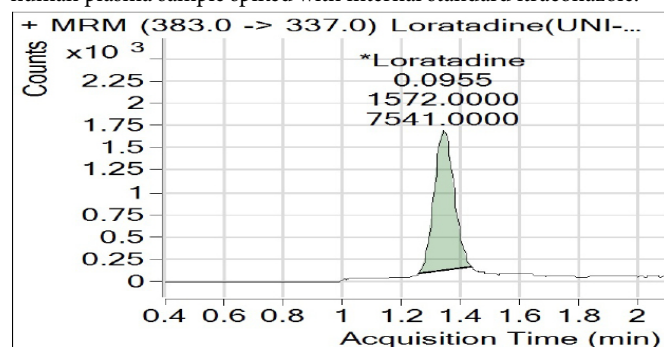


Figure 3: Sample chromatogram representing an MRM data of blank human plasma sample spiked with 0.05ng/ml loratadine and internal standard itraconazole.



Reference							
Subject	T <sub>max</sub>	C <sub>max</sub>	AUC <sub>last</sub>	AUC <sub>INF</sub>	Lambda <sub>z</sub>	t <sub>1/2</sub>	MRT <sub>INF</sub>
A	1.5	1.34148	20.2811	25.9565	0.02375	29.1854	45.2952
B	0.333	2.83813	11.3876	12.9661	0.03554	19.501	31.5755
C	0.75	1.73774	34.4088	37.7849	0.03137	22.0945	30.3295
D	0.75	4.40916	26.0494	27.5807	0.03918	17.6895	21.7585
E	0.5	7.60105	37.3893	38.9734	0.04159	16.6681	19.9755
F	2.5	7.11504	60.3607	66.2837	0.03022	22.9397	29.7998
G	1.5	2.77739	36.3754	47.9384	0.02382	29.105	47.6117
H	2	5.24442	49.9299	56.233	0.0374	18.535	27.6745
I	1	6.87602	46.1556	51.0214	0.04125	16.8035	26.9378
J	1	4.31205	27.8765	33.1211	0.03476	19.9412	34.255
K	3	4.10985	53.6978	62.4771	0.02974	23.3089	36.0146
L	1.5	5.7906	33.6403	38.2732	0.03034	22.845	28.9835
M	1.5	7.74371	53.8507	60.4603	0.03054	22.6951	32.1991
N	1.5	7.00874	64.586	66.8072	0.04154	16.688	21.6528
O	1	7.41284	67.3895	69.3063	0.04221	16.4232	22.4599
P	0.75	8.52161	50.3561	52.0271	0.04578	15.1411	24.0349
Q	3	5.25433	63.5424	69.623	0.03538	19.5922	26.1669
R	1.5	3.41738	25.7631	27.4308	0.03498	19.8133	22.3605
S	0.75	3.82562	23.2236	26.2029	0.03495	19.8308	30.4172
T	0.333	7.18506	39.3398	47.18	0.02648	26.1741	40.1723
U	1	4.41894	89.1306	101.424	0.02984	23.2277	32.9004
V	3	6.09665	79.4598	88.1425	0.03605	19.2258	28.7707
W	2	7.14766	81.289	85.8432	0.04448	15.5849	23.0244
X	1.5	7.19241	35.3212	39.8062	0.03643	19.0257	27.3371
Mean	1.42358	5.39075	46.2835	51.3693	0.0349	20.5016	29.6545
SD	0.80982	2.04836	20.665	22.1563	0.00614	3.88311	7.19818
CV%	56.8861	37.9978	44.6488	43.1315	17.5803	18.9405	24.2735
Min	0.333	1.34148	11.3876	12.9661	0.02375	15.1411	19.9755
Max	3	8.52161	89.1306	101.424	0.04578	29.1854	47.6117
Median	1.5	5.52247	42.7477	49.4799	0.03518	19.7027	28.8771

Table 3: Pharmacokinetic parameters of LORATADINE following administration of single oral dose of Loratadine 10mg Rapid Dissolve Tablets (Reference product) to 24 Volunteers.

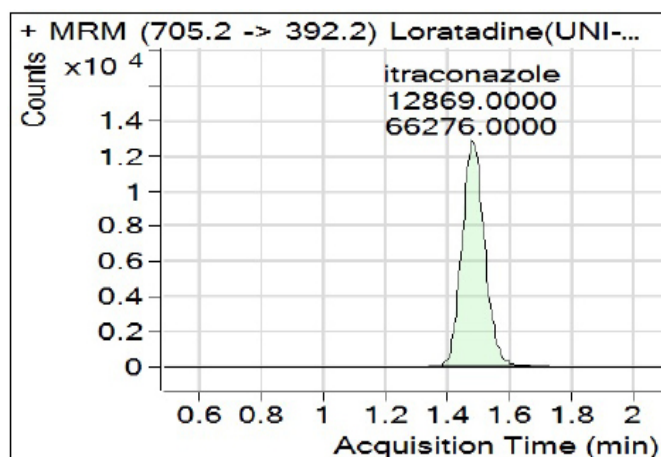
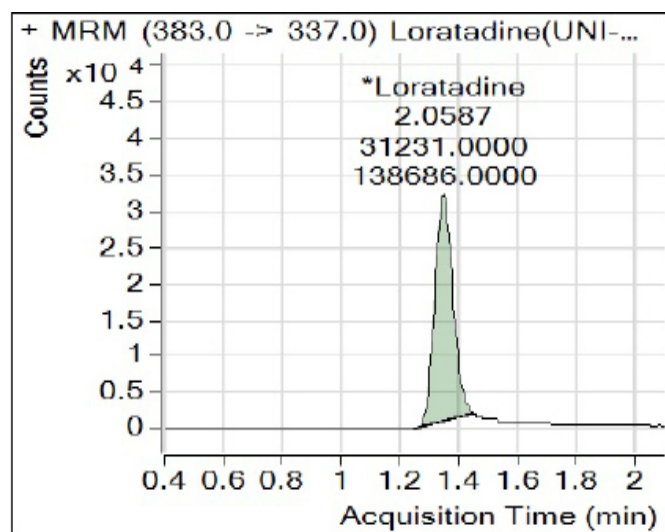


Figure 4: Sample chromatogram representing an MRM data of blank human plasma sample spiked with 2 ng/ml loratadine and internal standard itraconazole.

Test							
Subject	T <sub>max</sub>	C <sub>max</sub>	AUC <sub>last</sub>	AUC <sub>INF</sub>	Lambda <sub>z</sub>	t <sub>1/2</sub>	MRT <sub>INF</sub>
A	1.5	1.3696	16.3635	19.9672	0.02779	24.9397	42.7288
B	0.5	3.14745	17.0303	20.5191	0.02994	23.1525	37.886
C	0.75	3.1156	15.73	19.0808	0.02906	23.8526	38.3215
D	1	3.12827	31.1266	33.1376	0.0411	16.8635	26.6466
E	0.75	8.66104	58.1602	67.5178	0.03641	19.037	32.1573
F	0.75	7.21098	56.5941	63.4714	0.02996	23.135	32.504
G	2	3.07894	31.5977	37.9853	0.0279	24.8443	39.8116
H	0.75	6.2269	43.4588	53.1368	0.03427	20.2268	37.4979
I	1	6.96263	34.8732	39.931	0.03873	17.8987	29.9915
J	1	6.86389	64.8857	73.267	0.03054	22.6941	33.2603
K	1.5	3.98689	37.3706	45.3272	0.03035	22.8413	37.5294
L	0.5	7.82417	65.3198	70.8808	0.03752	18.4723	27.5323
M	1	5.8808	33.1465	36.8415	0.04294	16.1412	26.0765
N	4	6.47711	77.1714	84.5555	0.03284	21.1064	26.7005
O	1	6.77925	77.3203	78.7683	0.05164	13.4228	20.7299
P	1.5	8.74915	98.9943	99.9767	0.05751	12.0527	19.5202
Q	2.5	6.76089	50.512	55.7743	0.03345	20.722	28.7109
R	0.5	4.08388	39.1155	43.7087	0.03189	21.7389	32.9819
S	0.333	5.8827	31.766	36.5155	0.03418	20.2787	33.1579
T	1.5	7.868	62.8452	73.5363	0.0326	21.2613	32.4357
U	2.5	4.579	59.569	64.8248	0.03557	19.4863	26.8492
V	0.333	6.81588	77.3222	82.101	0.04289	16.1595	22.5506
W	1	6.80975	60.6873	66.0357	0.03579	19.3665	26.9329
X	2.5	7.45377	33.9627	37.047	0.04021	17.2386	22.7106
Mean	1.27775	5.82152	48.9551	54.3295	0.03605	19.8722	30.6343
SD	0.87943	2.01278	21.9226	22.3423	0.0073	3.39929	6.28431
CV%	68.8268	34.5748	44.781	41.1237	20.2404	17.1058	20.514
Min	0.333	1.3696	15.73	19.0808	0.02779	12.0527	19.5202
Max	4	8.74915	98.9943	99.9767	0.05751	24.9397	42.7288
Median	1	6.619	46.9854	54.4556	0.03422	20.2527	31.0744

Table 4: Pharmacokinetic parameters of LORATADINE following administration of single oral dose of Loratadine 10mg Oral Disintegrated Tablets (Test product) to 24 Volunteers.

## Conclusion

It can be concluded that the bioanalytical method developed for the determination of Loratadine in human plasma is valid, sensitive, specific, precise and accurate, and could be used for the determination of drug pharmacokinetic parameters. Besides, results of the bioequivalence study of loratadine oral disintegrated tablet (test product) compared to, versus the reference product are bioequivalent, since they deliver equivalent amounts of loratadine to the systemic circulation at the same rate.

## References

1. Kassem N, Roman I, Gural R, Dver JG, Robillard N (1988) Effects of loratadine (SCH 29851) in suppression of histamine-induced Skin wheals. *Ann Allergy* 60: 505-507
2. Barenholtz AH, McLeod DC (1989) Loratadine: a non-sedating antihistamine with once-daily dosing. *DICP* 23: 445-450.
3. Kay GG, Harris AG. (1999) Loratadine: a non-sedating antihistamine. Review of its effects on cognition, psychomotor performance, mood and sedation. *Clin Exp Allergy* 3: 147-150.
4. Claritin Redi Tabs 5 mg Tablet, Clinical pharmacology and biopharmaceutics Review (2006) NDA 21-993, page 4.
5. Hilbert J1, Radwanski E, Weglein R, Luc V, Perentesis G, et al. (1987) Pharmacokinetics and dose proportionality of loratadine, *J Clin Pharmacol* 9: 694-698.
6. Kenilworth NJ (2000) Claritin Tables, syrup and rapidly disintegrating tablets prescribing information, Schring Crop.
7. US Food and Drug Administration, CDER Data Standards Manual, 2003.
8. European Directorate for quality of Medicines.
9. Song JH, Shin SC (2009) Development of the loratadine gel for enhanced transdermal delivery. *Drug Dev Ind Pharm.* 8: 897-903.
10. Villacampa J, Alcantar F, Rodriguez JM, Morales JM, Herrera J, et al. (2003) Pharmacokinetic properties of single-dose loratadine and ambroxol alone and combined in tablet formulations in healthy men. *Clin Ther* 8: 2225-2232.
11. Pavalache G, Dorneanu V (2011) Validation Of An Analytical Method Based On High Performance Liquid Chromatography For Determination Of Loratadine In Pharmaceutical Preparations And Biological Environments. *FARMACIA* 59: 2.
12. Zhong D, Blume H (1994) HPLC-determination of loratadine and its active metabolite descarboethoxylo-ratadine in human plasma *Pharmazie.* 49: 736-739.
13. Vlase L, Imre S, Muntean D, Leucuta SE., (2007) Determination of loratadine and its active metabolite in human plasma by high-performance liquid chromatography with mass spectrometry detection, *J Pharm Biomed Anal.*3: 652-657.
14. Dordevic S, Rusic B, Denic K, Kilibarda V, Vukcevic-Perkovic N, et al. (2013) Simultaneous Determination Of Loratadine And Descarboethoxylo-Ratadine In Human Serum By High-Per-Formance Liquid Chromatography (HPLC) – Atmospheric Pressure Chemical Ionization-Mass Spectrometry (APCI-LC-MS) *Method. MD-Medical Data* 1: 027-030.
15. Naidong W, Addison T, Schneider T, Jiang X, Halls TD (2003) A sensitive LC/MS/MS method using silica column and aqueous-organic mobile phase for the analysis of loratadine and descarboethoxy-loratadine in human plasma. *J Pharm Biomed Anal* 32: 609-617.
16. CFR 2013, subpart B, Section 320.26: Guidelines on the design of a single-dose in vivo bioavailability or bioequivalence study Ch.I (4-1-13), page 198.
17. Guidance for Industry Bioanalytical method Validation.
18. Guidance for Industry (2003) Bioavailability and Bioequivalence Studies for Orally Administered Drug Products - General Considerations.
20. Choi YW, Nam D, Kang KH, Ha KW, Han IH, et al. (2006) High-Performance Liquid Chromatographic-Tandem Mass Spectrometric Determination of Itraconazole in Human Plasma for Bioavailability and Bioequivalence Studies. *Bull Korean Chem Soc* 27: 291.
21. Study CL2004-01) Claritin Redi Tabs 5 mg Tablet, Clinical pharmacology and biopharmaceutics Review, NDA 21-993, page 11.