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ScienceDirect
Journal of Pharmaceutical and Biomedical Analysis 43 (2007) 1236–1242
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Simultaneous determination of loratadine and desloratadine in pharmaceutical preparations using liquid chromatography with a microemulsion as eluent

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Received 30 August 2006; received in revised form 12 October 2006; accepted 17 October 2006
Available online 28 November 2006

Abstract

A rapid HPLC procedure for analytical quality control of pharmaceutical preparations containing the antihistaminic drug substance loratadine and/or its analog desloratadine (which is also an active metabolite of loratadine) was developed using a microemulsion as the eluent. The separation was performed on a column packed with cyanopropyl bonded stationary phase adopting UV detection at 247 nm using a flow rate of 1 ml/min. The optimized microemulsion mobile phase consisted of 0.1 M sodium dodecyl sulphate, 1% octanol, 10% *n*-propanol and 0.3% triethylamine in 0.02 M phosphoric acid, pH 3.0. The developed method was validated in terms of specificity, linearity, lower limit of quantification, lower limit of detection, precision and accuracy. With the proposed method satisfactory resolution between loratadine and desloratadine (resolution factor = 3.85). The method requires a minimum of sample handling and is rapid (10 min), and reproducible (R.S.D. < 2.0%). The mean recoveries of the analytes in pharmaceutical preparations were in agreement with those obtained from a reference method, as revealed by statistical analysis of the obtained results using the Student's *t*-test and the variance ratio *F*-test. Pseudoephedrine, the co-formulated drug substance, did not interference with the assay and was successfully separated using the developed HPLC method.

Keywords: Loratadine; Desloratadine; HPLC; Microemulsion; Pharmaceutical preparations

1. Introduction

Loratadine, ethyl-4-(8-chloro-5,6 dihydro-11H-benzo[5,6] cyclohepta [1,2 *b*] pyridin-11-ylidene)-1-piperidine carboxylate, is a long acting antihistamine drug [1]. Loratadine (LOR) undergoes extensive first pass metabolism in the liver, forming an active metabolite, desloratadine (DSL = descarboethoxy loratadine) (Fig. 1).

Loratadine and desloratadine are selective peripheral H1 receptor antagonists, devoid of any substantial effect on the central and autonomic nervous system [2]. Desloratadine exhibits qualitatively similar pharmacodynamic activity with a relative oral potency in animals two to three-fold greater than loratadine probably due to a higher affinity for histamine H1 human receptors [3].

In the literature several methods have been described for determination of LOR in pharmaceutical preparations including UV spectrophotometry [4–10], colorimetry [5,11–14], spectrofluorometry [5], atomic absorption spectrometry [14], polarography [15], densitometry [6,16], capillary electrophoresis [17–19] and high performance liquid chromatography [4,6,7,20]. The determination of DSL in pharmaceutical preparations has only been described in one paper dealing with CE [21]. The simultaneous determination of LOR and DSL in pharmaceutical preparations adopting liquid chromatography with UV detection was reported by Qi et al. [22].

Microemulsions are clear, thermodynamically stable isotropic mixtures containing oil, water, surfactant and most often also a medium chain alcohol acting as a cosurfactant. They can be considered as two-phase solvents consisting of a micellar

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doi:10.1016/j.jpba.2006.10.027

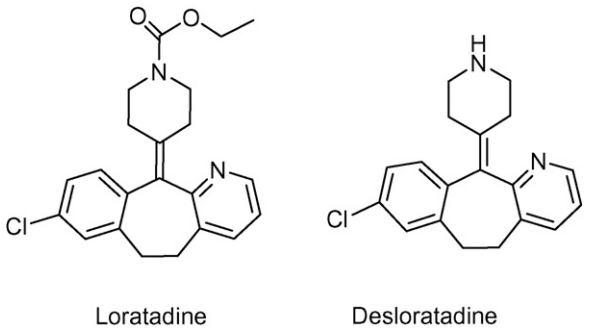

Fig. 1. Structural formula of loratadine and desloratadine.

phase surrounded by either an aqueous or an organic phase. The micellar phase may contain either an organic solvent or an aqueous phase (reversed micelles). Thus, the microemulsions may either be oil-in-water (o/w) or water-in-oil (w/o) microemulsions [23], where the o/w microemulsions are the preferred for HPLC. The partitioning and the interfacial adsorption of the analytes in the microheterogenous systems are responsible for the separations obtained [23]. In previous reports on microemulsion liquid chromatography (MELC) [24–29] the potential of application of microemulsions as mobile phases in LC analysis was proven.

The aim of the present work was to develop, validate and apply an efficient and novel liquid chromatographic method using microemulsion as mobile phase for the rapid simultaneous determination of both LOR and DSL in pharmaceutical preparations, in a single chromatographic run.

2. Experimental

2.1. Chemicals

Loratadine and desloratadine were kindly provided by Schering-Plough Corporation, USA. Pharmaceutical preparations containing loratadine include; Claritine tablets labeled to contain 10 mg LOR per tablet, Loratan D tablets labeled to contain 5 mg LOR and 120 mg pseudoephedrine sulphate per tablet, Claritine syrup labeled to contain 1 mg/ml LOR. Areius tablets labeled to contain 5 mg DSL per tablet. All the pharmaceutical preparations were purchased from a local pharmacy.

Sodium dodecyl sulphate (SDS) 99% purity was obtained from Park Scientific Limited, Northampton, UK. 1-Propanol, methanol and diisopropyl ether (all of HPLC grade) as well as triethylamine (TEA) were obtained from Riedel-deHäen (Seelze, Germany). 1-Butanol and tetrahydrofuran (HPLC grade) were obtained from Merck (Darmstadt, Germany). 1-Octanol (HPLC grade) was obtained from Aldrich (Gillingham, UK). 1-Butyl acetate was obtained from Fluka (Buchs, Switzerland). Orthophosphoric acid for analysis was obtained from Prolabo (Paris, France).

2.2. Apparatus

Separation was performed with a Perkin-Elmer™ Series 200 chromatograph equipped with a Rheodyne injector valve with a 20 μl loop and a UV/vis detector operated at 247 nm. Total Chrom workstation was applied for data collecting and processing (MA, USA).

2.3. Columns and mobile phases

Separation was achieved on a Hibar®, Lichrosorb®, cyanopropyl column (250 mm × 4.6 mm i.d., 5 μm particle size) from Merck. A Hibar®, Lichrosorb® RP-18 pre-packed column (250 mm × 4 mm i.d., 5 μm particle size) combined with a guard column from Merck was used for the reported reference method. The columns were operated at ambient temperature. The analytical system was washed daily with 60 ml of 1:1 mixture of water and HPLC grade methanol to eliminate the mobile phase and this did not cause any change in the column performance. The components of the microemulsion were 0.1 M SDS, 10% 1-propanol, 1% 1-octanol and 0.3% TEA in 0.02 M phosphoric acid. All the microemulsion components were mixed together and the pH was adjusted to the desired value using TEA. Then the mixture was treated on an ultrasonic bath for 30 min. The resulting transparent mobile phase was filtered through a 0.45 μm membrane filter (Millipore, Ireland). Microemulsion was stable for at least 2 months. The column hold up volume was measured as the first deviation of the base line obtained.

The reference HPLC method was a modification of an earlier reported one, in this method, a (250 mm × 4.6 mm) C18 column was used as a stationary phase, and a mixture of acetonitrile–20 mM sodium dihydrogen phosphate–triethylamine (43:57:0.02, v/v/v), pH 2.4, was used as mobile phase, at a flow rate of 1.0 ml/min, the only modification was employing UV detection at 247 nm instead of fluorescence detection.

2.4. Sample preparation and procedures

Standard solution of loratadine and desloratadine (200 μg/ml) were prepared in methanol. The standard solutions were kept in the refrigerator and were found to be stable for at least 10 days.

2.4.1. Generation of calibration curve

To a set of 10 ml volumetric flasks, increasing volumes of the standard solutions of LOR and DSL were quantitatively transferred so as to give solutions containing the two drug substances within the concentration range of 4–56 and 2–48 μg/ml, respectively, after being diluted to 10.0 ml with the microemulsion. Injection into the HPLC was performed at ambient temperature (25 °C). Twenty microliter aliquots were injected (in triplicate) and the calibration curves were constructed by plotting the peak area against the final concentration of both drugs. Alternatively the corresponding regression equations were derived.

2.4.2. Analysis of the pharmaceutical preparations

For Claritine®, Loratan D and Aerius tablets. Ten tablets were after weighing finely powdered, and a portion of the tablet powder equivalent to 5 mg active substance was transferred quantitatively into a 25 ml measuring flask and suspended in

20 ml methanol. After sonication for 15 min, the flask was made up to volume with methanol. The final solution was centrifuged (4000 × *g*) for 15 min, and filtered.

For Claritine syrup 5 ml aliquot of the syrup containing 5 mg LOR, was transferred into 25 ml volumetric flask and was mixed well, then it was made up to volume with methanol. This solution was used without any further treatment.

All samples were filtered through 0.45 μm sample filters (RC 25, Sartorius AG, Goettingen, Germany) prior to injection into the HPLC system. "The nominal content of the pharmaceutical preparation were calculated using the corresponding regression equation."

3. Results and discussion

DSL is synthesized by hydrolytic decarboxylation of LOR, and LOR may therefore be contained in the final product due to the incomplete reaction or purification. DSL may also be present as an impurity in pharmaceutical drug preparations containing LOR due to hydrolysis and decarboxylation.

A microemulsion mobile phase has been utilized in this work in the separation of the two drug substances in pure form as well as in drug preparations. The different parameters affecting the separation selectivity of the MELC system have been investigated and optimized.

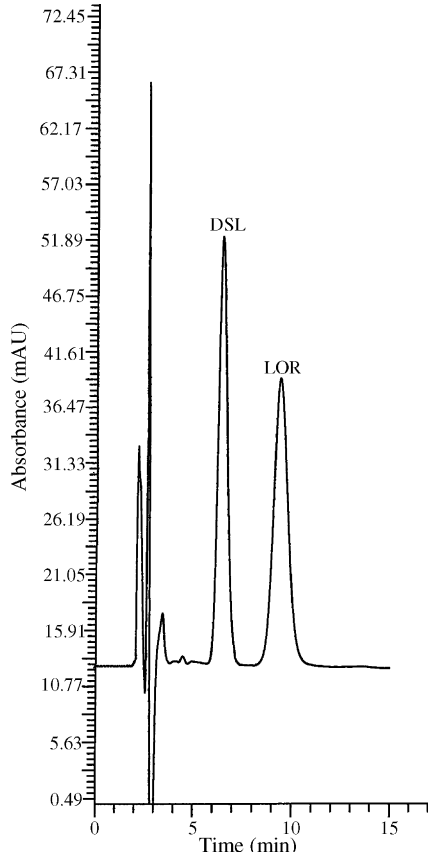

Fig. 2. Typical chromatogram for the separation of desloratadine (40 μg/ml, 6.7 min) and loratadine (40 μg/ml, 9.2 min) using micremulsion mobile phase. Chromatographic system: column, cyanopropyl (5 μm) 250 mm × 4.6 mm. Mobile phase microemulsion, 0.1 M SDS, 10% *n*-propanol, 1% *n*-octanol, 0.3% triethylamine, in 0.02 M phosphoric acid, pH 3.0. Flow rate, 1 ml/min, UV detection at 247 nm; column temperature, ambient.

3.1. Method development

Using a mobile phase consisting of 0.1 M SDS, 10% 1-propanol, 1% 1-octanol and 0.3% TEA in 0.02 M phosphoric acid of pH 3.0 an optimum separation of the two drug substances, with a resolution factor of 3.85, was achieved in a reasonable time less than 10 min, with maximum detector response. Fig. 2 represents the obtained chromatogram of DSL and LOR containing 40 μg/ml of each.

3.1.1. The concentration of the surfactants

The effect of SDS concentration on retention time and detector response (as peak area) was investigated using microemulsions containing SDS concentrations from 0.05 to 0.15 M. It was

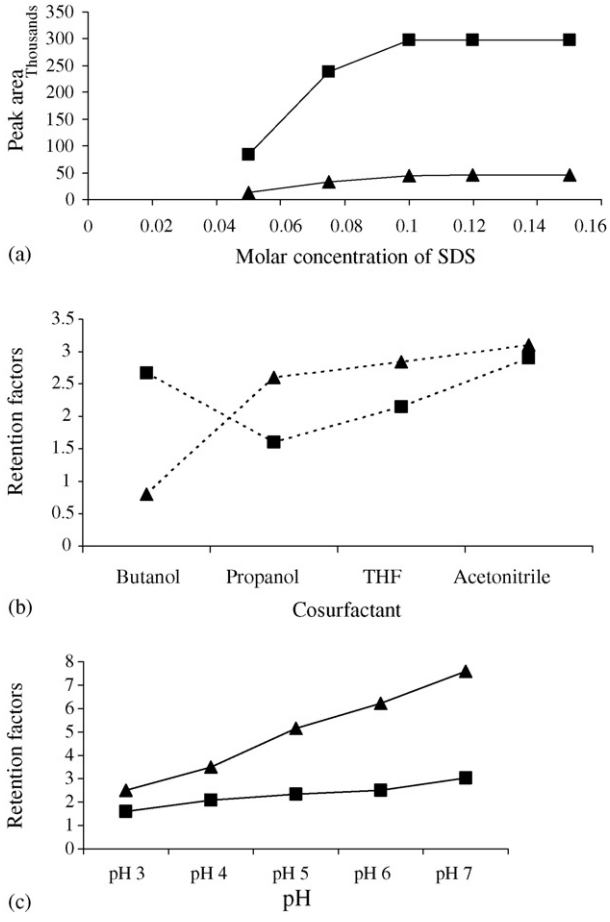

Fig. 3. (a) Effect of SDS molar concentration on the peak area of loratadine (▲) 20 μg/ml and desloratadine (■) 5 μg/ml of each using microemulsion mobile phases consisting of different SDS molar concentration, 10% *n*-propanol, 1% *n*-octanol, 0.3% triethylamine, in 0.02 M phosphoric acid, pH 3.0. (b) Retention factors of loratadine (▲) and desloratadine (■) vs. different cosurfactants using microemulsion mobile phases consisting of 0.1 M SDS, 10% different cosurfactant, 1% *n*-octanol, 0.3% triethylamine, in 0.02 M phosphoric acid, pH 3.0. (c) Retention factors of loratadine (▲) and desloratadine (■) vs. different pH using microemulsion mobile phases consisting of 0.1 M SDS, 10% *n*-propanol, 1% *n*-octanol, 0.3% triethylamine, in 0.02 M phosphoric acid of different pH values.

found that an increase in the concentration of SDS decreased the retention time of both substances continuously all over the investigated range due to their distribution into the increased volume of the microemulsion droplets or to the surface of the droplets which run with the speed of the mobile phase. Meanwhile, increasing SDS concentration increased the peak area of both drugs up to 0.1 M; further increase in SDS concentration up to 0.15 M did not affect the peak area of both substances. Fig. 3a illustrates the results obtained. A concentration of 0.1 M was found to be suitable for routine use as it provides adequate elution time and selectivity.

3.1.2. The effect of cosurfactant

Ten percent propanol was replaced with either tetrahydrofuran, 1-butanol, acetonitrile or methanol in an attempt to study the effect of the nature of the cosurfactant on the selectivity. Only methanol cannot be used as alternative to propanol, as it did not provide a steady base line chromatogram. The other three cosurfactants may be used. The retention factors of the two substances are given in Fig. 3b as a function of the cosurfactants investigated and major differences in selectivity were observed. In order to visualize the selectivity changes obtained upon using different cosurfactants, the data points of each drug substance are joined together but only by dotted lines. 1-Butanol and tetrahydrofuran provided reasonable resolution of the two peaks, while the use of acetonitrile resulted in overlapped peaks. It is interesting to notice that the retention of the analytes was greatly affected by the nature of the cosurfactant, which is in accordance with previous conclusion in evaluating the effect of different cosurfactant on the separation selectivity in microemulsion eluents [25,26,28,29].

Increasing the cosurfactant concentration over the range 6–12%, resulted in decreased retention times of the two drugs in general.

3.1.3. The effect of pH

The pH of the mobile phase was changed in the interval from 3 to 7 using increasing amounts of triethylamine in phosphoric acid. The retention factors of the two drugs were plotted against different pH values. As illustrated in Fig. 3c it was found that both drugs were considerably retained upon increasing the pH value. However, the increase in retention time of LOR was more significant than that of DSL. The two drugs differ in hydrophobicity and dissociation constants as expressed by their $\log P$ (octanol/water) and pK_a values, respectively. LOR has $\log P$ value of 5.2 and pK_a value of 5.0 [30], while DSL has $\log P$ value of 3.2 two pK_a values of 4.2 and 9.7 [31], thus the ionisation of both drug substances

Table 1
Analytical parameters for the HPLC determination of loratadine and desloratadine in pure form using microemulsion as mobile phase

Parameter	Loratadine	Desloratadine
Concentration range (μg/ml) seven concentrations	4–56	2–48
Regression equation		
Intercept (a)	-4.2×10^3	4.3×10^4
Slope (b)	6.4×10^4	9.9×10^4
Correlation coefficient (r)	0.9999	0.9999
$S_{y/x}$	4.2×10^4	1.7×10^4
S_a	1.4×10^4	6.4×10^3
S_b	8.5×10^3	4.1×10^2
LOD (μg/ml)	0.8	0.2
LOQ (μg/ml^{-1})	2.3	0.6
S.D. (%)	0.8	0.8
Error (%)	0.3	0.3

$S_{y/x}$, standard deviation of the residuals; S_a, standard deviation of the intercept of regression line; S_b, standard deviation of the slope of regression line; error (%), R.S.D. (%)/$\sqrt{n}$.

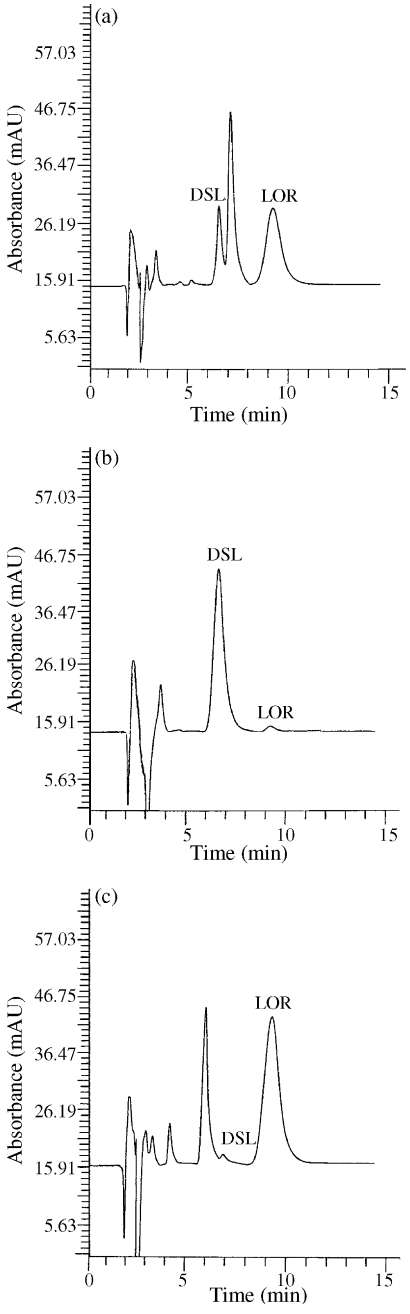

Fig. 4. Chromatograms obtained for some of the pharmaceutical preparations analyzed using microemulsion mobile phases consisting of 0.1 M SDS, 10% n-propanol, 1% n-octanol, 0.3% triethylamine, in 0.02 M phosphoric acid of pH 0.3. (a) Claritine syrup (36 μg/ml); (b) Aerius tablets (36 μg/ml); (c) Loratan D tablets (40 μg/ml).

will decrease with increasing pH and the log *P* values will be expressed.

In this study, a pH value of 3.0 seemed to be optimal for the separation and detection of both analytes in a short run.

3.1.4. The internal organic phase

Three different organic solvents 1-octanol, butyl acetate and diisopropylether were tested as internal organic phases (1%) so as to present a range of polarity. It was found that the separation could be successfully achieved using each of the three solvents. Butyl acetate provided the shortest retention time (4.2 and 6.3 min for DSL and LOR, respectively). Diisopropylether provided intermediate retention time when compared with 1-octanol (5.8 and 8.1 for DSL and LOR, respectively). However, 1-octanol seemed to be optimal for separation and detection of both analytes because butyl acetate and diisoprobyl ether resulted in slight decrease in their peak area.

A micellar mobile phase identical to the microemulsion system but without the internal phase *n*-octanol, was investigated in our initial attempts for separation achievement. It was found that the two peaks overlapped and the total run time was reduced. However, the internal organic phase representing the hydrophobic solvent may also be distributed to the hydrophobic stationary phase on the surface of the column packing material resulting in an increase in the amount of the stationary phase and thus changing the selectivity of the system.

3.2. Method validation

The developed analytical method was then subjected to method validation according to FDA and ICH guidelines [32]. The following parameters were considered: specificity, sensitivity, linearity, intra- and inter-day precision and accuracy.

Specificity of the method was also proved as no interference was encountered from tablet excipients or when co-formulated with other drugs such as pseudoehpedrine.

The limit of detection (LOD) and quantitation (LOQ) for both LOR and DSL were determined according to ICH guideline Q2B [32]. LOD was defined as $3.3\sigma/S$ and LOQ was $10\sigma/S$ based on 'standard deviation of the response and slope' based on the calibration curve. The standard deviation of *y*-intercepts of the regression lines was used as σ (the standard deviation of the response) and *S* is the slope of the calibration curve (Table 1).

The linear dependence of the peak area versus the concentration of each analyte was shown for both LOR and DSL by calculation of the regression equations over the ranges given in Table 1.

Table 2
Application of the proposed HPLC method using microemulsion as mobile phase to the determination of loratadine and desloratadine in dosage forms

Preparation	Taken (μg/ml)	Found (μg/ml)	Percentage of declared amount	Comparison method (33)
Loratan D tablets (loratadine (5 mg) + 120 mg pseudoephedrine sulphate))	24	23.9	99.6	99.7
	36	36.7	101.9	100.8
	48	48.3	100.6	100.9
Mean found (%)			100.7	100.5
±S.D.			1.2	0.7
Student's *t*-value			0.3 (2.78)	
Variance ratio *F*-test			2.9 (19.00)	
Claritine tablets (loratadine (10 mg)/tablet)	24	24.0	100.0	100.5
	36	35.6	98.9	101.0
	48	47.5	98.9	99.0
Mean found (%)			99.3	100.2
±S.D.			0.6	1.0
Student's *t*-value			1.3 (2.78)	
Variance ratio *F*-test			2.8 (19.00)	
Claritine syrup (loratadine (5 mg)/5 ml)	12	9.7	80.8	82.0
	24	19.4	80.8	83.6
	36	29.5	81.9	80.5
Mean found (%)			81.2	82.0
±S.D.			0.6	1.6
Student's *t*-value			0.8 (2.78)	
Variance ratio *F*-test			7.1 (19.00)	
Aerius tablets (desloratadine (5 mg)/tablet)	24	23.6	98.3	99.0
	36	35.3	98.1	98.3
	48	47.2	98.3	98.6
Mean found (%)			98.2	98.6
±S.D.			0.1	0.4
Student's *t*-value			1.7 (2.78)	
Variance ratio *F*-test			16 (19.00)	

N.B., figures between parenthesis are the tabulated values of *t* and *F*, respectively, at $p = 0.05$ (34).

3.3. Assay of dosage forms

The applicability of the method was tested by determination of loratadine and/or desloratadine in four dosage forms (Table 2). The content of each drug in the pharmaceutical formulations was determined by triplicate injections of three independently prepared solutions. As can be observed in Table 2, the recoveries obtained for all the studied preparations were close to 100%, except for Claritine syrup which contains 1 mg LOR/ml and Aerius tablets which contain 5 mg DSL/tablet, where the percentage recoveries obtained were about 80 and 98%, respectively.

Fig. 4 illustrates the obtained chromatograms for some pharmaceutical preparations analysed. Fig. 4a depicts the chromatogram obtained in the analysis of Claritine syrup. A peak of DSL is obvious in this chromatogram which corresponds to the amount of the degraded LOR (about 20% of the added concentration), however the DSL peak in Claritine syrup was partially overlapped with another peak which was thought to be the peak of any of the inactive ingredients (propylene glycol, glycerine, citric and, sodium benzoate, sugar and peach flavour) which are present in the syrup formulation. By injecting a reference solution of sodium benzoate it was verified that the unknown peak corresponds to the preservative benzoate. The low content of LOR in Claritine syrup was confirmed when using the reference HPLC method (Table 2).

Fig. 4b shows the chromatogram obtained in the analysis of Areius tablets. This chromatogram reveals the presence of LOR as an impurity (about 2% of the added concentration), which may be contained in DSL due to the incomplete reaction or purification when synthesized by the hydrolytic decarboxylation of LOR.

Fig. 4c shows a typical chromatogram of an extract from Loratan D tablets at which LOR is co-formulated with pseudoephedrine, it is noticed that the two drugs were successfully separated, where pesudoephedrine was eluted at 5.9 min as confirmed by injecting a reference solution of pseudoephedrine. All the previous results obtained were in agreement with those obtained with a comparison HPLC method [33] reported for LOR determination in human plasma at which separation of the two drug substances was possible. The results obtained were validated for accuracy and precision by measuring the mean percentage recoveries and standard deviations. Excellent percentage recoveries and S.D. (less than 2.0) were obtained as illustrated in Table 2. The Common tablet excipients such as talc, lactose, starch, avisil, gelatin or magnesium stearate, did not interfere with the assay. Statistical analysis of the results obtained by the proposed method, and those given by the

Table 3
Intra-day accuracy and precision for determination of loratadine and desloratadine in dosage forms using microemulsion as mobile phase

Pharmaceutical preparation	Percentage recovery, repeatability (20 μg/ml)	Percentage recovery, repeatability (40 μg/ml)
(1) Loratan D tablets (5 mg loratadine + 120 mg pseudoephedrine sulphate)	99.2 100.4 99.6	100.0 100.1 100.4
Mean found (%)	99.7	100.2
±S.D.	0.6	0.2
R.S.D. (%)	0.6	0.2
(2) Claritine tablets (10 mg loratadine/tablet)	98.5 99.8 98.9	98.3 99.4 98.7
Mean found (%)	99.1	98.7
±S.D.	0.7	0.6
R.S.D. (%)	0.7	0.6
(3) Claritine syrup (5 mg loratadine/5 ml)	81.1 81.0 81.7	81.5 80.3 80.9
Mean found (%)	81.3	80.9
±S.D.	0.4	0.6
R.S.D. (%)	0.4	0.6
(4) Aerius tablets (5 mg desloratadine/tablet)	98.6 98.4 98.1	98.3 98.7 98.1
Mean found (%)	98.4	98.4
±S.D.	0.3	0.3
R.S.D. (%)	0.3	0.3

N.B., each result is the average of three separate determinations.

Table 4
Inter-day accuracy and precision for determination of loratadine and desloratadine in dosage forms on 3 successive days using microemulsion as mobile phase

Pharmaceutical preparation	Percentage recovery, repeatability (20 μg/ml)	Percentage recovery, repeatability (40 μg/ml)
(1) Loratan D tablets (5 mg loratadine + 120 mg pseudoephedrine sulphate)	101.5 99.4 100.7	99.8 101.3 100.5
Mean found (%)	100.5	100.5
±S.D.	1.1	0.8
R.S.D. (%)	1.1	0.8
(2) Claritine tablets (10 mg loratadine/tablet)	99.5 98.8 100.2	98.6 100.3 98.8
Mean found (%)	99.5	99.2
±S.D.	0.7	0.9
R.S.D. (%)	0.7	0.9
(3) Claritine syrup (5 mg loratadine/5 ml)	81.1 80.4 81.5	80.5 81.7 81.2
Mean found (%)	81.0	81.1
±S.D.	0.6	0.6
R.S.D. (%)	0.6	0.6
(4) Aerius tablets (5 mg desloratadine/tablet)	98.6 98.8 98.1	98.9 98.1 98.0
Mean found (%)	98.5	98.3
±S.D.	0.4	0.5
R.S.D. (%)	0.4	0.5

N.B., each result is the average of three separate determinations.

comparison method was performed using the Student's *t*-test and the variance ratio *F*-test [34]. As illustrated in Table 2, the calculated values did not exceed the theoretical ones, indicating no significance difference in the performance of the compared methods regarding accuracy and precision, respectively.

The intra-day precision and accuracy of the assays were measured by analyzing three samples of LOR and DSL in their pharmaceutical preparations at each level (20 and 40 μg/ml) in 1 day. The inter-day precision and accuracy were determined over 3 successive days by analyzing different samples of LOR and DSL at each level (20 and 40 μg/ml). The obtained results for both the intra- and inter-day precision and accuracy are abridged in Tables 3 and 4, respectively.

4. Conclusions

A reliable and specific HPLC method for the simultaneous determination of LOR and DSL in pharmaceutical preparations using microemulsion as mobile phase with UV detection has been developed. The method has a relatively short turnover time (10 min) and the LOD and R.S.D. values are sufficiently good for the applicability of this method for quality control laboratories with HPLC availability. The method could be used as a limit test for measuring the purity of LOR and DSL in each other. The method can be used for determining both LOR and DSL in pharmaceutical preparations in a single chromatographic run.

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