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Journal of Pharmaceutical and Biomedical Analysis 36 (2005) 1011–1018
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Stability studies on some benzocycloheptane antihistaminic agents

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Received 5 April 2004; received in revised form 8 September 2004; accepted 9 September 2004
Available online 5 November 2004

Abstract

The photostability of selected benzocycloheptane antihistaminic agents, namely, loratadine (**I**), pizotifen (**II**), ketotifen fumarate (**III**) and cyproheptatidine (**IV**), was investigated. Both **I** and **II** were photolabile while **III** and **IV** were photostable. To perform stability studies on the photolabile compounds (**I** and **II**), specific stability-indicating high performance liquid chromatographic (HPLC) methods were established. The accuracy, precision and reliability of the developed HPLC methods for the assay of **I** and **II** in their pharmaceutical dosage forms were reported. Assay results for both drugs were within R.S.D. values <2%. The stability-indicating power of the developed methods was validated through study of UV-degraded solutions of **I** and **II** contained in quartz cells. The photostability of both drugs was studied under UV-irradiation at 254 nm. The photodegradation kinetics of both drugs, studied in different solvents, are also reported. TLC fractionation of photodegraded solutions of both drugs, revealed two fluorescent photodegradates of drug **I**. The use of UV-absorbers (ascorbic acid and *p*-aminobenzoic acid (PABA)) enhanced the photostability of both drugs possibly through a spectral-overlay effect.

Keywords: Loratadine; Pizotifen; Ketotifen; Cyproheptatidine; HPLC; UV-irradiation; Sunlight; Photodegradation; Kinetics; Photostabilization

1. Introduction

Some drug molecules undergo degradation upon exposure to light, which would necessitate special storage conditions and protection from light. The photolability of such molecules can be established by forced degradation testing (stress testing). Thus the stress testing serves the multipurpose of evaluating the photosensitivity of such drugs and developing and validating the stability-indicating power of the developed method [1].

The drugs selected for the stability studies in this project are the commonly used antihistaminic agents (H_1-antagonists) of the benzocycloheptane type. These are *loratadine* (**I**, 4-(8-chloro-5,6-dihydro-11H-benzo[5,6]cyclohepta[1,2-b]pyridine-11-ylidene-1-piperidinecarboxylic acid ethyl ester)), *pizotifen malate* (**II**, 9,10-dihydro-4-(1-methyl-4-piperidylidene)-4H-benzo[4,5]cyclohepta[1,2-b]thiophene hydrogen malate), *ketotifen fumarate* (**III**, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta [1,2-b]thiophen-10-one hydrogen fumarate) and *cyproheptadine hydrochloride* (**IV**, 4-(5H-dibenzo[a,d]cycloheptene-5-ylidene)-1-methylpiperidine hydrochloride (Scheme 1)).

Pizotifen (**II**) and ketotifen (**III**) can be regarded as analogs of cyproheptadine (**IV**) in which the –CH=CH– of one of the benzene rings of the dibenzocycloheptane nucleus is replaced by isosteric sulfur atom, while in loratadine (**I**) the sp^2 carbon of cyproheptadine is replaced by an isosteric ring nitrogen.

Exposure of each compound to UV light is expected to cause $\pi \rightarrow \pi^*$ and $n \rightarrow -\pi^*$ transitions that may lead to chemical bond cleavage and hence photodecomposition of the drugs.

Preliminary photostability investigations of these compounds revealed the photostability of compounds **III** and **IV**, whereas compounds **I** and **II** were found to be pho-

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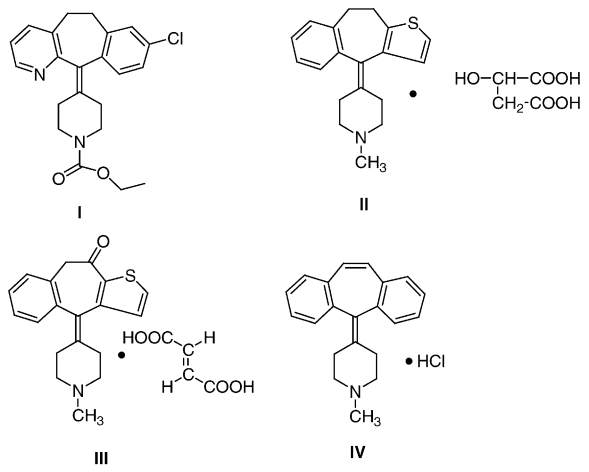
doi:10.1016/j.jpba.2004.09.019



Scheme 1. Structural formulae of the studied compounds.

tolabile and were subjected to further photostability studies.

Loratadine (**I**) is an H_1 receptor antagonist used for allergic conditions such as rhinitis, allergic dermatitis and ocular allergy [2]. Methods have been described in the literature for the determination of loratadine whether alone or in combination with other drugs or in presence of its metabolites. The methods cited in the literature for the determination of loratadine as raw material or in dosage form (single or combined) included HPLC [3–9], capillary electrophoresis [10] spectrophotometric [5–7,11–14], polarographic [15,16] and densitometric method [7,17]. Methods used for the determination of loratadine in human plasma included HPLC [18–20] and a gas liquid chromatographic method [21]. The HPLC methods [3–6] reported for the determination of loratadine in dosage forms were not specified as stability indicating. Methods [7–10] were stability-indicating HPLC and capillary electrophoresis procedures reported for the determination of loratadine in presence of alkaline degradation products [7] or loratadine related impurities [8–10]. No previous work has been reported on the kinetic study of the stability of loratadine under the effect of light, though it is stated that the drug should be stored protected from light [2].

Pizotifen maleate (**II**) is an H_1-receptor antagonist used for prophylaxis of migraine [2]. Some of the reported methods for the determination of **II** include atomic absorption and colorimetric methods [12], HPLC [22,23] and titrimetry (bulk form) [23]. No previous work is reported on the photostability of pizotifen although it is directed to be stored protected from light [23].

This work covers the development of stability-indicating HPLC methods suitable for the assay of **I** and **II** in the presence of their photodegradation products and a preliminary photodegradation kinetic study of both drugs irradiated at 254 nm in quartz cells. The influence of *p*-aminobenzoic acid and ascorbic acid as UV-absorbers on the photostability of **I** and **II** is also presented.

2. Experimental

2.1. Materials and methods

Loratadine, pizotifen maleate, ketotifen hydrogen fumarate and cyproheptadine hydrochloride were obtained from the Quality Control Central Lab., Riyadh, Saudi Arabia. Claritine® tablets (10 mg) (Shering-Plough Spimaco) and Moseqor® tablets (0.5 mg) and syrup (0.005 g/100 ml) were obtained from the local market in Riyadh, Saudi Arabia. Acetonitrile and methanol were of HPLC grade (Hipersolv^{TM}, BDH, Poole, UK). Columns used were Lichrosorb RP-18 (10 u) 250 mm × 4.6 mm i.d. (Alltech) and Bondesil CN (5 u) 250 mm × 4.6 mm i.d. (Varian®). All other chemicals were analytical grade reagents.

2.2. Apparatus

A Waters liquid chromatograph consisting of a 600 E system controller, Rheodyne 7161 injector, tunable absorbance detector 486, and 746 data module was used. Ultraviolet spectrophotometric and spectrofluorimetric studies were carried out using a Shimadzu UV 1601 PC spectrophotometer (Kyoto, Japan) and SFM 25 (Kontron Instruments) equipped with a 150 W xenon-high pressure lamp and driven by a PC Pentium **II** computer, respectively. The photodegradation process was carried out using a UV-lamp model UVGL-2 (Minerlight® Lamp multiband UV-254/366 nm, 215–250 V, 50/60 Hz, 0.12 A, San Gabriel, USA) fixed to a wooden cabinet in a horizontal position.

2.3. Analytical procedures

2.3.1. HPLC assay of **I** and **II**

2.3.1.1. Optimal HPLC conditions. The optimal HPLC conditions for the study of **I** and **II** are listed as follows:

Parameter	Loratadine	Pizotifen
Column	Lichrosorb (250 mm × 4.6 mm)	Bondesil CN (250 mm × 4.6 mm)
Mobile phase	CH_3CN:Na acetate 0.01 M, pH 3.5 or H_2O (90:10 v/v)	CH_3CN:Na acetate 0.01 M, pH 3.5 (75:25 v/v)
Flow rate	2 ml min^{-1}	2 ml min^{-1}
λ_{max}	247 nm	254 nm
Attenuation	32	32
Injected volume	20 μl	20 μl

2.3.1.2. Standard curves. A stock solution of either drug prepared in methanol containing 250 μg ml^{-1} was diluted

with the mobile phase to give 50 μg ml^{-1} as working solutions. Before completion to volume with the appropriate mobile phase of each drug, 1–5 ml of the working solutions were transferred into 10 ml volumetric flasks. Duplicate injections of each solution were made, and the standard curve, detector response versus concentration (μg ml^{-1}) at the specified λ_{max} in terms of peak area was plotted. Regression data was obtained for each curve.

2.3.1.3. Assay of loratadine and pizotifen in formulations.

A. Lortadine (Claritine®) 10 mg/tablet: average weight of five tablets was computed and a weight of 10 mg was transferred into 50 ml volumetric flask, shaken with 40 ml of methanol for 25 min before completion to 50 ml with methanol and filtered, and 2 ml of aliquot of the filtrate was diluted to 25 ml volume with methanol. Six 20 μl volumes were injected. Concentration was calculated from the standard curve data or using an equivalent injected standard.
B. Pizotifen
   (i) Tablets (Mosegor®) 0.5 mg/tablet: average weight of six tablets was computed and the weight of one tablet was transferred into 20 ml volumetric flask, shaken with the mobile phase for 25 min using an ultrasonic bath; filtered and 2 ml aliquot of the filtrate was diluted to 10 ml with the mobile phase. Six 20 μl volumes were injected. Concentration was calculated from standard curve data or from an equivalent injected standard.
   (ii) Syrup (Mosegor® 0.005 g/100 ml pizotifen base): 2 ml syrup was diluted with water to 10 ml. Six 20 μl volumes were injected. Concentration was calculated from the standard curve or using an equivalent standard solution.

2.4. Photodegradation study

*2.4.1. Effect of solvents on photodegradation of **I** and **II***

Three solutions of **I** or **II** (30 μg ml^{-1}) were prepared in methanol, methanol:H_2O (3:7 v/v) and the appropriate mobile phase of each drug. Each of the three solutions contained in a quartz cell was UV-irradiated at 254 nm. At suitable time intervals, each solution was monitored by UV-scanning and by the proposed HPLC methods. Samples monitored by the HPLC methods were subjected to kinetic analysis utilizing peak areas of each drug at zero time (AR_0) as proportional to the initial concentration; the peak area (AR_t) after irradiation was taken as proportional to the remaining concentration as a function of time (t) in minutes. Regression analysis of the data of $\log(AR_t/AR_0)$ versus time was then performed.

*2.4.2. Photostabilization of **I** and **II** with p-aminobenzoic acid (PABA) and ascorbic acid*

To a solution of each drug (30 μg ml^{-1}) in methanol:H_2O (3:7), different concentrations of ascorbic acid or PABA (ranging between 5% and 40% final solution) were added before exposure to UV light. A blank solution was run at the same time. Solutions were exposed to UV light in quartz cells (LKB) and samples were withdrawn at suitable time intervals of at least five time intervals. A plot of log remaining drug versus time was done.

2.5. Effect of sunlight on solutions of **I** and **II**

Solutions of the drugs (30 (g ml^{-1}) in methanol:H_2O (3:7) contained in glass vials were exposed to sunlight for 10 days (test solution). Solutions of the drugs in glass vials wrapped with insulating material were used as blanks.

3. Results and discussion

The stability studies and storage guidelines set for many drugs usually refer to temperate climates and may not be relevant to extreme climate conditions. Thus the stability of medicines distributed and used in hot and sunny climates can pose serious problems. In countries like Saudi Arabia, where strong heat and sunlight prevail, investigation of the photodegradation of some drugs under these extreme conditions should receive major concern.

It has long been recognized that chemical changes in organic molecules can be effected by means of ultraviolet light. Drugs, like other organic molecules, absorb radiations in this region of the electromagnetic spectrum and this radiation is capable of breaking the chemical structure. Many organic reactions, including oxidation, reduction, elimination and substitution may be consequent upon absorption of light by organic molecules [24,25]. Studies in the area of drug photodegradation are now gaining utmost importance by drug analysts [26–28]. The progress in this field has been aided by advances in procedures available for separation and identification of the components of mixtures.

The purpose of stability studies is to provide evidences on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors [1]. Stability testing permits the establishment of recommended storage conditions, retest periods, shelf-life and may lead to suggestion of alternative pharmaceutical formulations.

Photolytic degradation is an important limiting factor in the stability of pharmaceuticals. The predicted shelf-life of a drug can be greatly affected by improper drug storage and handling especially during drugs transportation from one area to another due to environmental changes (temperature, moisture, etc.) and light exposure. Thus quality control laboratories are concerned with the development of a validated stability-indicating methods that can be useful in assaying, detecting related or possible degradation products of a drug throughout its shelf-life.

The photostability of the compounds under investigation (**I**–**IV**) was initially tested by a spectrophotometric

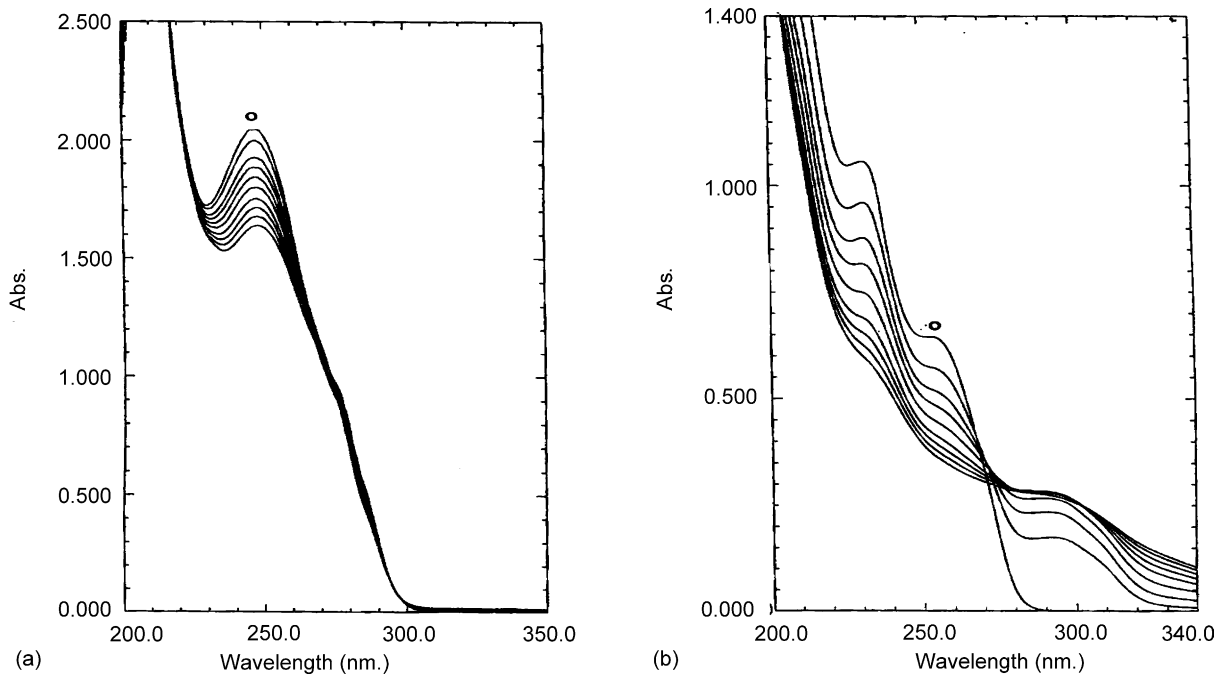


Fig. 1. (a) Spectral changes of the UV-irradiated methanolic solution of loratadine (50 μg ml^{-1}) at different time intervals (0, 1, 2, 3, 4, 5, 6, 7, 8, and 9 min) in quartz cells; (b) spectral changes of the UV-irradiated methanolic solution of pizotifen (25 μg ml^{-1}) at different time intervals (0, 5, 10, 15, 20, 25, 30, 35 and 40 min) in quartz cells.

method. Solutions of these compounds (25 μg ml^{-1} each) were scanned between 200 and 400 nm, and their λ_{max} were recorded. These solutions were then irradiated at 254 nm in quartz cells for different time intervals. Only loratadine and pizotifen were found to be photolabile showing a decrease in absorption at their λ_{max} with subsequent changes in their zero-order absorption curves (Fig. 1a and b). Further photostability studies were thereafter limited to loratadine and pizotifen.

Preliminary trials were conducted to establish a stability-indicating HPLC methods for the two compounds using different columns ranging from selected normal phase to reverse-phase columns. Mobile phases with different compositions of methanol, acetonitrile, water, sodium acetate (0.01 M, pH 3.5) and ammonia were tried. A successful isocratic stability-indicating HPLC method was obtained for loratadine using a Lichrosorb column with mobile phase composed of acetonitrile 90% v/v and sodium acetate 0.01 M, pH 3.5 10% v/v or water (Section 2.3); as for pizotifen, the optimal condition was reached by the use of a CN column and a mobile phase composed of acetonitrile 75% v/v and 25% v/v sodium acetate 0.01 M, pH 3.5 (Section 2.3). Cyano columns normally provide separations characteristic of either reversed phase or normal phase mode, depending on the ratio of the traditional solvents used in reversed phase mode, i.e. water or buffer:organic solvent (acetonitrile or methanol) mixtures. They are more useful than C18 columns for basic compounds retention (highly retentive phase for analytes containing amino functionality). The retention of such basic compounds depends on the ratio of the organic modifier, i.e. more organic modifier ratio lead to more retention of the basic compound. This property was needed to establish stability-indicating method for pizotifen. At 75% v/v acetonitrile and 25% v/v water (normal phase mode), pizotifen peak was broad, short, and late eluting with retention time about 7 min (separation factor $\alpha = 7.8$). To keep the separation mode at the normal phase mode, a 25% v/v sodium acetate 0.01 M, pH 3.5 was used instead of water. The strength and pH of the acetate buffer greatly improved the shape and retention of the pizotifen peak (separation factor, $\alpha = 3.8$). Thus increasing or decreasing the strength of the buffer without changing the percentage v/v the peak retention decreases or increases accordingly. The optimum condition was 75%:25% v/v acetonitrile:sodium acetate 0.01 M, pH 3.5. The stability-indicating power of each of the optimized HPLC methods was validated by injecting UV-degraded solutions of either drug onto the column. The resultant chromatograms showed a decrease of the peaks of these compounds and the appearance of resolved photodegradates (Figs. 2 and 3). The resolution pattern of the photodegradates of both compounds indicated their higher polarity compared to the parent compounds (i.e. before loratadine in the reverse phase mode and after pizotifen in the normal phase mode for chromatograms run for at least 10 min where no further apparent photodegradates were observed other than those indicated in Figs. 2 and 3).

The HPLC methods adopted in this work for the stability studies of loratadine and pizotifen enabled the quantitative analysis of both compounds in their available dosage forms within concentration range of 5–25 μg ml^{-1}. Standard curves were linear with correlation coefficients not less than 0.999

for both compounds. The regression analysis data was calculated at 95% confidence level for the slope ($b \pm ts_b$) and the intercept ($a \pm ts_a$) using the formula:

$$P = (b \pm ts_b)x + (a \pm ts_a)$$

where P is the peak area, b the slope, s_b the standard deviation for the slope, t the t-value at 95% confidence level for $(n-2)$, s_a the standard deviation for the intercept, and x the concentration ($\mu g\,ml^{-1}$).

The results for loratadine were

$$P = (51\,638 \pm 1570)x + (4396 \pm 22\,764) \quad r = 0.9998$$

And the results for pizotifen were

$$P = (30984 \pm 1287)x + (7019 \pm 18\ \ 652) \quad r = 0.9995$$

The reproducibility, accuracy and precision of the HPLC method was confirmed by replicate injections of standard solution (15 $\mu g\,ml^{-1}$ each) of each drug (interday measurements) or by the follow-up of the consistency of the slope and intercept of the standard curve for at least 7 days which remained within R.S.D. values less than 2%. This also reflected the stability of the solutions exposed to artificial day light. To study the accuracy of the proposed method and to check the interference from excipients used in the formulations, recovery experiments were carried out by the standard addition method. The following formula was adopted to calculate the

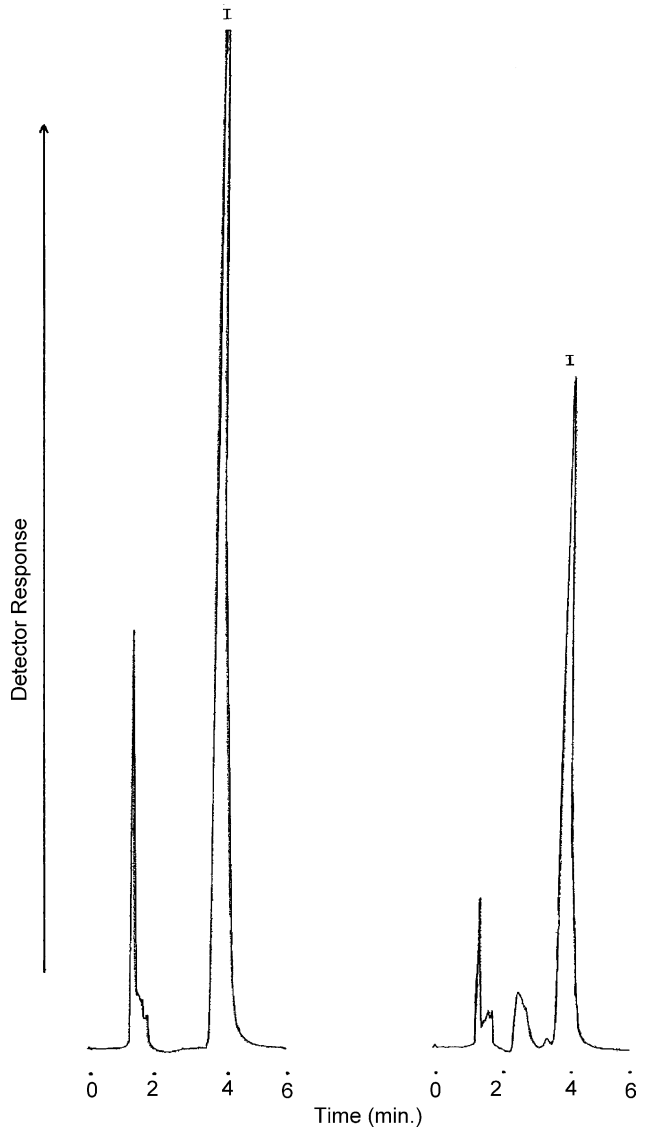


Fig. 2. Typical chromatogram of loratadine solution peak (1) (30 $\mu g\,ml^{-1}$) in CH_3OH:H_2O 3:7 v/v (left); typical chromatogram of UV-irradiated loratadine solution (30 $\mu g\,ml^{-1}$) in CH_3OH:H_2O 30:70 v/v (4 min UV-exposure) in quartz cells (right).

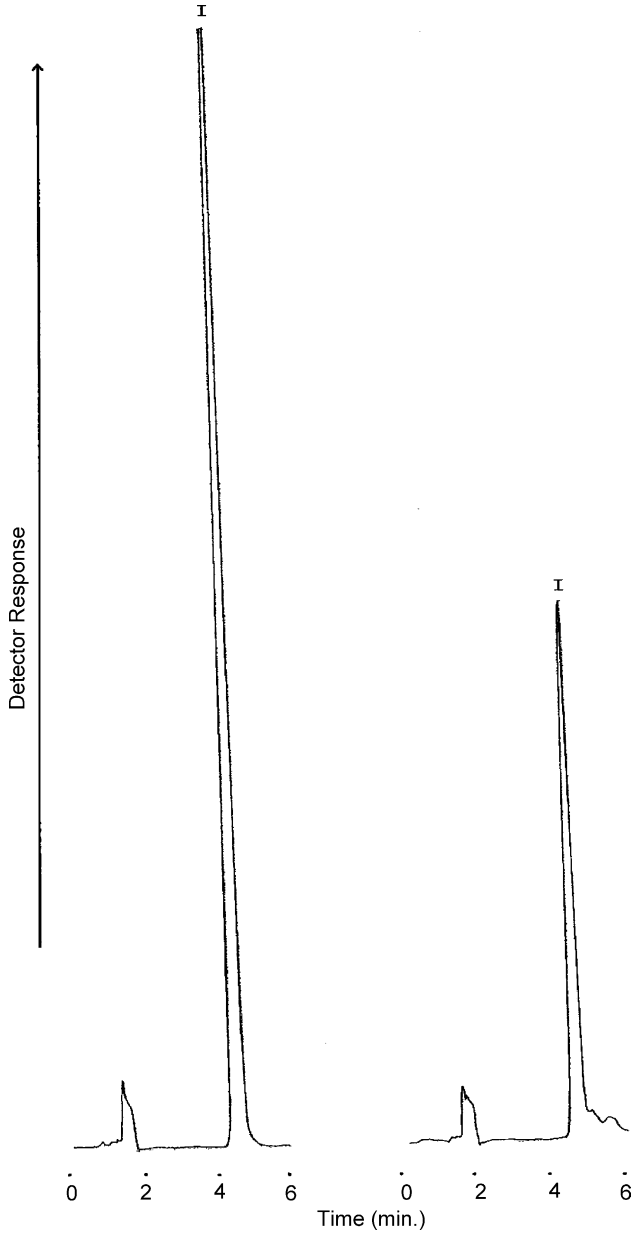


Fig. 3. Typical chromatogram of pizotifen solution peak (1) (30 $\mu g\,ml^{-1}$) in CH_3OH:H_2O 30:70 v/v (left); typical chromatogram of UV-irradiated pizotifen solution peak (1) (30 $\mu g\,ml^{-1}$) in CH_3OH:H_2O 30:70 v/v (15 min UV-exposure) in quartz cells (right).

Table 1
Data for assay results ± S.D. and added recovery

Drug	Assay (%) ± S.D. (n)[a] R.S.D.	Added recovery[b] $\bar{x}$ ± S.D. (n[a]) R.S.D.
Loratadine tablets	100.75 ± 0.66 (6), 0.66	100.17 ± 1.84 (6), 1.84
Pizotifen tablets	99.25 ± 0.39 (6), 0.39	100.57 ± 1.35 (6), 1.34
Syrup	101.85 ± 1.88 (6), 1.85	102.2 ± 1.65 (6), 1.61

[a] Number of replicates.
[b] Based on standard solution (5 μg ml^{-1}) added to claimed sample solution (10 μg ml^{-1}).

% recovery:

$$\%\,\text{recovery} = \frac{P_{(d)} - P_{(sp)}}{P_{(std)}} \times 100$$

where $P_{(d)}$ is the peak area for added solution, $P_{(sp)}$ the peak area for sample solution, and $P_{(std)}$ the peak area for standard solution.

Table 1 summarizes the results obtained for the assay (%) ± S.D. and added recovery of the proposed HPLC methods.

Study of the effect of diluting solvents, methanol, methanol:water (30:70) and acetonitrile:water (90:10) on the photodegradation of both drugs (Table 2) revealed that loratadine is less stable in solutions containing water compared to pizotifen which experienced no solvent effect on its photodegradation. It was observed that polar solvents tend to increase the breakdown of drug molecules that produce degradates that are more polar than the original drug, and non-polar solvents enhance the breakdown of polar compounds that produce less polar degradates [29]. Loratadine is a carbamate-containing compound (Scheme 1) that is expected to produce more polar degradates than loratadine itself. This could be a possible explanation for the decreased stability of the drug in solutions containing water.

TLC fractionation of the UV-degraded drugs utilizing silica gel sheets 60 F_{254} (5 cm × 10 cm with 0.2 mm thickness; run with solvent composed of chloroform:methanol:ammonia, 8:2:0.2 ml; visualized under UV 254 and 366 nm) revealed three photodegradation products for loratadine which were more polar than loratadine, i.e. with R_f values less than the parent compound. Two of these photodegradates were fluorescent, with the most polar photodegradate having more fluorescence. Excitation and emission wavelengths for photodegraded loratadine solution (more than 30 min UV-exposure) were 304/440 nm. Fig. 4 shows the fluorescence spectra of loratadine solutions (10, 30 and 50 μg ml^{-1} in CH_3CN:H_2O 70:30) exposed to UV light for 30 min.

Table 2
Effect of solvent on the degradation of the studied compounds

Solvent	Drug	$t_{1/2}$ (min)
Methanol	Loratadine	15.57
	Pizotifen	15.55
Methanol:H_2O (30:70)	Loratadine	3.96
	Pizotifen	14.45
CH_3CN:H_2O (90:10)	Loratadine	3.53
	Pizotifen	15.28

r-Values of the plots are between 0.995 and 0.999; values for $t_{1/2}$ are within ±2% for replicates.

The results of Table 3 reflect the stabilizing effect of ascorbic acid and PABA on both drugs irradiated at 254 nm in quartz cells. UV-absorbers of the type employed as sunscreens (e.g. PABA) have been used as internal protectors for drugs absorbing at about the same region (spectral overlay or competitive absorption) [30]. Thus the photostabilization effects experienced by both drugs in the presence of PABA could be attributed to a competitive mechanism. The effect of the reducing agent, ascorbic acid, which is used as an antioxidant was thought to be through the quenching of a free radical reaction of light with both drugs; however, solutions bubbled with nitrogen gave about the same results relative to control solutions. Thus a spectral overlay effect could be the mechanism for the protecting effect of ascorbic acid. The quenching effect by PABA or ascorbic acid is linear, i.e. con-

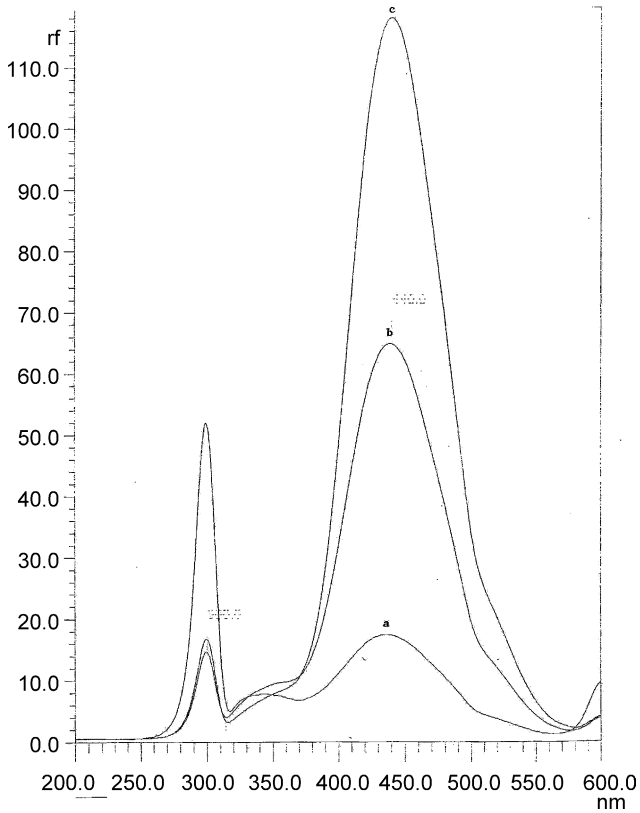


Fig. 4. Typical fluorescence spectra for a 30 min UV-irradiated loratadine solutions in CH_3CN:H_2O 70:30 v/v: (a) 10 μg ml^{-1}, (b) 30 μg ml^{-1} and (c) 50 μg ml^{-1}.

Table 3
Effect of stabilizers on the stability of loratadine and pizotifen

Drug	Stabilizing agent	Stabilizing agent (concentration, mg%)	$t_{1/2}$	Relative protection
Loratadine	Ascorbic acid	0	3.96	1.0
		10	30.14	7.6
		20	58.98	14.9
		40	122.44	30.92
	PABA	10	42.0	10.6
		20	82.2	21.0
		40	164.7	41.6
Pizotifen	Ascorbic acid	0	14.45	1.0
		5	55.19	3.8
		10	109.53	7.6
		20	214.0	14.8
	PABA	5	83.7	8.8
		10	148.96	10.3
		20	299.6	20.7

r-values are between 0.99 and 0.999 for replicates; $t_{1/2}$ are within 2% R.S.D. for replicates (solvent methanol:H_2O 3:7).

centration dependent as reflected by the calculated $t_{1/2}$ values or the relative protection values (Table 3).

The effect of sunlight on the two drugs showed that both test and blank solutions were affected, however, the test solutions showed more drug degradation indicating possibility of the effect being mediated by both heat and UV rays. Heating solutions at 70 °C for 2 h confirmed the effect of heat on the drug degradation. Pizotifen was affected to a lesser extend than loratadine. Sun exposed or direct UV-irradiated loratadine solutions turned yellow in colour. For loratadine, which is most affected by sunrays, UV-irradiation and heat (to some extent) showed only two degradates coinciding with each other for these different conditions at retention times of about 2.2 and 2.56 min.

The developed stability-indicating HPLC methods and the photochemical investigation results reported in this work for loratadine and pizotifen are considered preliminary as they do not completely meet the ICH guidelines [31]. They served the purpose of validation of the developed HPLC methods and pointed out the photolability of both drugs under stress-testing conditions. The results indicated that special care should be followed in handling and storing these drugs protected from light. Confirmatory studies will be required to actually provide more practical information necessary for handling, packaging and labelling of these drugs. As for loratadine, the reported stability-indicating HPLC and capillary electrophoresis methods [8–10] for the determination of loratadine and its related impurities besides their usefulness as limit tests for these impurities (qualitative and quantitative) can serve as a complementary tools for the identification of the light-induced degradation products of loratadine. This can be achieved by injecting a loratadine UV-degraded solution and comparing the retention times of the known standard impurities of loratadine with the eluting photodegradates. Another criterion of identification of these photodegrades, the fluorescent ones, is through checking the fluorescence characteristics, if any, of the polar related impurities of loratadine. The results will definitely be useful indicators for the possible origin of some of these related impurities so that suitable measures can be undertaken in handling and storing of this drug.

The photodegradation kinetic results presented in this study is now being extended for the isolation and characterization of the photodegradates of loratadine and pizotifen and the identification of pathways for the photodegradation processes.

4. Conclusion

The HPLC methods described in this work were validated as stability-indicating assay procedures for compounds **I** and **II** in the presence of their photodegradation products. The presence of water in solution seems to increase the photolability of loratadine. *p*-Aminobenzoic acid and ascorbic acid proved to have good photostabilizing effect on both drugs. Both loratadine and pizotifen were stable at room temperature when left exposed to artificial room light for at least 2 weeks.

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