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Acid–base equilibria and solubility of loratadine and desloratadine in water and micellar media

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ABSTRACT

Acid–base equilibria in homogeneous and heterogeneous systems of two antihistaminics, loratadine and desloratadine were studied spectrophotometrically in Britton–Robinson's buffer at 25 °C. Acidity constant of loratadine was found to be pK_a 5.25 and those of desloratadine pK_{a1} 4.41 and pK_{a2} 9.97. The values of intrinsic solubilities of loratadine and desloratadine were 8.65×10^{-6} M and 3.82×10^{-4} M, respectively. Based on the pK_a values and intrinsic solubilities, solubility curves of these two drugs as a function of pH were calculated. The effects of anionic, cationic and non-ionic surfactants applied in the concentration exceeding critical micelle concentration (cmc) on acid–base properties of loratadine and desloratadine, as well as on intrinsic solubility of loratadine were also examined. The results revealed a shift of pK_a values in micellar media comparing to the values obtained in water. These shifts (ΔpK_a) ranged from −2.24 to +1.24.

1. Introduction

Loratadine and desloratadine, belonging to the second generation of antihistaminic agents, represent selective and moderately strong histamine H_1-receptor antagonists. After oral administration, loratadine is rapidly absorbed and extensively metabolized primarily affording its descarboethoxy metabolite—desloratadine, reported to be a more potent H_1-receptor antagonist and a more potent inhibitor of histamine release. Due to a slow dissociation of the loratadine-H_1 receptor complex, as well as to the formation of its active metabolite, loratadine was shown to express a prolonged antihistaminic action [1]. A very important feature of this generation of antihistaminics is that, when applied in therapeutic concentrations, they have poorly expressed sedating effect, because only small amounts of these drugs penetrate the blood brain barrier [2].

From chemical point of view, loratadine and desloratadine (Scheme 1) represent the bases whose non-protonated forms are poorly soluble in water. Loratadine molecule contains a single basic centre, pyridine nitrogen atom, while in addition to this, desloratadine molecule contains another basic centre, piperidine nitrogen atom. The studies on protolytic equilibria and solubility of pharmacologically active substances is of a special significance in biochemical pharmacology, because absorption of drugs in gastrointestinal tract and transport through the cell membranes are known to be affected by the properties of the chemical species involved. Besides, knowledge on the distribution of species as a function of pH is very important for the choice of optimal conditions in drug analyses. Loratadine pK_a value of 4.58 has been previously determined on the basis of the partition (log P) and distribution (log D) coefficients measured in dodecane/water system [3]. At the same time, only one desloratadine acidity constant pK_a of 8.65 has been determined by a potentiometric approach [3]. There are the reports on the solubility of loratadine free base form at the temperatures of 30 °C ($\leq 3.6 \times 10^{-6}$ M) [4] and 37 °C (1.0×10^{-5} to 1.6×10^{-5} M) [5]. However, the data on determination of desloratadine solubility are still lacking in the available literature.

Surfactant micellar media, interalia, can increase the solubility of the substances poorly soluble in water and modify acid–base properties of protolytes. This is of a special significance for the understanding of the mechanisms underlying drug action, since aqueous micellar systems can simulate far more complex biological systems. Because of that, the interest on the effects of surfactants on drug properties is continously increasing [6–12].

Since complete data on pK_a values and solubility of loratadine and desloratadine are still lacking in the available literature, the present study was aimed at the examinations of acid–base equilibria in homogeneous and heterogeneous aqueous systems of these two drugs.

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Besides, the effects of several surfactants such as sodium dodecyl sulphate (SDS), cetyltrimethylammonium bromide (CTAB) and Triton X 100 (TX 100) on pK_a values of loratadine and desloratadine, as well as on intrinsic solubility of loratadine were investigated.

To determine pK_a values of slightly soluble compounds, such as loratadine and desloratadine, potentiometric and spectrophotometric methods have been the most frequently applied approaches till present. The problem of poor solubility of the samples has been solved employing mixed-solvent systems for potentiometric determination. Also, procedures for reliable potentiometric determination pK_a of slightly soluble compounds have been evaluated in a variety of cosolvent systems [13–15]. Generally speaking, these procedures were based on the application of four-parameter technique (Four-Plus^{TM} method [15]) for glass electrode calibration and Yasuda–Shedlovsky extrapolation to zero percent organic content. Since numerous substances remain insoluble in single component organic solvent–water mixtures, a multicomponent cosolvent system consisting of equal volumes of methanol, dioxane and acetonitrile (MDM) has been recently proposed. The MDM–water mixture represents a universal cosolvent system suitable to dissolve a wide range of slightly soluble, both hydrophobic and polar compounds. Spectrophotometric pK_a determination was performed in the solutions of low concentration and usually, the use of cosolvent was unnecessary (except in the case of extremely slightly soluble substances), but the difference in the absorption spectra of conjugated acid–base pair is indispensable for this approach. In order to avoid cosolvent procedure which requires extrapolation, in the present study, pK_a values of loratadine and desloratadine were determined by spectrophotometry.

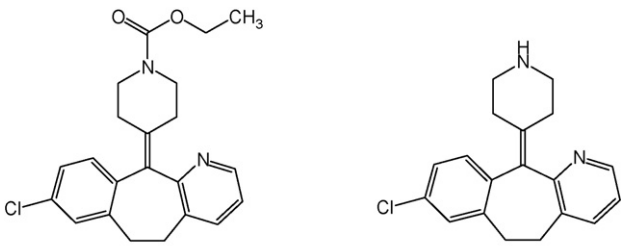
2. Materials and methods

2.1. Chemicals and apparatus

Loratadine and desloratadine were kindly provided by the Medicines and Medical Devices Agency of Serbia (Belgrade, Serbia). The surfactants, sodium dodecyl sulphate (JT Baker), cetyltrimethylammonium bromide (Acros), and Triton X 100 (Acros) were of analytical reagent grade. Other reagents used throughout the present study were Merck products of analytical grade of purity. All solutions were prepared in double distilled water.

A Britton–Robinson (BR) buffer solution (a mixture of acetic, boric and phosphoric acid, each at 0.04 M) was prepared and the required pH (2.5–12.0) adjusted with 0.2 M NaOH. The ionic strengths of Britton–Robinson buffer for the pH range applied in the present work are listed in Table 1. For the calculations the following pK_a values were employed—acetic acid 4.76, phosphoric acid 2.15, 7.20, 12.33, and boric acid 9.23.

For spectrophotometric measurements a GBC Cintra 20 spectrophotometer was used. The temperature of the samples was maintained at 25 ± 0.1 °C using a Huber Polystat CC2 thermostat. A Metrohm 798 MPT Titrino system with combined LL unitrode Pt1000 electrode, regularly calibrated with standard buffer solutions (pH 4.01, 7.00 and 9.21) served for pH measurements.



Loratadine Desloratadine

Scheme 1. Chemical structure of loratadine and desloratadine.

Table 1
Ionic strength of Britton–Robinson buffer (acetic, boric and phosphoric acid, each at 0.04 M).

pH	I	pH	I	pH	I
2.6	0.03	5.8	0.08	9.0	0.17
2.8	0.03	6.0	0.08	9.2	0.18
3.0	0.04	6.2	0.09	9.4	0.18
3.2	0.04	6.4	0.09	9.6	0.19
3.4	0.04	6.6	0.10	9.8	0.19
3.6	0.04	6.8	0.10	10.0	0.19
3.8	0.04	7.0	0.11	10.2	0.20
4.0	0.05	7.2	0.12	10.4	0.20
4.2	0.05	7.4	0.13	10.6	0.20
4.4	0.05	7.6	0.14	10.8	0.20
4.6	0.06	7.8	0.15	11.0	0.21
4.8	0.06	8.0	0.15	11.2	0.21
5.0	0.07	8.2	0.16	11.4	0.21
5.2	0.07	8.4	0.16	11.6	0.22
5.4	0.07	8.6	0.16	11.8	0.23
5.6	0.08	8.8	0.17	12.0	0.24

2.2. pK_a determination

pK_a values of loratadine and desloratadine were spectrophotometrically determined in BR buffer solutions pH 2.5–12.0. To extend the pH range, 0.1 and 0.01 M HCl, as well as 0.1 M NaOH solutions were employed. Determinations were performed in aqueous solutions in the absence and in the presence of aforementioned surfactants (1×10^{-2} M) at 25 °C. Absorption spectra were recorded in relation to the corresponding blank solutions. For the determination of pK_a values, the absorption spectra of the drugs within the pH interval concentrated mainly around the pK_a were used.

Acidity constants were calculated applying a classical spectrophotometric equation [16]:

$$pK_a = \mathrm{pH} + \log\frac{A_{BH^+} - A}{A - A_B} \quad (1)$$

and its transformed form:

$$A = A_B + \frac{1}{K_a}(A_{BH^+} - A)[H^+] \quad (2)$$

where A_{BH^+}, A_B and A represent the absorbancy of the protonated form, non-protonated form and mixture of these forms obtained at different pH values, respectively.

2.3. Solubility studies

In heterogeneous systems of loratadine (pH > pK_a + 2) and desloratadine (pH > pK_{a2} + 2), the equlibrium between the solid base (B_s) and its saturated solution defined by the constant K_{s0} was established:

$$B_s \rightleftarrows B, \quad K_{s0} = [B] = S_0 \quad (3)$$

The K_{s0} constant equals the concentration of non-protonated form (B) of the examined drugs in saturated solution and represents the intrinsic solubility (also referred to as S_0).

Intrinsic solubilities of loratadine and desloratadine were determined by treating solid phase excess with BR buffer solution, pH 7.5 and pH 12.0, respectively. The solutions were kept in a thermostat at 25 °C with constant stirring for the first 48 h and without stirring for the next 24 h in order to achieve phase separation. After that, the aliquots of the clear supernatants were diluted with the

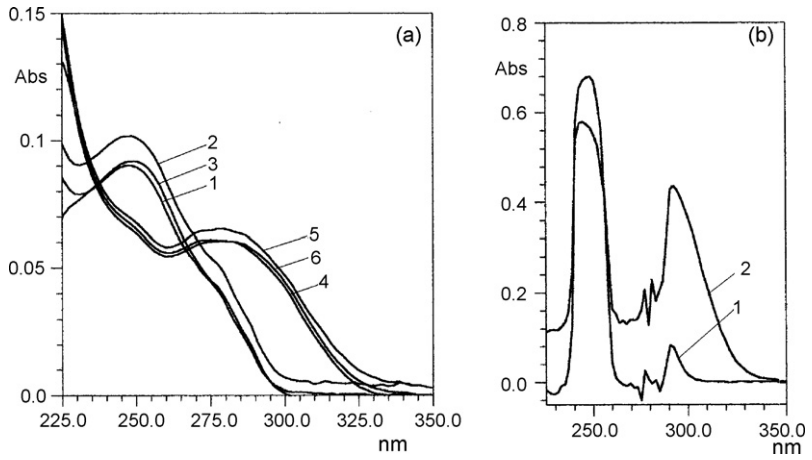


Fig. 1. Absorption spectra of non-protonated and protonated loratadine forms in the absence and in the presence of surfactants (1×10^{-2} M). (a) Non-protonated form: (1) BR buffer pH 7.5; (2) SDS—BR buffer pH 7.5 and (3) CTAB—BR buffer pH 7.5. Protonated form: (4) BR buffer pH 3.0; (5) SDS—BR buffer pH 3.0 and (6) CTAB—0.1 M HCl. (b) (1) TX 100—BR buffer pH 7.5 (non-protonated form) and (2) TX 100—0.1 M HCl (protonated form).

same buffers and the concentration of the examined drugs spectrophotometrically determined at 246 nm (loratadine), i.e. 250 nm (desloratadine).

The above procedure was also applied for solubility determination of non-protonated loratadine form in BR buffer pH 7.5 in the presence of the 1×10^{-2} M surfactants (SDS, CTAB and TX 100). The aliquots of the supernatants were diluted with the corresponding BR buffer pH 7.5—surfactant solution, except in the case of TX 100 where the aliquot of the supernatant was diluted with 0.1 M HCl and the absorbancy measured at 300 nm.

Taking into consideration the fact that loratadine represents a monoprotic base, besides the equilibrium shown by Eq. (3) in a heterogeneous system at $pH < pK_a + 2$ another equilibrium gets established:

$$B_s + H^+ \rightleftarrows BH^+, \quad K_{s1} = \frac{[BH^+]}{[H^+]} \tag{4}$$

The solubility (S) within this pH range is presented by the equation:

$$S = [B] + [BH^+] \tag{5}$$

Combination of Eqs. (3)–(5) gives:

$$S = K_{s0} + K_{s1}[H^+] \tag{6}$$

which represents linear dependence of solubility on $[H^+]$.

Solubility of loratadine at different pH values was experimentally determined within the pH range from 3 to 6 of heterogeneous systems prepared in BR buffer. The samples were treated as described above for the determination of intrinsic solubility and loratadine concentration after dilution of the supernatants determined at 266 nm (isobestic point of non-protonated and protonated loratadine forms).

3. Results and discussion

3.1. pK_a determination

Acidity constants of loratadine and desloratadine were spectrophotometrically determined both in aqueous medium and in the presence of the surfactants (SDS, CTAB and TX 100, 1×10^{-2} M). The concentration of the surfactants of 1×10^{-2} M chosen in order to examine their effects on pK_a values of loratadine and desloratadine was well above critical micelle concentration (cmc) and thus,

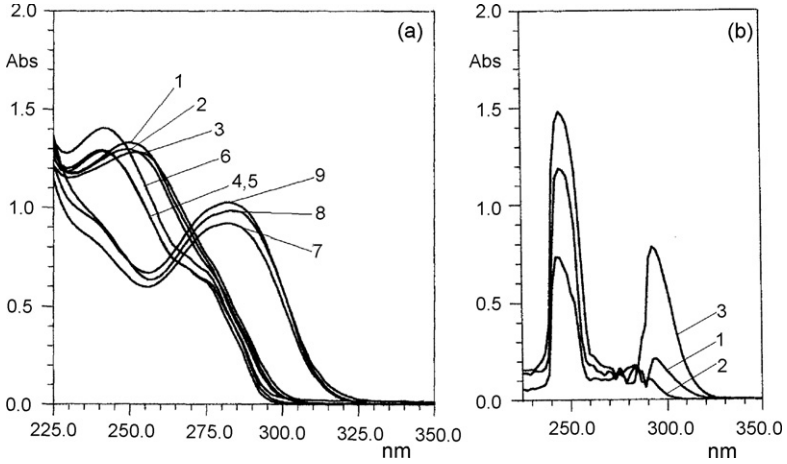


Fig. 2. Absorption spectra of non-protonated, monoprotonated and diprotonated desloratadine forms obtained in the absence and in the presence of surfactants (1×10^{-2} M). (a) Non-protonated form: (1) BR buffer pH 12.0; (2) SDS—0.1 M NaOH and (3) CTAB—BR buffer pH 11.0. Monoprotonated form: (4) BR buffer pH 7.5; (5) SDS—BR buffer pH 7.5 and (6) CTAB—BR buffer pH 6.5. Diprotonated form: (7) 0.01 M HCl; (8) SDS—0.01 M HCl and (9) CTAB—0.01 M HCl. (b) (1) TX 100—0.1 M NaOH (non-protonated form); (2) TX 100—BR buffer pH 7.5 (monoprotonated form) and (3) TX 100—0.01 M HCl (diprotonated form).

the changes in cmc due to the solute could be neglected. Absorption spectra of pure loratadine and desloratadine forms in different media are shown in Figs. 1 and 2. It can be seen that in the presence of SDS and CTAB, the absorption maximum of non-protonated (free base) loratadine form in water was shifted from 246.5 nm toward a longer wavelength of 248.5 nm (Fig. 1a), while the maximum of protonated form of this substance being in water at 281.1 nm was shifted toward shorter wavelengths in the presence of these two surfactants (279.2 and 273.4 nm, respectively). Spectral maxima of mono- and diprotonated desloratadine forms at 240.8 and 283 nm, respectively, have not been affected by either SDS or CTAB (Fig. 2a). Absorption maximum of non-protonated desloratadine form at 250.4 nm in water was shifted toward a shorter wavelength of 248.5 nm in the presence of SDS and toward a longer wavelength in the presence of CTAB (252.3 nm). Reliable spectra of the examined antihistaminics in the presence of TX 100 were impossible to obtain at wavelengths under 295 nm (Figs. 1b and 2b). At the TX 100 concentration of 1×10^{-2} M and the wavelengths over 295 nm, reproducible spectra were obtained (conformity with Lambert–Beer's law having being previously verified). Because of that, all spectrophotometric measurements in the presence of TX 100 were performed at 300 nm.

Acidity constants of loratadine and desloratadine were determined at the wavelengths at which the most conspicuous differences in the absorption spectra of the corresponding pure forms of these drugs were observed. So, spectrophotometric measurements of loratadine in all media studied here were performed at 300 nm. As to desloratadine, the constants K_{a1} and K_{a2} in water or in the media supplemented with either SDS or STAB were determined at 295 and 260 nm, respectively, while both constants in TX 100-containing medium were determined at 300 nm. A large difference in basicity between the pyridine and piperidine nitrogen atoms in desloratadine enabled determination of pK_{a1} and pK_{a2} values independently of each other.

Based on the absorbancy of the examined drug solutions obtained at different pH values, acidity constants of both loratadine and desloratadine were calculated applying Eq. (1) or (2) (Table 2). Eq. (2) was employed to calculate loratadine pK_a in water medium, as well as desloratadine pK_{a2} in the presence of SDS and TX 100. Eq. (2) represents linear dependence $A = f(A_{BH^+} - A)[H^+]$ with a slope equal to K_a^{-1}, thus enabling determination of the constants without knowing the spectra of pure non-protonated forms of the examined compounds. In this manner, it was possible to determine pK_a value of extremely slightly soluble loratadine (intrinsic solubility 8.65×10^{-6} M, see Table 3) in the solutions concentration of 1.5×10^{-5} M. The determinations were performed at $pH < pK_a$, at which the molecule is mostly present in protonated form and thus its solubility is improved. In the case of K_{a2} value of desloratadine in the presence of SDS and TX 100, application of Eq. (2) enabled to avoid the use of a strongly alkaline medium and determinations were performed at pH values under 12.0, representing the upper pH limit of the BR buffer used here. A representative diagram demonstrating linear dependence given by Eq. (2) used for the determination of desloratadine K_{a2} value in the presence of SDS as an example is depicted in Fig. 3.

Table 3
Equilibrium constants in the heterogeneous systems of loratadine and desloratadine.

	Loratadine	Desloratadine	n
K_{s0}[a]	$(8.65 \pm 0.09) \times 10^{-6}$	$(3.82 \pm 0.03) \times 10^{-4}$	12
$\log K_{s0}$	−5.06	−3.42	
K_{s1}	1.61 ± 0.06		6
$\log K_{s1}$	0.21		
pK_a[b]	5.27		

[a] Intrinsic solubility ($K_{s0} = S_0$).
[b] $pK_a = -\log K_{s0} + \log K_{s1}$.

In addition to the pK_a values of loratadine and desloratadine obtained throughout the present study and summarized in Table 2, related data from the literature were incorporated. Loratadine pK_a value of 5.25 is in a relatively satisfactory accordance with the calculated value of 4.81 (ACD software, SciFinder Scholar 2006), but a significant difference was observed in comparison with the indirectly obtained pK_a value of 4.58 calculated on the basis of $\log P$ and $\log D$ [3]. So far, only a single, potentiometrically determined desloratadine pK_a value of 8.65 [3] and calculated one of 10.27 (ACD software, SciFinder Scholar 2006) have been reported. Based on the pK_a values obtained in the present study it can be concluded that pyridine nitrogen atom in desloratadine molecule expressed less basic properties in relation to the same nitrogen atom contained within loratadine molecule. SDS, as an anionic surfactant acted increasing pK_a value of both examined drugs. This basicity increase could be explained in terms of electrostatic attraction between negatively charged interfacial layer of SDS and protonated forms of loratadine (BH^+) and desloratadine (BH_2^{2+} and BH^+). As expected, SDS expressed the strongest effect on pK_{a1} value of desloratadine, because of the charge type of this substance (2+/+) which corresponds to this acidity constant. The presence of a cationic surfactant such as CTAB results in electrostatical repulsion of positively charged micellar interface and protonated form of both examined drugs, leading to a decrease of basicity, i.e. of the pK_a value. CTAB expressed the strongest effect on pK_a value of loratadine, while expressing almost no effect on pK_{a1} value of desloratadine. A strong CTAB effect on pK_a value of loratadine can also be ascribed to more

Table 2
Acidity constants of loratadine and desloratadine in water and in the presence of surfactants (1×10^{-2} M) at 25 °C.

Medium	Loratadine pK_a	Desloratadine pK_a
Water	4.58[a] 4.81[b]	8.65[a] 10.27[b]

Medium	Loratadine	Desloratadine	
	$pK_a \pm$ S.D.	$pK_{a1} \pm$ S.D.	$pK_{a2} \pm$ S.D.
Water	5.25 ± 0.05	4.41 ± 0.02	9.97 ± 0.03
SDS	5.44 ± 0.03	5.65 ± 0.04	10.63 ± 0.04
CTAB	3.01 ± 0.02	4.42 ± 0.01	8.60 ± 0.04
TX 100	3.59 ± 0.05	4.17 ± 0.03	11.09 ± 0.08

[a] Ref. [3].
[b] Calculated value (ACD software, SciFinder Scholar 2006).

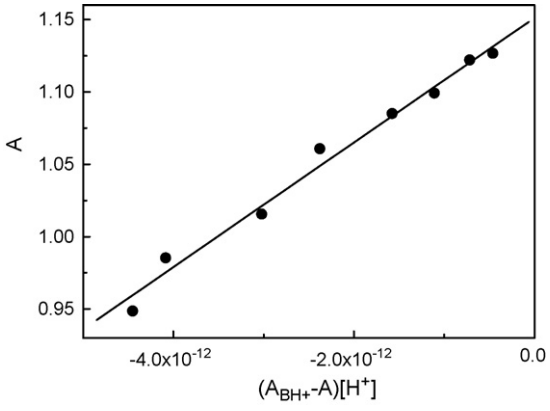


Fig. 3. A graph for determination of K_{a1} of desloratadine in the presence of SDS applying Eq. (2).

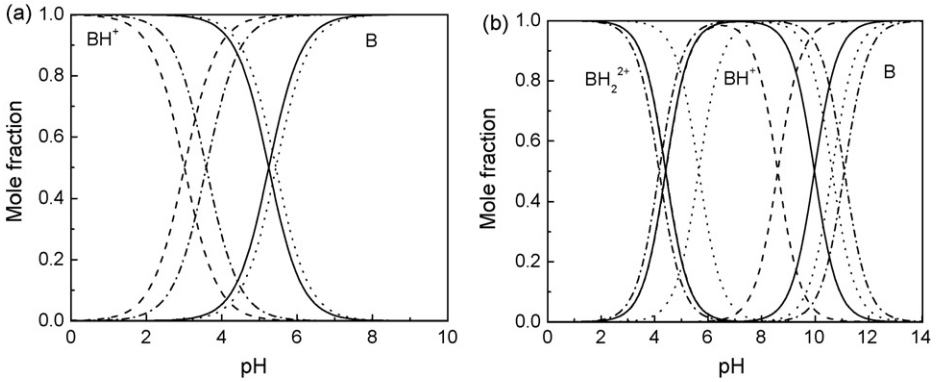


Fig. 4. Distribution diagrams as a function of pH of (a) loratadine and (b) desloratadine in water and micellar media: (—) water, (···) SDS, (– – –) CTAB, (–·–·–·) TX 100. B—non-protonated form; BH^+—monoprotonated form; BH_2^{2+}—diprotonated form.

Table 4
Intrinsic solubility of free base loratadine form in water and in the presence of surfactants (1×10^{-2} M) at 25 °C.

Medium	S_0 (μg/ml)	S_0 (M)	$\log S_0$ (M)	n
Water	3.31 ± 0.04	8.65×10^{-6}	−5.06	12
SDS	551.4 ± 42.1	1.44×10^{-3}	−2.84	12
CTAB	536.0 ± 8.2	1.40×10^{-3}	−2.85	12
TX 100	305.2 ± 2.5	7.97×10^{-4}	−3.10	12

expressed hydrophobic properties of loratadine itself, enabling stronger hydrophobic interactions of its non-protonated form with lipophilic side-chains of CTAB. The basicity of pyridine nitrogen atom in both examined drugs was decreased in the presence of a non-ionic surfactant TX 100, while at the same time the basicity of piperidine nitrogen atom of desloratadine (pK_{a2}) was increased.

The obtained pK_a values in water and micellar media served to calculate the distribution of equilibrium forms of the examined antihistaminics depending on the pH value (Fig. 4).

3.2. Solubility study

The intrinsic solubility (constant K_{s0}) of loratadine and desloratadine determined in the BR buffer pH 7.5 (loratadine) and 12.0 (desloratadine), as described under Section 2 are listed in Table 3. Taking into account extremely low intrinsic solubility of loratadine, the effects of the surfactants on its solubility were estimated. The results on the effects of SDS, CTAB and TX 100 applied in the concentration of 1×10^{-2} M each on loratadine solubility in BR buffer pH 7.5 are summarized in Table 4. The results clearly demonstrate a significant solubility increase of non-protonated form of this drug in the presence of either of the three surfactants, the effects of SDS and CTAB being very similar.

In addition to the examinations related to the influence of the above surfactants on loratadine solubility, pH effects were also investigated and pH-dependent solubility of loratadine determined within the pH range from 3 to 6 is listed in Table 5. On the basis of these data and Eq. (6) the K_{s1} constant was calculated from the slope of the corresponding curve by linear regression analysis (Fig. 5) and the value obtained is shown in Table 3. This dependence could not be employed to calculate the constant K_{s0} (intercept) because its value was within the limits of the experimental error.

Since the following relation is connecting the constants K_{s0}, K_{s1} and K_a:

$$K_a = \frac{K_{s0}}{K_{s1}} \quad (pK_a = -\log\ K_{s0} + \log K_{s1}) \tag{7}$$

it was possible to calculate one of these constants if the two others were known [17]. In this manner, the constant K_a of loratadine was calculated based on the determined values of K_{s0} and K_{s1}. The calculated loratadine pK_a value of 5.27 (Table 3) matches well the directly determined value of 5.25 of this constant (Table 2). This accordance of spectrophotometrically determined with calculated pK_a values was more than welcome because of undoubtedly confirming the accuracy of the measurement.

Based on the obtained values of loratadine K_{s0} and pK_a, i.e. desloratadine K_{s0} and pK_{a2} determined in water, solubilities of these two drugs depending on the pH were calculated applying the following equations:

$$\log\ S = \log K_{s0}(1 + 10^{pK_a - pH}) \quad \text{(loratadine)} \tag{8}$$

$$\log\ S = \log K_{s0}(1 + 10^{pK_{a2} - pH}) \quad \text{(desloratadine)} \tag{9}$$

In addition to the calculated solubility of both loratadine and desloratadine, experimentally obtained data on pH-dependent loratadine solubilities are depicted in Fig. 6. It can be seen (Fig. 6) that water solubility of desloratadine was much higher comparing

Table 5
Solubility (S) of loratadine at various pH.

pH	S (M)
5.19	1.99×10^{-5}
4.58	3.94×10^{-5}
4.02	1.28×10^{-4}
3.80	2.51×10^{-4}
3.72	3.13×10^{-4}
3.56	4.46×10^{-4}

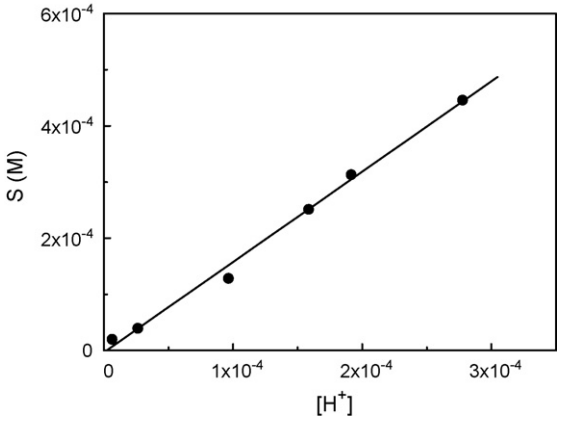


Fig. 5. A graph for determination of equilibrium constant K_{s1} in a heterogeneous system of loratadine applying Eq. (6).

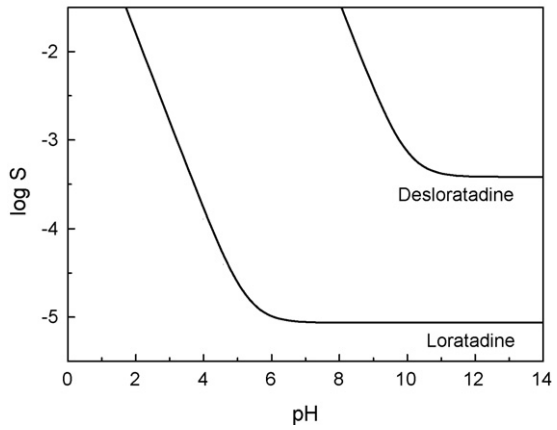


Fig. 6. Solubility—pH profile of loratadine and desloratadine.

to that of loratadine. The solubility of loratadine of 3.82×10^{-4} M, corresponding to intrinsic solubility of desloratadine, was not achieved above the pH value of 3.6.

4. Conclusion

Basicity of desloratadine is much higher than that of loratadine because of a possibility for the protonation of piperidine nitrogen atom within desloratadine molecule. Micellized surfactants modified all pK_a values, with the exception of CTAB which did not influence pK_{a1} value of desloratadine. The shift of pK_a values in the presence of the applied surfactants in relation to those in water (ΔpK_a) ranged from −2.24 to +1.24. At physiologically important pH values of 1.0, 7.4 and 9.0, loratadine and desloratadine occur in different forms. So, at pH 1.0, loratadine occurred in monoprotonated and desloratadine in diprotonated form. At pH 7.4, loratadine was in non-protonated and desloratadine in monoprotonated form. At pH 9.0 loratadine was in non-protonated and desloratadine mostly in monoprotonated form except in the presence of CTAB when its non-protonated form was a bit predominant. The results of the present study demonstrated 40 times higher intrinsic solubility of desloratadine comparing to that of loratadine. An extremely slight hydrosolubility of non-protonated loratadine form was increased approximately 90 times in the presence of TX 100 and about 160 times in the presence of either SDS or CTAB.

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