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Acid−Base Equilibria of Rupatadine Fumarate in Aqueous Media

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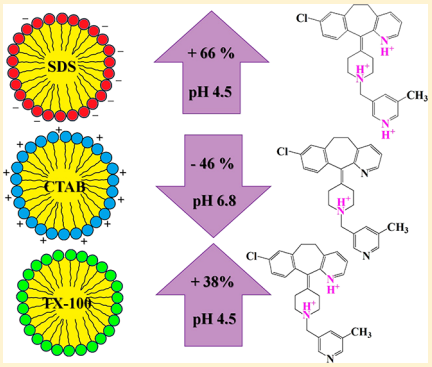
ABSTRACT: The acid−base equilibria of rupatadine fumarate were investigated in the absence and the presence of differently charged anionic (sodium dodecyl sulfate), cationic (cetyltrimethylammonium bromide), and nonionic (4-octylphenol polyethoxylate) surfactants. The pK_a values of rupatadine and fumaric acid were potentiometrically determined at 25 °C and at a constant ionic strength (0.1 M NaCl). The obtained potentiometric data were evaluated with use of the computer program Hyperquad. Ionization in the surfactant-free media was defined, and the effects of surfactants on protolytic equilibria of rupatadine were estimated, based on a shift of the apparent ionization constants determined in micellar solutions against the pK_a values in water. The anionic SDS micelles caused an increase in the pK_a values of all the rupatadine ionization centers (ΔpK_a up to +1.44), while the shift of protolytic equilibria in different directions was observed in the case of the cationic CTAB (ΔpK_a from −1.99 to +0.14) and the nonionic TX-100 (ΔpK_a from −0.72 to +0.38) micelles. Distribution diagrams of the equilibrium forms as a function of pH indicate that the change in distribution is most strongly expressed in the pH range 4−8 which includes biopharmaceutically important pH values.



INTRODUCTION

Rupatadine belongs to the selective second generation, nonsedating, long-acting antagonists of the peripheral histamine H_1 receptors, used in seasonal allergic rhinitis and chronic urticaria. In the *in vitro* and *in vivo* studies, it was shown that rupatadine antagonizes receptors of the platelet activation factor (PAF), which was not observed with the other second generation antihistamines.[1] This drug expresses its antiallergic properties by inhibition of the mast cells degranulation induced by immunological and nonimmunological stimulus and by inhibition of the cytokines release, particularly of TNF in the human mast cells and monocites.[2]

Rupatadine contains three ionizable basic centers, two aromatic amines and one cyclic aliphatic amine (Figure 1). The pharmaceutical dosage forms for oral administration contain rupatadine fumarate as an active substance. A complex system of protolytic equilibria is established in the rupatadine fumarate solution, which involves three basic centers of rupatadine and two carboxylic groups of fumaric acid.

The liberation process of active pharmaceutical ingredients (API) from pharmaceutical dosage forms and their absorption are affected by physicochemical properties of the drug compounds, the properties of the dosage form, and the conditions at the site of administration and/or absorption.[3−7] In addition to solubility and lipophilicity, the most important physicochemical parameter is the pK_a value.[8] Although solubility has been proven to have an essential effect on the success of a drug candidate in drug discovery and its permeability is accepted as a major determinant of oral absorption, it has been shown that permeability can be controlled by both the un-ionized and ionized species.[9] The knowledge of the pK_a values enables calculation of the relative percentages of the ionized and un-ionized form of a compound at any given pH value, which helps prediction of water solubility, absorption, and excretion for a given drug.[7] However, for the prediction of bioavailability and pharmacokinetic properties of the drugs in physiological conditions, data on protolytic equilibria determined in a pure aqueous solution might not be sufficient. Under physiological conditions that are significantly more complex, interactions with polar and charged biomolecules may affect protolytic equilibria of drugs.[9]

The absorption process involves passing of a drug through biological membranes whereby drugs often interact with various components of biomembranes, or with other molecules present in body fluids. Protolytic equilibria can be shifted due to possible interactions, so that the degree of ionization determined in the "pure" aqueous solution can significantly vary under physiological conditions. For this reason, a better understanding of the behavior of ionizable drugs in aqueous compartments of a living system separated by the lipid membranes could be achieved by investigating their physicochemical properties under the conditions more similar to physiological. Micellar solutions of the surfactants have been used as biomembrane mimetic systems, due to their

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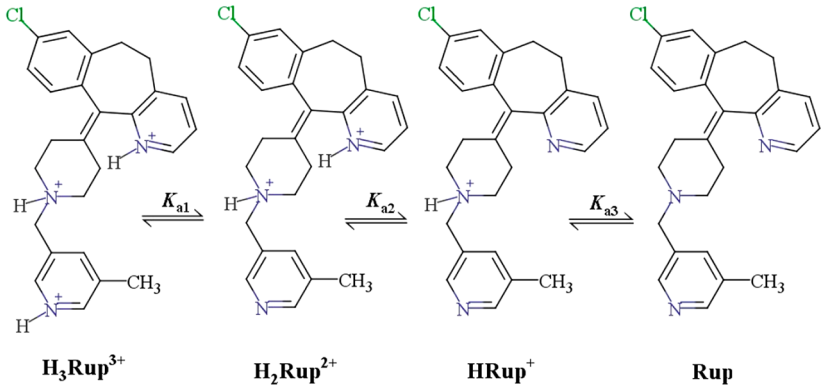

Figure 1. Ionization profile of rupatadine.

biomimetic nature based on structural and functional properties, which are considered to mimic the most elementary membrane functions and which can shift the pK_a values determined in pure water.[10−12] The molecules of surfactants can self-associate in a manner analogous to the membrane phospholipids, thus contributing to the compartmentalization of the molecules and to the reactions similar to those in biological cells. Therefore, interactions observed between the drugs and the micelles can point to a possible drug distribution within the body compartments.[13] Moreover, our previous research[14−16] has shown that one cannot generally anticipate whether the acidity of drugs would increase or decrease, not even in the case of the structurally similar compounds belonging to the same pharmacological class. Consequently, it is necessary to experimentally investigate for each individual compound its ionization pattern in a micellar solution.

In general, the ionization constants obtained in micellar media are the apparent constants[17,18] because they represent a kind of a hybrid between drug ionization in the aqueous phase and that within the micellar pseudophase.[19,20] The micellar pseudophase can be considered as a kind of an organic solvent or the water−organic mixture, where the equilibria between the molecular and the ionized form of the dissolved compound may differ from that in water.[21,22]

Although rupatadine has been approved for the treatment of the adults and children for allergic rhinitis and chronic urticaria approximately 15 years ago, it is still considered as a novel chemical entity[2] and the literature survey reveals that the information on its pK_a values is still lacking. Therefore, the aim of this work was to potentiometrically determine the rupatadine pK_a values in the rupatadine fumarate solution containing a complex system of protolytic equilibria. Besides, there are no available data in the literature on ionization of rupatadine in the presence of micelles. After defining the ionization in the surfactant-free solution, the values were also determined in micellar solutions of surfactants: anionic, sodium dodecyl sulfate (SDS); cationic, cetyltrimethylammonium bromide (CTAB); and nonionic, 4-octylphenyl polyethoxylate (TX-100) (Figure 2). The effect of surfactants on protolytic equilibria of rupatadine was evaluated, and possible interactions of rupatadine with the micelles of different charge and polarity were described.

EXPERIMENTAL SECTION

Apparatus and Reagents. Automatic titrator 798 MPT Titrino (Metrohm, Switzerland) with a combined electrode LL unitrode Pt 1000 (Metrohm, Switzerland) was used for

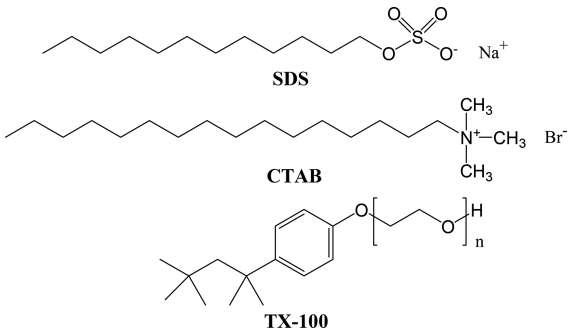

Figure 2. Chemical structures of applied surfactants.

potentiometric determinations. Prior to the titration, the electrode used for the pH measurements was regularly calibrated with the standard buffer solutions (pH 4.01, 7.00, and 9.21, Hamilton Duracal, Switcerland). For interpretation of the measured pH values (pH = −log a_H) in terms of the hydrated proton concentration, i.e., of the pcH values (pcH = −log c_H), the correction factor A was used. Factor A = 0.12 was determined experimentally by titrating the standard HCl solution at the ionic strength of 0.1 M (NaCl) with the standard NaOH solution, and it was used in the relation pcH = pH − A.[23,24] Apart from the method used in this study, one can also apply some other approaches to the evaluation of stoichiometric dissociation constants from electrochemical cell data.[25−27] The constant temperature of the titrated solutions was maintained at 25 °C using a Huber Polystat CC2 thermostat.

Rupatadine fumarate, 8-chloro-6,11-dihydro-11-[1-[(5-methyl-3-pyridyl)methyl]-4-piperidylidene]-5*H*-benzo[5,6]-cyclohepta[1,2-*b*]pyridine fumarate, and fumaric acid were kindly donated from the Medicines and Medical Devices Agency of Serbia (Belgrade, Serbia). Sodium dodecyl sulfate (J.T. Baker, ≥ 95% purity), CTAB (Acros Organic, ≥ 99% purity), and Triton TX-100 (Acros Organic, ≥98% purity) were used to prepare the micellar solutions. All solutions were prepared with use of double distilled water. Standard solutions of HCl and the carbonate-free NaOH were potentiometrically standardized.

Potentiometric Titration. The ionization constants of fumaric acid and rupatadine were determined in the absence and in the presence of the 10^{-2} M surfactants (SDS, CTAB, and TX-100). The corresponding titration curves are shown in Figures 3 and 4. An addition of the surfactants in the above concentration had no significant effect on the pH of the buffers

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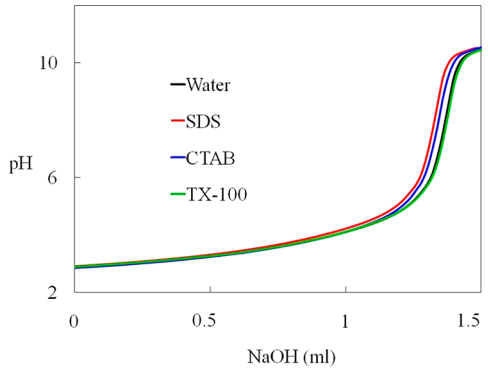

Figure 3. Potentiometric curves for fumaric acid solutions in the absence and in the presence of 10^{-2} M surfactants (SDS, CTAB, TX-100) titrated with standard NaOH solution. I = 0.1 M (NaCl) and t = 25 °C.

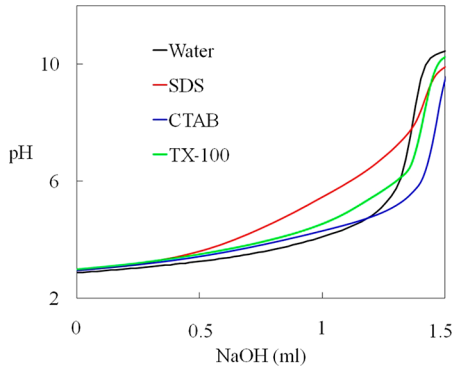

Figure 4. Potentiometric curves for rupatadine fumarate solutions in the absence and in the presence of 10^{-2} M surfactants (SDS, CTAB, TX-100) titrated with standard NaOH solution. I = 0.1 M (NaCl) and t = 25 °C.

(under ±0.02 pH units). All surfactants were used at concentrations significantly above their critical micellar concentration (CMC); thus, the influence of the other molecules present in the solution at CMC can be neglected.

All measurements were carried out under the same conditions at 25 °C with continuous magnetic stirring. The constant ionic strength was adjusted to 0.1 M with NaCl. Solutions (5×10^{-4} M) of fumaric acid and rupatadine fumarate in the surfactant-free and the surfactant-containing media were titrated with the 0.02 mL aliquots of the standard NaOH solution (0.0983 M). Prior to the titration, to all titrated solutions 1 mL of 0.1015 M HCl standard solution was added to suppress dissociation of the carboxyl groups of fumaric acid and to achieve total protonation of the ionizable rupatadine centers. The experimental data obtained by potentiometric titration were analyzed with use of the computer program Hyperquad[28] which allows determination of the pK_a values in complex systems by characterization with the overlapped acid−base equilibria, even in the case of the solutions containing two compounds with ionizable centers. The computer program Hyperquad provides computational approaches based on the least-squares curve-fitting procedures. The pK_a values independently determined for fumaric acid were further used as input parameters for the determination of the rupatadine pK_a values from the potentiometric data obtained by titrating the rupatadine fumarate solution.

RESULTS AND DISCUSSION

pK_a Determination in Pure Aqueous Media. From the chemical point of view, rupatadine represents the triprotic base containing three ionizable centers, two aromatic amines and one cyclic, aliphatic, tertiary amine (Figure 1). The pharmaceutical dosage forms for oral administration contain the API as a salt, rupatadine fumarate. In solutions of ionizable drugs formulated as salts with an organic diacid, complex protolytic equilibria are established. Fumaric acid is among the most frequently used acids in the drug salt preparations of the drug compounds.[1] Determination of the pK_a value of organic acids helps define the ionization profile of the corresponding ionizable drug. This becomes an especially important when the drug contains two or more functional groups with similar pK_a values and when the environment that a molecule is in is even more complex, such as the human body.[1] Determination of the pK_a values represents a particular challenge in this case because a complex system of protolytic equilibria in the rupatadine fumarate solution that includes the ionization of three basic centers of rupatadine and two carboxylic groups of fumaric acid must be taken into account. The pK_a values of fumaric acid separately determined under the same experimental conditions as those for rupatadine (in the surfactant-free and the surfactant containing media) are used as an input parameter in the Hyperquad program for the analysis of potentiometric data obtained by titration of the rupatadine fumarate solution. The pK_a values of fumaric acid determined in "pure" water (pK_{a1} = 2.86 ± 0.04; pK_{a2} = 4.26 ± 0.04) (Table 1) remain in agreement with the available literature results.[29−34]

Table 1. pK_a Values of Fumaric Acid Potentiometrically Determined in This Study and Data from the Literature

fumaric acid	this study	literature data	ref
pK_{a1}	2.86 ± 0.04	3.03	29
		3.02	30
		3.03	31
		3.00	32
		3.02	33
		3.02	34
pK_{a2}	4.26 ± 0.04	4.44	29
		4.39	30
		4.38	31
		4.40	32
		4.38	33
		4.39	34

The experimentally determined pK_a values of rupatadine are pK_{a1} (pyridine in the side chain) 3.45 ± 0.07, pK_{a2} (pyridine in tricycle) 4.72 ± 0.06, and pK_{a3} (tertiary aliphatic amine) 6.75 ± 0.07 (Table 2). Attribution of the determined values to the corresponding ionizable groups was done based on the MarvinView 16.5.2.0 software prediction (ChemAxon).[35]

pK_a Determination in Micellar Media. After determination in "pure" water, the pK_a values of fumaric acid and rupatadine were then determined under the same working conditions in micellar solutions. From the pK_a values determined for fumaric acid in the presence of the micelles (Table 3), it can be concluded that the protolytic equilibria are not significantly affected by the micelles, except for pK_{a1} in CTAB (ΔpK_a = −0.12) and pK_{a2} in SDS (ΔpK_a = +0.30). An overall effect of the micelles on ionization of fumaric acid can

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Table 2. pK_a Values of Rupatadine Determined by Potentiometry and Values Predicted by MarvinView 16.5.2.0 Software

rupatadine	this study	MarvinView
pK_{a1}	3.45 ± 0.07	3.38
pK_{a2}	4.72 ± 0.06	4.20
pK_{a3}	6.75 ± 0.07	7.19

be estimated from distribution diagrams (Figure 5) constructed based on eqs 1−3 that describe the ionization process of the compound which contains two ionizable centers.

$$\%H_2Fum = \frac{100}{1 + 10^{pH-pK_{a1}} + 10^{2pH-pK_{a1}-pK_{a2}}} \quad (1)$$

$$\%HFum^- = \frac{100 \times 10^{pH-pK_{a1}}}{1 + 10^{pH-pK_{a1}} + 10^{2pH-pK_{a1}-pK_{a2}}} \quad (2)$$

$$\%Fum^{2-} = \frac{100 \times 10^{2pH-pK_{a1}-pK_{a2}}}{1 + 10^{pH-pK_{a1}} + 10^{2pH-pK_{a1}-pK_{a2}}} \quad (3)$$

The pK_a values of rupatadine determined in the presence of differently charged surfactants (SDS, CTAB, and TX-100) and the ΔpK_a values that represent the differences in relation to the values determined in water are listed in Table 4. From the pK_a values given in Table 4, it can be found out that all the employed surfactants exert a shift in the protolytic equilibria of rupatadine.

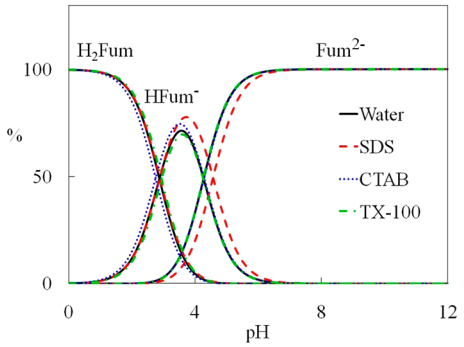

Figure 5. Distribution of the equilibrium forms of fumaric acid (H_2Fum) in the presence and in the absence of surfactants as a function of pH.

On the basis of the potentiometrically determined pK_a values and eqs 4−7 that describe the ionization process of the compound with the three ionizable centers, the distribution diagrams of the rupatadine equilibrium forms in the function of pH were constructed. The shifts in distribution of the rupatadine equilibrium forms in the presence of the micelles can clearly be seen from the distribution diagrams (Figure 6).

$$\%H_3Rup^{3+} = \frac{100 \times 10^{(-pK_{a1}-pK_{a2}-pK_{a3})} \times 10^{(pK_{a1}+pK_{a2}+pK_{a3}-3pH)}}{10^{-pK_{a1}-pK_{a2}-pK_{a3}} + 10^{-pK_{a1}-pK_{a2}-pH} + 10^{-pK_{a1}-2pH} + 10^{-3pH}} \quad (4)$$

$$\%H_2Rup^{2+} = \frac{100 \times 10^{(-pK_{a1}-pK_{a2}-pK_{a3})} \times 10^{(pK_{a2}+pK_{a3}-2pH)}}{10^{-pK_{a1}-pK_{a2}-pK_{a3}} + 10^{-pK_{a1}-pK_{a2}-pH} + 10^{-pK_{a1}-2pH} + 10^{-3pH}} \quad (5)$$

$$\%HRup^{+} = \frac{100 \times 10^{(-pK_{a1}-pK_{a2}-pK_{a3})} \times 10^{(pK_{a3}-pH)}}{10^{-pK_{a1}-pK_{a2}-pK_{a3}} + 10^{-pK_{a1}-pK_{a2}-pH} + 10^{-pK_{a1}-2pH} + 10^{-3pH}} \quad (6)$$

$$\%Rup = \frac{100 \times 10^{-pK_{a1}-pK_{a2}-pK_{a3}}}{10^{-pK_{a1}-pK_{a2}-pK_{a3}} + 10^{-pK_{a1}-pK_{a2}-pH} + 10^{-pK_{a1}-2pH} + 10^{-3pH}} \quad (7)$$

Interactions of Rupatadine with Micelles. The shift in protolytic equilibria is a confirmation of an existence of interactions between rupatadine and the micelles. However, different types of interactions can occur and changes in the ionization mode in relation to the surfactant-free media can mainly be attributed to the properties of the differently charged micelles. The hydrophobic parts of the drug could participate in hydrophobic interactions with the lipophilic interior of a micelle while the ionizable groups could be included in electrostatic effects with the charge surface of ionic micelles.[36]

Table 3. pK_a Values of Fumaric Acid Determined by Potentiometry in the Presence of 10^{-2} M Surfactants[a]

fumaric acid	SDS		CTAB		TX-100	
pK_a	pK_a	ΔpK_a	pK_a	ΔpK_a	pK_a	ΔpK_a
pK_{a1}	2.87 ± 0.04	0.01	2.74 ± 0.02	−0.12	2.93 ± 0.01	0.07
pK_{a2}	4.56 ± 0.04	0.30	4.28 ± 0.02	0.02	4.25 ± 0.01	−0.01

[a] I = 0.1 M NaCl, t = 25 °C, $\Delta pK_a = pK_a^{app} - pK_a^{w}$.

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Table 4. pK_a Values of Rupatadine Determined by Potentiometry in the Presence of 10^{-2} M Surfactants[a]

	SDS		CTAB		TX-100	
rupatadine pK_a	pK_a	ΔpK_a	pK_a	ΔpK_a	pK_a	ΔpK_a
pK_{a1}	4.89 ± 0.07	+1.44	3.59 ± 0.04	+0.14	3.83 ± 0.05	+0.38
pK_{a2}	6.12 ± 0.07	+1.40	4.07 ± 0.04	−0.65	4.38 ± 0.05	−0.34
pK_{a3}	7.76 ± 0.07	+1.01	4.76 ± 0.03	−1.99	6.03 ± 0.05	−0.72

[a]I = 0.1 M NaCl, t = 25 °C, $\Delta pK_a = pK_a^{app} - pK_a^{w}$.

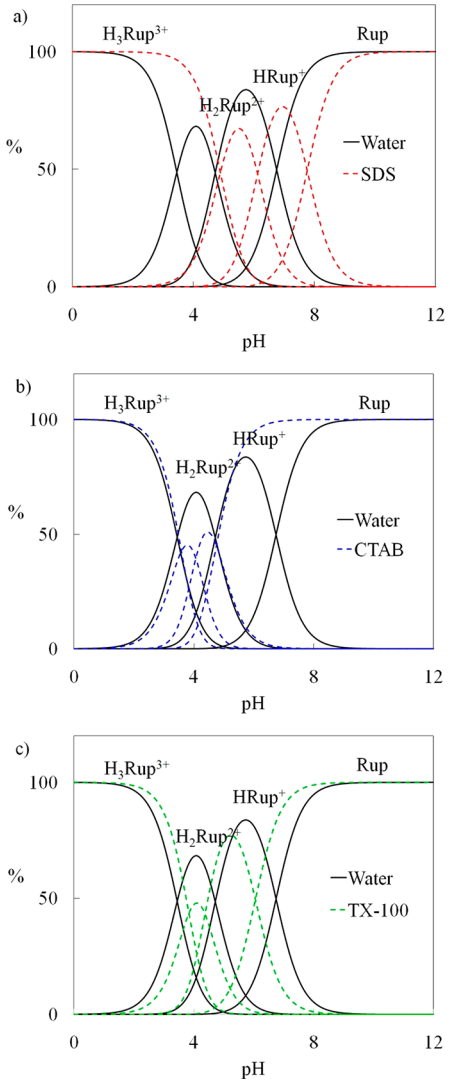

Figure 6. Distribution of the equilibrium forms of rupatadine (Rup) in the presence and in the absence of surfactants: (a) SDS, (b) CTAB, and (c) TX-100 as a function of pH.

Formation of the hydrogen bonds and the dipole interactions with solubilized drugs are possible in the noncharged but hydrophilic surface layers of nonionic micelles.[37] In the case of compounds containing ionizable groups, it is necessary to take into account the direction of the protolytic equilibria shift for a more detailed assessment of the dominant interactions.

Types of interactions that predominate between the rupatadine equilibrium forms and the surfactant micelles can mainly be explained in terms of properties of the differently charged micelles and the ionized rupatadine forms which are positively charged. The anionic micelles have a negatively charged surface which can be involved in electrostatic attractions with the positively charged rupatadine forms. A significant effect on the ionization of all rupatadine basic centers (ΔpK_a from +1.01 to +1.44) is observed for the negatively charged SDS micelles. In the presence of the SDS micelles, attraction forces with the ionized centers of rupatadine shift the equilibria toward protonation (H_3Rup^{3+}), which leads to an increase in the pK_a values (Table 4). On the other hand, in the case of the cationic micelles in which the surface is positively charged, the repulsion electrostatic forces would predominate in the interactions with positively charged rupatadine forms. The CTAB micelles with a positively charged surface, by the repulsion electrostatic interactions, hinder the ionization and shift the equilibria in the direction of the molecular form of the pK_{a2} (ΔpK_a = −0.65) and the pK_{a3} (ΔpK_a = −1.99) rupatadine groups. The effect of CTAB on the pK_{a1} of rupatadine is different (ΔpK_{a1} = +0.14), when compared with the effect on pK_{a2} and pK_{a3}, indicating the specific orientation of the rupatadine molecules, when interacting with the positively charged micelles.

The micelles of the nonionic surfactant TX-100 have no charged surface but contain a hydrated surface layer formed by polar oxyethylene groups. The polar moiety of the drug, its proton donor, and proton acceptor groups can be retained in the hydrophilic layer of the nonionic micelles or in the hydrophobic micelle interior.[38] It has been shown that the nonionic micelles have the least pronounced effect on protolytic equilibria of rupatadine (ΔpK_{a1} from −0.72 to +0.38). However, based on the observed pK_a shift, it can be assumed that rupatadine is probably retained in the hydrated surface layer of the nonionic micelles, where the ionizable

Table 5. Percentage of the Equilibrium Forms of Rupatadine at pH Values of Biopharmaceutical Importance in the Surfactant-Free and the Surfactant-Containing Media[a]

	pH 1.2				pH 4.5				pH 6.8				pH 7.4			
	TC	DC	MC	M	TC	DC	MC	M	TC	DC	MC	M	TC	DC	MC	M
water	99	1	0	0	5	1	36	0	0	0	47	53	0	0	18	82
SDS	100	0	0	0	71	29	1	0	0	16	76	8	0	4	67	29
CTAB	100	0	0	0	2	19	51	28	0	0	1	99	0	0	0	100
TX-100	100	0	0	0	8	39	51	2	0	0	15	85	0	0	4	96

[a]Rupatadine equilbrium forms: TC, H_3Rup^{3+}; DC, H_2Rup^{2+}; MC, $HRup^+$; M, molecular.

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centers are involved in dipole interactions and hydrogen bonds that nonspecifically affect protolytic equilibria.

Distribution diagrams point out that the change in the distribution of the rupatadine equilibrium forms is the most strongly pronounced in the pH range from 4 to 8, which is biopharmaceutically important. The shift in the protolytic equilibria of rupatadine under the influence of the micelles indicates that the distribution changes can also occur under physiological conditions, in the presence of biomolecules of different polarities and charges. An effect of surfactants on distribution of the equilibrium forms of rupatadine at biopharmaceutically significant pH values (pH 1.2; 4.5; 6.8; 7.4) is shown in Table 5. At pH 1.2, such as in the stomach, the presence of micelles does not affect the distribution of rupatadine. However, a significant shift in distribution of the equilibrium forms can be observed at the other considered pH values. At pH 4.5 which matches the value in the proximal part of the small intestine where the largest numbers of orally administered drugs are absorbed but where many charged and polar biomolecules are present, the micelles caused a marked change in the distribution. An increase in the content of the tricationic form H_3Rup^{3+} (+66%) in the presence of SDS, the dicationic form H_2Rup^{2+} (+38%) in the presence of TX-100, and the molecular form (+28%) in the presence of CTAB has been noticed. The content of the ionized forms responsible for drug solubility at the application site is increased under the influence of the anionic SDS and the nonionic TX-100 micelles. On the other hand, the content of the less soluble nonionized molecular form which is necessary for drug absorption and for passing through the lipophilic biological membranes is increased in the presence of the cationic CTAB micelles. This finding indicates that interactions of rupatadine with the negatively charged and the noncharged polar molecules can increase its solubility in the small intestine, while interactions with the positively charged molecules can affect an increase in the absorption and bioavailability of rupatadine.

At pH 6.8, physiologically found in the distal part of the intestine, the content of monocationic form $HRup^+$ decreases (−46%) in the presence of CTAB and the molecular form decreases (−45%) in the presence of the SDS micelles. At the same time, interactions of the ionizable centers of rupatadine with the cationic and nonionic micelles lead to the shift of equilibria toward the molecular form (+46% under the influence of CTAB and +32% under the influence of TX-100).

Under the conditions which match the plasma blood pH 7.4, the most expressed effect has been observed in the presence of negatively charged SDS micelles, where the content of the monocationic ($HRup^+$) form is increased (+49%) and the content of the molecular (Rup) form is decreased (−53%). This observation could suggest possible interactions of rupatadine with the negatively charged molecules present in plasma, which might affect its bioavailability.

On the basis of the distribution diagram, one can expect that at pH 4.5 (corresponding to the proximal part of small intestine) the presence of the negatively charged biomolecules significantly favors formation of the tricationic form of rupatadine (H_3Rup^{3+}). On the other hand, in the distal part of the small intestine, at a pH of 6.8, the positively charged molecules would potentially shift the equilibria to the molecular form of rupatadine.

CONCLUSION

In this study, the pK_a values of rupatadine were for the first time experimentally determined in aqueous media. The shift in protolytic equilibria was observed under the influence of the micelles of the differently charged surfactants as membrane mimicking systems. Changes in the ionization mode (the ΔpK_a values) indicate that the ionizable groups of rupatadine are involved in the interactions with the charged surface layer of the ionic micelles and with the polar hydrophilic layer of the nonionic micelles. Changes in distribution of the equilibrium forms of rupatadine at the biopharmaceutically important pH values indicate that interactions of rupatadine with the differently charged or polar molecules could be potentially considered under physiological conditions.

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Notes

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