organics

MDPI

Article

Protolytic Equilibria of Cetirizine in the Presence of Micelle-Forming Surfactants

Marija Popović-Nikolić [1,*], Gordana Popović [2], Slavica Oljačić [1] and Katarina Nikolić [1]

[1] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11221 Belgrade, Serbia; slavica.oljacic@pharmacy.bg.ac.rs (S.O.); katarina.nikolic@pharmacy.bg.ac.rs (K.N.)
[2] Department of General and Inorganic Chemistry, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11221 Belgrade, Serbia; gpopovic@pharmacy.bg.ac.rs
* Correspondence: majap@pharmacy.bg.ac.rs

Abstract: The acid–base equilibria of cetirizine were investigated with and without the presence of differently charged micelle-forming surfactants (anionic, cationic, nonionic). The pK_a values were potentiometrically determined at 25 °C and at a constant ionic strength (0.1 M NaCl). Experimental data were analyzed by applying the computer program Hyperquad 5.2.15. Based on a shift in the ionization constants (ΔpK_a) in micellar solutions against the pK_a values determined in "pure" water under the same conditions, the effects of micelles on the protolytic equilibria of cetirizine were estimated. Applied micelles caused a shift in the protolytic equilibria of all cetirizine ionizable centers, with the piperazine function connected to aliphatic side moiety (ΔpK_{a1} from −0.47 to +1.42), carboxyl group (ΔpK_{a2} from −0.92 to +2.02), and piperazine nitrogen connected to phenyl rings (ΔpK_{a3} from −2.01 to +2.19). Anionic SDS and nonionic Brij 35 micelles caused an increase in the pK_a values of the ionizable centers of cetirizine, while a decrease in the pK_a values was detected under the influence of cationic CTAB and nonionic TX-100 micelles. The change in the ionization pattern by micelles at pH values with biopharmaceutical significance provides indications of possible interactions of cetirizine with biomolecules of different charge and polarity under physiological conditions.

Keywords: cetirizine; acid–base equilibria; micelles; antihistamine; Hyperquad; potentiometry

Academic Editor: Stéphane P. Roche

Received: 23 September 2024
Revised: 21 November 2024
Accepted: 30 December 2024
Published: 2 January 2025

Citation: Popović-Nikolić, M.; Popović, G.; Oljačić, S.; Nikolić, K. Protolytic Equilibria of Cetirizine in the Presence of Micelle-Forming Surfactants. *Organics* **2025**, *6*, 2. https://doi.org/10.3390/org6010002

1. Introduction

Cetirizine belongs to the second generation of orally active and selective histamine (H_1) receptor antagonists, which are also considered to be a human metabolite of the first generation H_1 antihistamine, hydroxyzine [1]. Its main effect is therefore achieved through the selective inhibition of peripheral H_1 receptors [2]. Cetirizine is used to effectively treat the symptoms of seasonal allergic rhinitis, perennial allergic rhinitis and chronic idiopathic urticaria in adult, adolescent and pediatric patients [3]. The advantages of cetirizine compared to other H_1 receptor antagonists are a rapid onset of action, a long duration of action and a low potential for interactions with drugs metabolized by the cytochrome P450 enzyme system of the liver [3]. Cetirizine has been shown to attenuate platelet-activating factor (PAF)-induced eosinophil chemotaxis and the TNF-a-induced adherence of eosinophils to endothelial cells, which has led to consideration of its use in dermatology [4]. In addition, due to its significant reduction in inflammatory cell infiltrate and prostaglandin D2 production, the potential use of topical cetirizine in the therapeutic treatment of androgenetic alopecia is being investigated [5]. Cetirizine has been available

for more than 30 years [6], but it is still considered one of the most commonly administered second-generation H_1 antihistamines in the medical care of children with allergic conditions [7].

From the chemical point of view, cetirizine is an amholyte with three ionizable functional groups, one acidic (carboxyl group) and two basic (piperazine nitrogens) (Figure 1). Awareness of the importance of the ionization constants (pK_a) of drugs in drug discovery and medicinal chemistry research has long since grown due to the knowledge that the presence of the ionizable groups may cause problems with oral bioavailability, pharmacokinetics or toxicity [8–10]. Pharmacokinetic properties of cetirizine, different from those of first-generation antihistamines, were thought to be the consequence of intramolecular interactions via folded conformations of ionization equilibrium forms [11]. In addition to this, it is important to consider the possibility of intermolecular interactions of ionization equilibrium forms. The main physicochemical properties of pharmacologically active compounds (ionization and solubility) in physiological conditions may differ from those determined in "pure" water solutions as a consequence of interactions with molecules present at the sites of administration and/or absorption, which can in turn affect their pharmacokinetic profiles (ADME) [12,13]. Due to the importance of cetirizine and its frequent use in a specific pediatric population, as well as other mentioned possible pharmacological effects, it is important to examine and predict the behavior of cetirizine in conditions that are more similar to physiological ones.

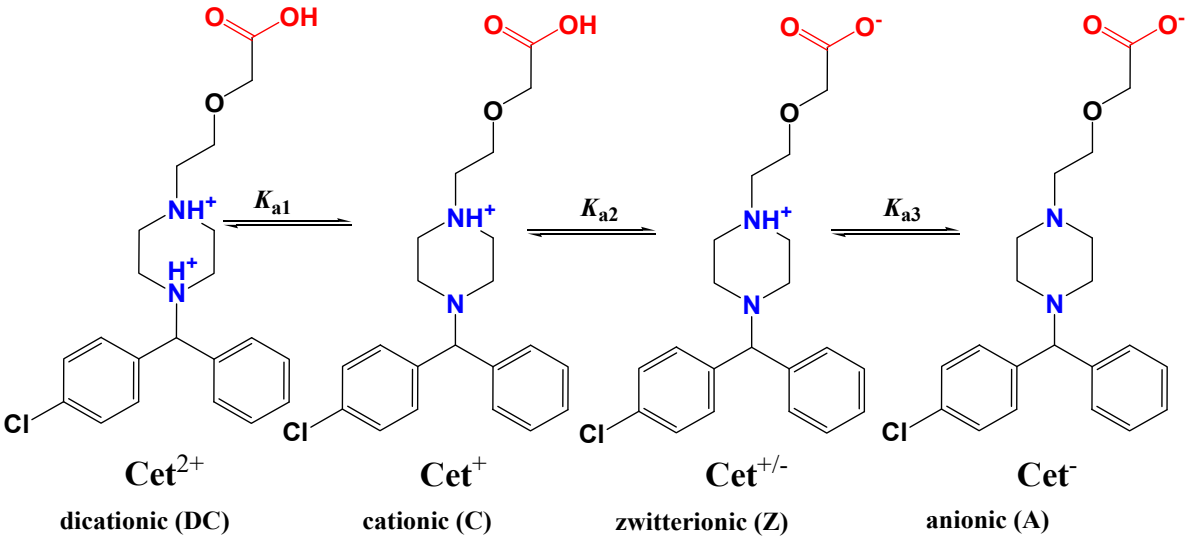

Figure 1. The ionization profile of cetirizine (Cet).

The membrane-mimicking approach is based on the philosophy of compartmentalization of molecules in systems which may affect reaction rates, properties and stereochemistry that, in turn, differ from those observed in "pure" aqueous solutions [14,15]. There is no ideal model that fully reproduces all the complexities of biomembranes [16], but a large variety of simplified membrane mimetic systems are available [17–19]. Since their properties are well understood at the chemical level, micellar solutions of differently charged surfactants are the most commonly used systems to mimic the desired functions of cells membranes [14,20]. In our previous studies, we showed that protolytic equilibria (acid–base equilibria) of ionizable drugs may significantly shift in micellar solutions [21–25]. Our results suggest that is not possible to predict the direction and intensity of the shift, which requires comprehensive experimental consideration of every single compound. Drug compounds containing two or more ionizable centers represent the greatest challenge, especially when the pK_a values are near to each other and the ionization processes

overlap [12]. Assessing the biopharmaceutical profile of these drugs by applying pK_a values exclusively defined in "pure" water can be misleading, as possible interactions with biomolecules may significantly change the assumed ionization patterns. In these terms, this study aimed to investigate the protolytic equilibria of cetirizine in solutions of differently charged micelle-forming surfactants: cationic, cetyltrimethylammonium bromide, (CTAB); anionic, sodium dodecyl sulfate (SDS); nonionic, 4-octylphenol polyethoxylate (TX-100); and polyoxyethylene lauryl ether (Brij 35). The chemical structures of the surfactants are presented in Figure 2.

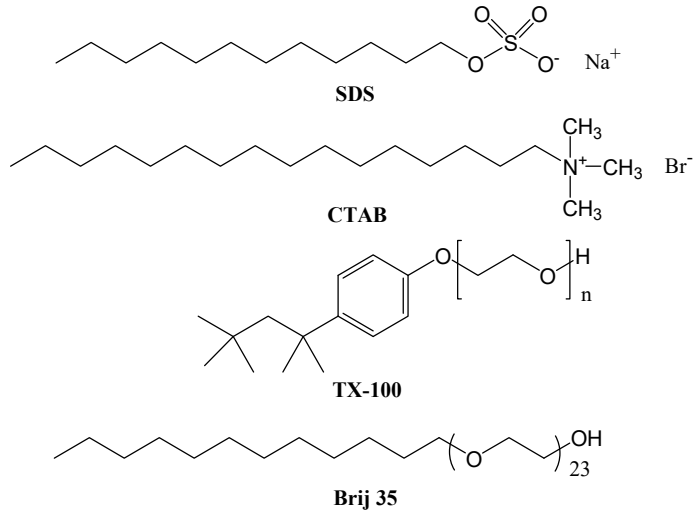

Figure 2. Differently charged surfactants used in this study.

2. Materials and Methods

2.1. Materials

Cetirizine dihydrochloride, 2-[2-[4-[(4-chlorophenyl)-phenylmethyl]piperazin-1-yl]ethoxy]acetic acid; dihydrochloride, was kindly provided by ALIMS (Belgrade, Serbia). Surfactants, SDS (J.T. Baker, Phillipsburg, NJ, USA, ≥95% purity), CTAB (Acros Organic, Antwerpen, Belgium, ≥99% purity), Triton TX-100 (Acros Organic, Antwerpen, Belgium, ≥98% purity), and Brij 35 (Sigma-Aldrich, Darmstadt, Germany, ≥99% purity) were used for the preparation of the micellar solutions. All solutions were prepared using double-distilled water. Standard carbonate-free NaOH and HCl solutions were potentiometrically standardized. All other chemicals used in this study were of analytical grade. All reagents were used as purchased without further purification.

2.2. Potentiometric Titrations

For potentiometric determinations, an Automatic Titrator 798 MPT Titrino (Metrohm, Switzerland) with a combined electrode LL unitrode Pt 1000 (Metrohm, Switzerland) was employed. Before titration, standard buffer solutions (pH 4.01, 7.00, and 9.21) were used for regular calibration of the electrode. Correction factor A was used to interpret the measured pH values (pH = $-\log [H^+]$) in relation to the pcH values (pcH = $-\log c_H$). The standard NaOH solution was used to titrate the standard HCl solution with ionic strength 0.1 M (NaCl) in order to experimentally determine the correction factor A, which was used in the relation pcH = pH − A [26,27]. A Huber Polystat CC2 thermostat was used for maintaining a constant temperature of 25 °C for the titrated solutions.

To obtain comparable data, the ionization constants of cetirizine were determined without (the "pure" water) and with the presence of the 10^{-2} M differently charged micelles (SDS, CTAB, TX-100 and Brij 35) under the same conditions. NaCl was used to adjust the ionic strength to 0.1 M. The presence of surfactants in the concentration used in these

experiments had no significant influence on the pH of the buffers (under ±0.02 pH units). The surfactant concentrations used were well above their critical micelle concentration (CMC), so that the effect of other molecules under experimental conditions on the CMC can be regarded as negligible. Solutions of cetirizine dihydrochloride with and without the presence of micelles were titrated with 0.02 mL aliquots of the standard NaOH solution (0.09905 M). To prevent ionization of the carboxyl group and fully protonate the piperazine nitrogens, 0.5 to 1 mL of standard HCl solution (0.1017 M) was added to 40 mL solutions of cetirizine dihydrochloride (5×10^{-4} M) and titrated with the 0.02 mL aliquots of standard NaOH solution (0.09905 M). Obtained titration curves are presented on Figure 3.

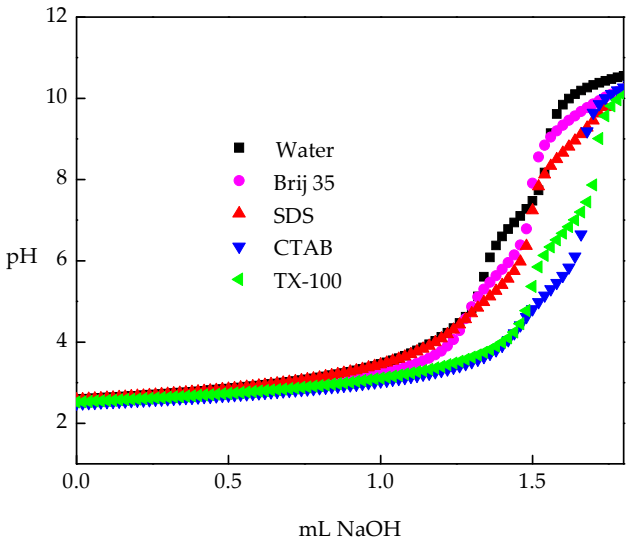

Figure 3. Cetirizine solution potentiometric curves with and without the presence of 10^{-2} M surfactant (SDS, CTAB, TX-100 and Brij 35) titrated with standard NaOH solution. I = 0.1 M (NaCl) and t = 25 °C.

To calculate the pK_a values, the potentiometric data were analyzed using the Hyperquade computer program 5.2.15 [28].

3. Results and Discussion

3.1. Determination of the pK_a Values in "Pure" Water

Chemically, cetirizine is an amholyte with three ionizable centers, one acidic (carboxyl group) and two basic (piperazine nitrogens) (Figure 1). Its ionization profile includes a complex system of protolityic equilibria that establish in solution, containing four equilibrium forms, dicationic (Cet^{2+}), monocationic (Cet^{+}), zwitterionic ($Cet^{+/-}$) and anionic (Cet^{-}) (Figure 1). Resolving this complex system of protolytic equilibria could be a particular challenge, taking into account that the pK_a values are close and the ionization processes overlap. In this case, the strategy that offers the possibility of a precise pK_a determination is potentiometry combined with the evaluation of the experimental data in the Hyperquad program [28].

The pK_a values of cetirizine potentiometrically determined in "pure" water are listed in Table 1 and compared with the pK_a values available from the literature, as well as with the values predicted by MarvinView 16.5.2.0 software (ChemAxon, Budapest, Hungary) [29]. The ionization order (Figure 1) is defined according to the prediction of MarvinView software and explanations from the literature [30]. In some studies, two pK_a values were listed (pK_{a1} for the first piperazine nitrogen connected to phenyl groups and the pK_{a2} as the average value for ionization of the carboxyl group and second piperazine nitrogen connected to aliphatic moiety [31]), or lower pK_a for the carboxyl group and higher pK_a value for more

basic piperazine nitrogen [32], while in others three pK_a values are listed [30,33], as in this study. The results in Table 1 show that the pK_{a1} values potentiometrically determined in this study are closer to values experimentally determined in the literature, while pK_{a2} and pK_{a3} agree better with the values predicted by MarvinView software. Generally, slight deviations in values may be the result of different methods or experimental conditions of determination, which are not specified for most of the listed data from the literature in Table 1.

Table 1. Potentiometrically determined pK_a values of cetirizine, experimental data from the literature and values predicted by MarvinView software.

pK_a	**Experimentally Determined in This Study**	**Literature Experimental Values**	**MarvinView 16.5.2.0 Software**
pK_{a1} (1st piperazine nitrogen)	2.19 ± 0.07	/ [32] 2.20 [33] 2.52 [31] 2.19 [30]	1.55
pK_{a2} (carboxyl group)	3.65 ± 0.07	3.60 [32] 2.90 [33] / [31] 2.93 [30]	3.59
pK_{a3} (2nd piperazine nitrogen)	7.31 ± 0.07	7.79 [32] 8.00 [33] 8.21 [31] 8.00 [30]	7.42

3.2. pKa Determination in Micellar Media

To obtain comparable results, the ionization constants of cetirizine were determined in solutions of differently charged micelles under the same conditions as without the presence of micelles (temperature 25 °C, ionic strength 0.1 M NaCl and constant stirring). The pK_a values determined in the presence of micelles can be observed as the apparent constants [34–36], which represent a hybrid of drug ionization in the aqueous phase and within the micellar pseudophase [37]. Accordingly, the micellar pseudophase can be considered as an organic solvent or a water–organic mixture in which the equilibria between ionized and nonionized equilibrium forms of the investigated drug may differ from that in water [38]. The results of potentiometric determinations, along with the differences relative to the pK_a values in "pure" water (ΔpK_a), are presented in Table 2.

Table 2. The pK_a values of cetirizine potentiometrically obtained in the presence of 10^{-2} M micellar solutions. ΔpK_a—differences in a relation to the pK_a values obtained in surfactant-free media.

pK_a	**SDS**	**ΔpK_a**	**CTAB**	**ΔpK_a**	**TX-100**	**ΔpK_a**	**Brij 35**	**ΔpK_a**
pK_{a1}	3.61 ± 0.04	+1.42 ± 0.08	1.72 ± 0.05	−0.47 ± 0.09	1.99 ± 0.08	−0.20 ± 0.11	2.38 ± 0.06	+0.19 ± 0.09
pK_{a2}	5.26 ± 0.04	+1.61 ± 0.08	2.73 ± 0.05	−0.92 ± 0.09	3.47 ± 0.08	−0.18 ± 0.11	5.67 ± 0.06	+2.02 ± 0.09
pK_{a3}	8.72 ± 0.04	+1.41 ± 0.08	5.30 ± 0.05	−2.01 ± 0.09	6.71 ± 0.08	−0.60 ± 0.11	9.50 ± 0.06	+2.19 ± 0.09

It is evident that the presence of micelles contributed to the shift in protolytic equilibria observed in "pure" water, overall from −2.01 to +2.19. The shift was detected in the interval between −0.47 (CTAB) and +1.42 (SDS) for pK_{a1}, between −0.92 (CTAB) and +2.02 (Brij 35) for pK_{a2} and between −2.01 (CTAB) and +2.19 (Brij 35) for pK_{a3}. The detected trend of shift direction points to an increase in the pK_a values caused by anionic SDS and nonionic Brij 35 micelles, and a decrease in the pK_a values in the presence of cationic CTAB and nonionic

TX-100 micelles. The most significant shifts, but in opposite directions, are observed for the ionization of the pK_{a3} under the influence of CTAB (−2.01) and Brij 35 (+2.19).

3.3. Interactions of Cetirizine with Micelles

The shift in pK_a values determined in solutions supplied with surfactants relative to "pure" water confirms the existence of interactions between cetirizine and micelles which directly involve its ionizable functional groups. The direction of the shift in protolytic equilibria can give better insight into the type of the most prevalent interactions [39]. Ionic micelles, whose surface is charged, may interact with the ionized form of functional groups of drugs through electrostatic forces of attraction or repulsion [40,41]. If attraction forces are predominant, cationic forms of functional groups (protonated nitrogens) will interact with the negatively charged surface of anionic micelles (SDS), or anionic forms of functional groups (carboxyilic anion) will interact with positively charged surfaces of cationic micelles (CTAB). Therefore, electrostatic interactions may promote ionization, shifting the protolytic equilibria toward the ionized form of the drug [42]. At the same time, predominant repulsion forces between ionized groups and the micelle surface of the same charge will hinder the ionization. All pK_a values increase under the influence of SDS, but the effect of the anionic SDS micelles on the direction of the protolytic equilibria shift differs depending on the nature of the functional group. From Table 2, the increase in the pK_a values of the piperazine nitrogens (ΔpK_{a1} = +1.42 and ΔpK_{a3} = +1.41) in the presence of SDS indicates the shift of the equilibria towards the ionized form and the increase in the degree of ionization. At the same time, the degree of ionization of the carboxyl group (ΔpK_{a2} = +1.61) is decreased in the presence of anionic SDS micelles. On the other hand, all pK_a values decrease under the influence of the cationic CTAB micelles. In terms of their nature, a decrease in the pK_a values of the piperazine nitrogens (ΔpK_{a1} = −0.47 and ΔpK_{a3} = −2.01) observed in the presence of CTAB suggests the shift of the equilibria towards the nonionized form. Accordingly, the degree of ionization of the carboxyl group (ΔpK_{a2} = −0.92) is increased in the presence of cationic CTAB micelles. The direction of the carboxyl group's protolytic equilibria shift in the presence of ionic micelles is actually opposite to that previously explained in terms of electrostatic forces, suggesting that hydrophobic interactions might be predominant [43]. These results indicate potential interactions of cetirizine-ionizable groups with a certain layer of ionic micelles, and may point to cetirizine orientation in micelles, where the carboxyl group is oriented to the inner core while piperazine nitrogens are located on the charged surface of ionic micelles.

On the other hand, nonionic micelles (TX-100 and Brij 35) are without charged surfaces, but they are polar and contain an outer palisade layer [20]. Hydrogen bonds and dipole interactions dominate in the hydrated hydrophilic palisade layer of nonionic micelles, and thus contribute to the stabilization of their surface [44]. It is to be expected that proton donors and proton acceptor groups in drug molecules, as their polar parts, will be mainly distributed in the palisade layer of nonionic micelles [45]. A common feature of the nonionic surfactants used in the experiments of this study is that their monomers form spherical micelles with uncharged surface. On the other hand, the chemical structures of the surfactant monomers are different (Figure 2), as is the number of hydrophilic oxyethylene units, which directly affects the properties of different nonionic micelles which are not necessarily identical, and consequently leads to differences in the mode of interactions with the same drug [22,46]. Nonionic micelles applied in this study expressed different effects on cetirizine pK_a values in terms of the shift direction of protolytic equilibria. The presence of TX-100 micelles caused a slight decrease in all the pK_a values (ΔpK_a from −0.18 to −0.60), whereas the degree of ionization was increased for the carboxyl group and decreased for piperazine nitrogens (Table 2). In the presence of Brij 35 micelles, all the pK_a values of

cetirizine were increased (ΔpK_a from +0.19 to +2.19), with a decreased degree of ionization of the carboxylic group and an increased one for piperazine nitrogens. A slight shift in pK_a with almost the same intensity for the piperazine nitrogen, connected to phenyl moieties, can be observed for both types of nonionic micelles, but in the opposite directions. The shift of the carboxylic group (ΔpK_{a2} = +2.02) and other piperazine nitrogens (ΔpK_{a2} = +2.19) towards their protonated forms in the presence of Brij 35 micelles caused the decrease in acidity and increase in basicity, respectively. More expressed changes in ionization pattern in the presence of Brij 35 in relation to TX-100 micelles indicate a different mode of cetirizine interaction with two types of nonionic micelles.

Potentiometrically determined pK_a values and Equations (1)–(4), describing the ionization of drugs with three ionizable functional groups [23,47], were used for the construction of diagrams showing the distribution of cetirizine equilibrium forms in the function of pH (Figure 4).

$$\%Cet^{2+} = \frac{100 \times 10^{(-pK_{a1}-pK_{a2}-pK_{a3})} \times 10^{(pK_{a1}+pK_{a2}+pK_{a3}-3pH)}}{10^{-pK_{a1}-pK_{a2}-pK_{a3}} + 10^{-pK_{a1}-pK_{a2}-pH} + 10^{-pK_{a1}-2pH} + 10^{-3pH}} \quad (1)$$

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

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

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

It was shown that conformational effects in molecules of cetirizine contribute to the reduction in the polarity of the ionized equilibrium forms, due to partial intramolecular charge neutralization, making the zwitterionic form markedly more lipophilic than expected at physiological pH. Folding conformations affects their pharmacokinetic properties, allowing cetirizine to be lipophilic enough for good oral absorption but hydrophilic enough to have low cerebral absorption, resulting in a low incidence of side effects on the CNS [11]. Taking into account that pH changes in different physiological compartments (e.g., the stomach, intestines, blood plasma) affect the degree of drug ionization, which may influence its pharmacokinetic properties, the distribution of cetirizine equilibrium forms has been considered to take place at biopharmaceutically relevant pH values (Table 3).

Table 3. Content of cetirizine equilibrium species (%) at biopharmaceutically significant pH values, with and without the presence of differently charged micelles. Equilibrium forms are explained in Figure 1.

pH	Water				SDS				CTAB				TX-100				Brij 35			
	DC	C	Z	A	DC	C	Z	A	DC	C	Z	A	DC	C	Z	A	DC	C	Z	A
1.2	91	9	0	0	100	0	0	0	76	23	1	0	86	14	0	0	94	6	0	0
4.5	0	12	87	0	10	77	13	0	0	1	85	14	0	8	91	1	1	93	6	0
6.8	0	0	76	24	0	3	96	1	0	0	3	97	0	0	45	55	0	7	93	0
7.4	0	0	45	55	0	0	95	5	0	0	1	99	0	0	17	83	0	2	97	1

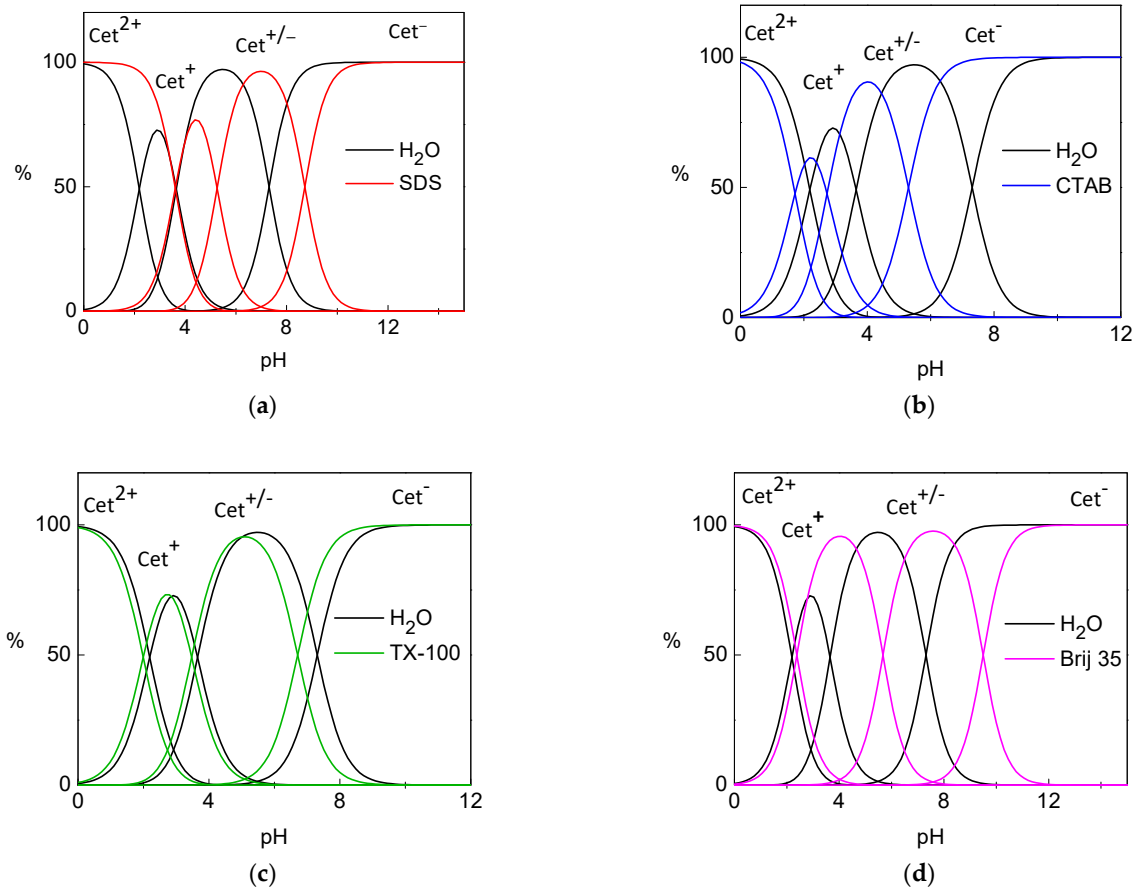

Figure 4. Cetirizine equilibrium forms' distribution in "pure" water and in the differently charged micelles supplied solutions, (**a**) SDS, (**b**) CTAB, (**c**) TX-100 and (**d**) Brij 35, as a function of pH.

The presence of micelles caused a change in the percentage of the equilibrium forms of cetirizine in relation to the distribution in "pure" water. At pH 1.2, relevant for gastric acidic conditions, where the absorption of the administered drug dose is usually minimal due to a smaller surface area, the percentage of the cetirizine zwitterionic form is not affected by the presence of micelles. At this pH value, the greatest influence was observed for the dicationic form in the presence of CTAB (−15%). After oral administration, the absorption of most drugs occurs mainly in the first part of the duodenum at a pH of 4.5 [48], where significant changes in the percentage of zwitterionic forms are observed (Table 3). Its content is reduced by 74% in the presence of anionic SDS micelles and 81% in the presence of nonionic Brij 35 micelles. At 6.8, found to be the average pH in distal ileum, the change in content of cetirizine zwitterionic forms ranged from −73%, under the influence of cationic CTAB micelles, to +20% under the influence of anionic SDS micelles. This suggests that specific interactions with other molecules, charged or polar, may affect the distribution of cetirizine at the sites of absorption. At 7.4, pH conditions similar to blood plasma, the content of zwitterionic form decreased by 44% in the presence of CTAB and by 28% in the presence of TX-100 micelles, and increased by 50% in the presence of SDS and by 52% in the presence of Brij 35 micelles.

The change in the pK_a values in the presence of micelles indicates the presence of interactions between cetirizine and micelles, confirming that ionizable functional groups of cetirizine participate in these interactions. This implies that interactions with charged or polar molecules or surfaces may also be expected under physiological conditions, which would lead to a completely different distribution than when calculated only on the basis of the pK_a values determined in "pure" water. The results of this study can serve as an

important initial point or guideline for further studies of the content of the equilibrium form required for absorption at the site of application, the form required at the site of action, and for binding to plasma proteins or the potential brain extraction ratio. In addition, knowledge about the influence of surfactants on protolytic equilibria could serve in the design of more effective pharmaceutical formulations or the improvement of drug delivery systems, suggesting appropriate pharmaceutical ingredients to help develop formulations that allow optimal absorption.

4. Conclusions

The pK_a values of cetirizine were determined with and without the presence of differently charged micelles, under the same conditions. The observed shift in protolytic equilibria in the presence of micelles (ΔpK_a values) indicates the existence of interactions between cetirizine ionizable groups and different parts of micelles. The directions and intensity of the protolyitic equilibria shift suggest that piperazine nitrogens are predominantly involved in electrostatic interactions with the charged surface layer of the ionic micelles, while the carboxyl group is predominantly oriented toward the inner part of micelles. More expressed changes in the ionization patterns of the carboxyl group and piperazine nitrogen, connected to a side aliphatic moiety, in the presence of Brij 35 in relation to TX-100 micelles, indicate a different mode of cetirizine interaction with two types of nonionic micelles. Changes in the distribution of the equilibrium forms of cetirizine affected by the presence of micelles, at pH values relevant to biopharmaceuticals, suggest that interactions of cetirizine with differently charged or polar molecules could potentially be considered under physiological conditions.

Author Contributions: Conceptualization, M.P.-N.; methodology, M.P.-N.; software, M.P.-N.; validation, M.P.-N. and G.P.; formal analysis, M.P.-N. and S.O.; investigation, M.P.-N.; data curation, M.P.-N.; writing—original draft preparation, M.P.-N.; writing—review and editing, M.P.-N., S.O., G.P. and K.N.; visualization, M.P.-N.; supervision, G.P. and K.N. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Ministry of Science, Technological Development and Innovation, Republic of Serbia, through two Grant Agreements with the University of Belgrade—Faculty of Pharmacy, No. 451-03-65/2024-03/200161 and No. 451-03-66/2024-03/200161.

Data Availability Statement: The original contributions presented in the study are included in the article; further inquiries can be directed to the corresponding author.

Acknowledgments: The authors thank the COST Action CA22125 of the European Community for support.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Portnoy, J.M.; Dinakar, C. Review of cetirizine hydrochloride for the treatment of allergic disorders. *Expert Opin. Pharmacother.* **2004**, *5*, 125–135. [CrossRef] [PubMed]
2. Blaiss, M.S.; Bernstein, J.A.; Kessler, A.; Pines, J.M.; Camargo, C.A.; Fulgham, P.; Haumschild, R.; Rupp, K.; Tyler, T.; Moellman, J. The role of cetirizine in the changing landscape of iv antihistamines: A narrative review. *Adv. Ther.* **2022**, *39*, 178–192. [CrossRef]
3. Curran, M.P.; Scott, L.J.; Perry, C.M. Cetirizine: A review of its use in allergic disorders. *Drugs* **2004**, *64*, 523–561. [CrossRef] [PubMed]
4. Hsieh, C.Y.; Tsai, T.F. Use of H-1 antihistamine in dermatology: More than itch and urticaria control: A systematic review. *Dermatol. Ther.* **2021**, *11*, 719–732. [CrossRef] [PubMed]
5. Rossi, A.; Campo, D.; Fortuna, M.C.; Garelli, V.; Pranteda, G.; De Vita, G.; Sorriso-Valvo, L.; Di Nunno, D.; Carlesimo, M. A preliminary study on topical cetirizine in the therapeutic management of androgenetic alopecia. *J. Dermatol. Treat.* **2018**, *29*, 149–151. [CrossRef] [PubMed]

6. Piovani, D.; Clavenna, A.; Bonati, M.; PeFAB group. Review of Italian primary care paediatricians identifies 38 commonly prescribed drugs for children. *Acta Paediatr.* **2014**, *103*, e532–e537. [CrossRef] [PubMed]
7. Zhou, P.; Jia, Q.; Wang, Z.; Zhao, R.; Zhou, W. Cetirizine for the treatment of allergic diseases in children: A systematic review and meta-analysis. *Front. Pediatr.* **2022**, *10*, 940213. [CrossRef] [PubMed]
8. Manallack, D.T.; Prankerd, R.J.; Yuriev, E.; Oprea, T.I.; Chalmers, D.K. The significance of acid/base properties in drug discovery. *Chem. Soc. Rev.* **2013**, *42*, 485–496. [CrossRef] [PubMed]
9. Balogh, G.T. Physicochemical characterisation in drug discovery. *Drug Discov. Today Technol.* **2018**, *27*, 1–2. [CrossRef] [PubMed]
10. Charifson, P.S.; Walters, W.P. Acidic and basic drugs in medicinal chemistry: A perspective. *J. Med. Chem.* **2014**, *57*, 9701–9717. [CrossRef]
11. Bouchard, G.; Pagliara, A.; van Balen, G.P.; Carrupt, P.A.; Testa, B.; Gobry, V.; Girault, H.H.; Caron, G.; Ermondi, G.; Fruttero, R. Ionic partition diagram of the zwitterionic antihistamine cetirizine. *Helv. Chim. Acta* **2001**, *84*, 375–387. [CrossRef]
12. Caron, G.; Ermondi, G. Updating molecular properties during early drug discovery. *Drug Discov. Today* **2017**, *22*, 835–840. [CrossRef]
13. Gaohua, L.; Miao, X.; Dou, L. Crosstalk of physiological pH and chemical pK_a under the umbrella of physiologically based pharmacokinetic modeling of drug absorption, distribution, metabolism, excretion, and toxicity. *Expert Opin. Drug Metab. Toxicol.* **2021**, *17*, 1103–1124. [CrossRef] [PubMed]
14. Fendler, J.H. Atomic and molecular clusters in membrane mimetic chemistry. *Chem. Rev.* **1987**, *87*, 877–899. [CrossRef]
15. Vance, J.A.; Devaraj, N.K. Membrane mimetic chemistry in artificial cells. *J. Am. Chem. Soc.* **2021**, *143*, 8223–8231. [CrossRef] [PubMed]
16. Sato, W.; Zajkowski, T.; Moser, F.; Adamala, K.P. Synthetic cells in biomedical applications. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnology* **2022**, *14*, e1761. [CrossRef]
17. Klöpfer, K.; Hagn, F. Beyond detergent micelles: The advantages and applications of non-micellar and lipid-based membrane mimetics for solution-state NMR. *Prog. Nucl. Magn. Reson. Spectrosc.* **2019**, *114*, 271–283. [CrossRef] [PubMed]
18. Miele, Y.; Holló, G.; Lagzi, I.; Rossi, F. Shape deformation, budding and division of giant vesicles and artificial cells: A review. *Life* **2022**, *12*, 841. [CrossRef] [PubMed]
19. Wiśniewska-Becker, A.; Gruszecki, W.I. Biomembrane models. In *Drug-Biomembrane Interaction Studies*; Woodhead Publishing: Sawston, UK, 2013; pp. 47–95. [CrossRef]
20. Rangel-Yagui, C.D.O.; Pessoa, A., Jr.; Tavares, L.C. Micellar solubilization of drugs. *J. Pharm. Pharm. Sci.* **2005**, *8*, 147–163. [PubMed]
21. Popović, M.R.; Popović, G.V.; Agbaba, D.D. The effects of anionic, cationic, and nonionic surfactants on acid–base equilibria of ACE inhibitors. *J. Chem. Eng. Data* **2013**, *58*, 2567–2573. [CrossRef]
22. Grujić, M.; Popović, M.; Popović, G.; Nikolic, K.; Agbaba, D. Protolytic equilibria of sartans in micellar solutions of differently charged surfactants. *J. Pharm. Sci.* **2016**, *105*, 2444–2452. [CrossRef] [PubMed]
23. Popović-Nikolić, M.R.; Popović, G.V.; Stojilković, K.; Dobrosavljević, M.; Agbaba, D.D. Acid–base equilibria of rupatadine fumarate in aqueous media. *J. Chem. Eng. Data* **2018**, *63*, 3150–3156. [CrossRef]
24. Popović-Nikolić, M.R.; Popović, G.V.; Agbaba, D.D. The effect of nonionic surfactant brij 35 on solubility and acid–base equilibria of verapamil. *J. Chem. Eng. Data* **2017**, *62*, 1776–1781. [CrossRef]
25. Popović-Nikolić, M.R.; Nikolić, K.M.; Popović, G.V. Protolytic equilibria of ACE inhibitors in micellar solution of nonionic surfactant Brij 35. *Monatsh. Chem. Chem. Mon.* **2023**, *154*, 615–624. [CrossRef] [PubMed]
26. Irving, H.M.; Miles, M.G.; Pettit, L.D. A study of some problems in determining the stoicheiometric proton dissociation constants of complexes by potentiometric titrations using a glass electrode. *Anal. Chim. Acta* **1967**, *38*, 475–488. [CrossRef]
27. Albert, A.; Serjeant, E.P. *The Determination of Ionization Constants*; Chapman and Hall: London, UK, 1984.
28. Gans, P.; Sabatini, A.; Vacca, A. Investigation of equilibria in solution. Determination of equilibrium constants with the HYPERQUAD suite of programs. *Talanta* **1996**, *43*, 1739–1753. [CrossRef] [PubMed]
29. ChemAxon, MarvinSketch 16.5.2.0 Budapest, Hungary. 2013. Available online: http://www.chemaxon.com (accessed on 10 May 2024).
30. Pagliara, A.; Testa, B.; Carrupt, P.A.; Jolliet, P.; Morin, C.; Morin, D.; Urien, S.; Tillement, J.P.; Rihoux, J.P. Molecular properties and pharmacokinetic behavior of cetirizine, a zwitterionic H1-receptor antagonist. *J. Med. Chem.* **1998**, *41*, 853–863. [CrossRef] [PubMed]
31. Geiser, L.; Henchoz, Y.; Galland, A.; Carrupt, P.A.; Veuthey, J.L. Determination of pK_a values by capillary zone electrophoresis with a dynamic coating procedure. *J. Sep. Sci.* **2005**, *28*, 2374–2380. [CrossRef] [PubMed]
32. Paczkowska, M.; Mizera, M.; Tężyk, A.; Zalewski, P.; Dzitko, J.; Cielecka-Piontek, J. Hydrophilic interaction chromatography (HILIC) for the determination of cetirizine dihydrochloride. *Arab. J. Chem.* **2019**, *12*, 4204–4211. [CrossRef]
33. Hancu, G.; Câmpian, C.; Rusu, A.; Mircia, E.; Kelemen, H. Simultaneous determination of loratadine, desloratadine and cetirizine by capillary zone electrophoresis. *Adv. Pharm. Bull.* **2014**, *4*, 161. [CrossRef]

34. Vodolazkaya, N.; Nikolskaya, M.; Laguta, A.; Farafonov, V.; Balklava, Z.; Stich, M.; Mchedlov-Petrossyan, N.; Nerukh, D. Estimation of Nanoparticle's Surface Electrostatic Potential in Solution Using Acid–Base Molecular Probes. III. Experimental Hydrophobicity/Hydrophilicity and Charge Distribution of MS2 Virus Surface. *J. Phys. Chem. B* **2022**, *126*, 8166–8176. [CrossRef]
35. von Stockar, U. *Thermodynamics in Biochemical Engineering*; EFPL Press: Lausanne, France, 2013.
36. Cassens, J.; Prudic, A.; Ruether, F.; Sadowski, G. Solubility of pharmaceuticals and their salts as a function of pH. *Ind. Eng. Chem. Res.* **2013**, *52*, 2721–2731. [CrossRef]
37. Cheipesh, T.A.; Mchedlov–Petrossyan, N.O.; Bogdanova, L.N.; Kharchenko, D.V.; Roshal, A.D.; Vodolazkaya, N.A.; Taranets, Y.V.; Shekhovtsov, S.V.; Rodik, R.V.; Kalchenko, V.I. Aggregates of cationic calix [4] arenes in aqueous solution as media for governing protolytic equilibrium, fluorescence, and kinetics. *J. Mol. Liq.* **2022**, *366*, 119940. [CrossRef]
38. Mchedlov-Petrossyan, N.O.; Farafonov, V.S.; Cheipesh, T.A.; Shekhovtsov, S.V.; Nerukh, D.A.; Lebed, A.V. In search of an optimal acid-base indicator for examining surfactant micelles: Spectrophotometric studies and molecular dynamics simulations. *Colloids Surf. A Physicochem. Eng. Asp.* **2019**, *565*, 97–107. [CrossRef]
39. Pokhrel, D.R.; Sah, M.K.; Gautam, B.; Basak, H.K.; Bhattarai, A.; Chatterjee, A. A recent overview of surfactant–drug interactions and their importance. *RSC Adv.* **2023**, *13*, 17685–17704. [CrossRef] [PubMed]
40. Pellosi, D.S.; Estevão, B.M.; Freitas, C.F.; Tsubone, T.M.; Caetano, W.; Hioka, N. Photophysical properties of erythrosin ester derivatives in ionic and non-ionic micelles. *Dyes Pigments* **2013**, *99*, 705–712. [CrossRef]
41. Guerrero-Hernández, L.; Meléndez-Ortiz, H.I.; Cortez-Mazatan, G.Y.; Vaillant-Sánchez, S.; Peralta-Rodríguez, R.D. Gemini and bicephalous surfactants: A review on their synthesis, micelle formation, and uses. *Int. J. Mol. Sci.* **2022**, *23*, 1798. [CrossRef]
42. Khossravi, D. Drug-surfactant interactions: Effect on transport properties. *Int. J. Pharm.* **1997**, *155*, 179–190. [CrossRef]
43. Rub, M.A.; Sheikh, M.S.; Khan, F.; Azum, N.; Alghamdi, Y.G.; Asiri, A.M. Impact on micellization between promethazine hydrochloride and ester bonded gemini surfactant in distinct solvents: A multi-faceted procedure. *J. Mol. Liq.* **2021**, *342*, 117477. [CrossRef]
44. Narang, A.S.; Delmarre, D.; Gao, D. Stable drug encapsulation in micelles and microemulsions. *Int. J. Pharm.* **2007**, *345*, 9–25. [CrossRef]
45. Dar, A.A.; Chat, O.A. Cosolubilization of Coumarin30 and Warfarin in cationic, anionic, and nonionic micelles: A micelle–water interfacial charge dependent FRET. *J. Phys. Chem. B* **2015**, *119*, 11632–11642. [CrossRef] [PubMed]
46. Kumbhakar, M.; Goel, T.; Mukherjee, T.; Pal, H. Role of micellar size and hydration on solvation dynamics: A temperature dependent study in Triton-X-100 and Brij-35 micelles. *J. Phys. Chem. B* **2004**, *108*, 19246–19254. [CrossRef]
47. Popović-Nikolić, M.R.; Čakar, M.; Todorović, N.; Nikolić, K.; Popović, G. Study on protolytic equilibria and the effects of pH, cyclodextrins and polysorbate 80 on solubility of raloxifene hydrochloride. *Chem. Pap.* **2024**, *78*, 4401–4410. [CrossRef]
48. Alagga, A.A.; Pellegrini, M.V.; Gupta, V. *Drug Absorption*; StatPearls Publishing: Tampa, FL, USA, 2024.