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THE IONIZATION OF FLUOROQUINOLONES IN THE PRESENCE OF DIFFERENTLY CHARGED SURFACTANTS

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ABSTRACT

The pK_a values of ciprofloxacin (CPF) and norfloxacin (NRF) were determined potentiometrically, with and without the presence of differently charged micelles, as biomembrane mimetic models. The shift in protolytic equilibria are observed in the presence of surfactants, SDS (ΔpK_{a1} = +2.02; ΔpK_{a2} = +0.57); CTAB (ΔpK_{a1} = -0.09; ΔpK_{a2} = -0.23) and TX-100 (ΔpK_{a1} = +0.24; ΔpK_{a2} = +0.29). The change in distribution of equilibrium forms is most expressed in pH range 6 – 8 which may indicate on potential interactions with molecules of different polarity and charge under physiological conditions.

INTRODUCTION

Fluoroquinolones (FQs) are synthetic antimicrobial drugs which exhibit bactericidal effect by inhibition of the enzymes DNA gyrase and topoisomerase IV, resulting in nonfunctional DNA chains which leads to the death of bacterial cells [1]. The structural characteristics of FQs significantly

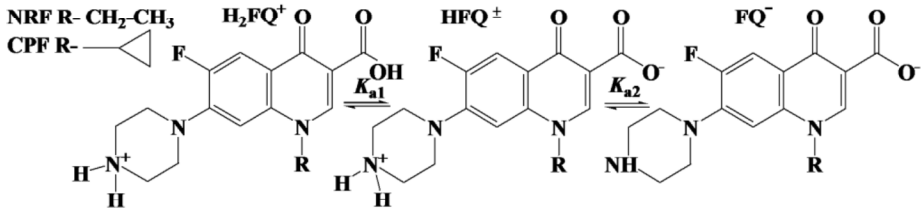

Figure 1. Ionization profile of NRF and CPF.

influence their antimicrobial effect and the pharmacokinetic properties. From a chemical point of view, NRF and CPF are ampholytes containing two ionization centers, the carboxylic group (acidic center) and secondary alkylamine (basic center) (Figure 1).

One of the most important physico-chemical parameters of drugs is pK_a value, which allows a quantitative assessment of the drug ionization at the given pH of the solution. The knowledge of the drug pK_a value plays a major role in the estimation of the pharmacokinetic parameters, definition of the experimental conditions in the analytical procedures, as well as in the development of pharmaceutical dosage forms. Under physiological conditions drugs can interact with biomolecules of different polarity and charge which could change the ionization profile in relation to aqueous solution. By investigating the interactions of drugs with biomembrane mymetic systems, such as micelles [2], a better insight into the behavior of drugs under physiological conditions could be provided. In this paper the pK_a values of NRF and CPF have been potentiometrically determined in the presence and in the absence of surfactants; anionic, sodium dodecylsulphate (SDS); cationic, cetyltrimethylammonium bromide (CTAB) and non-ionic, 4-octylphenol polyethoxylate (TX-100). The effect of differently charged micelles, as biomembrane mimetic systems, on the ionization of NRF and CPF was estimated.

EXPERIMENTAL

Potentiometric measurements were carried out on Automatic titrator 798 MPT Titrino (Metrohm, Switzerland) with a combined electrode LL unitrode Pt 1000 (Metrohm, Switzerland). Norfloxacin and ciprofloxacin were kindly donated from Medicines and Medical Devices Agency of Serbia (Belgrade, Serbia). The surfactants, SDS (J.T. Baker), CTAB (Acros Organic) and TX-100 (Acros Organic) were used for the preparation of micellar solutions. All solutions were prepared in double distilled water. Standard solutions of HCl and carbonate-free NaOH were standardized potentiometrically.

All solutions (5×10^{-4} M) of examined FQs, with and without the presence of 10^{-2} M surfactants (SDS, CTAB and TX-100), were titrated with 0.0998 M NaOH at a 25 °C and a constant ionic strength (0.1 M NaCl). Surfactants were used at a concentration higher than their critical micellar concentrations. Experimental data obtained by potentiometric titration were analyzed by the program Hyperquad.

RESULTS AND DISCUSSION

The pK_a values of NRF and CPF have been potentiometrically determined and ionization in aqueous media was defined. Due to the formation of the intramolecular hydrogen bond with the ketone at the C-4, the ionization of the carboxyl group is suppressed, resulting in a pKa_1 values (pK_{a1} = 6.07 for NRF; pK_{a1} = 6.01 for CPF) greater than the usual for carboxylic acids. The pK_{a2} values (pK_{a2} = 8.24 for NRF; pK_{a2} = 8.22 for CPF) corresponds to the

secondary alkylamine in the side piperazinyl group. The only difference between structures of norfloxacin and ciprofloxacin is the substituent at position C-1 (Figure 1), which does not significantly affect the ionization. On the basis of the values determined in the micellar solutions (Table I), the shift in protolytic equilibria of examined FQs can be observed in the presence of all applied surfactants.

Table 1. The pK_a values of NRF and CPF potentiometrically determined in micellar solutions and differences with respect to values determined in surfactant free solutions (ΔpK_a).

FQ	pK_a	SDS	ΔpK_a	CTAB	ΔpK_a	TX-100	ΔpK_a
NRF	pK_{a1}	7.94	+1.87	5.98	-0.09	6.31	+0.24
	pK_{a2}	8.50	+0.26	8.01	-0.23	8.50	+0.26
CPF	pK_{a1}	8.18	+2.02	5.95	-0.06	6.15	+0.14
	pK_{a2}	8.65	+0.57	8.19	-0.03	8.51	+0.29

The anionic SDS micelles expressed the most pronounced effect on the ionization of the carboxylic group of CPF (ΔpK_{a1} = + 2.17), and the least pronounced effect exhibited the CTAB micelles on the ionization of NRF secondary alkylamine (pK_{a2} = -0.03). In the case of negatively charged SDS micelles the electrostatic interactions can be assumed: repulsion with the negatively charged ionized form of carboxylic group and attraction with a positively charged ionized form of the amino group. This kind of interactions shifted the equilibria toward the molecular form of carboxylic group (increased pK_a and lower acidity) and ionized form of amino group (increased pK_a and higher acidity). The cationic CTAB micelles, with a positively charged surface, did not express significant influence on NRF and CPF ionization (ΔpK_a up to -0.23). However, the protolytic equilibria have been slightly shifted in the opposite direction comparing to SDS, which indicate that ionizable centers of examined FQs could be also involved in electrostatic interactions with positively charged micelles. The change in pK_a values in the presence of TX-100 micelles, which are not charged, indicates on the possible dipole interactions and hydrogen bonds in the hydrophilic layer of nonionic micelles with the ionizable centers of FQs (ΔpK_a up to +0.29). The change in the distribution of the equilibrium forms under the influence of surfactants are the most expressed in pH range 6 – 8 which involves biopharmaceutically important pH values. This can be clearly seen on the distribution diagrams as a function of pH (Figure 2).

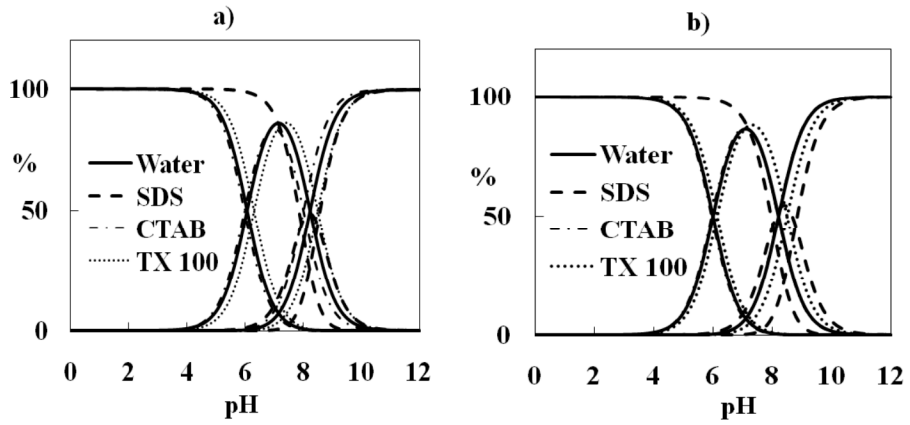

Figure 2. Distribution of a) NRF and b) CPF equilibrium forms as a function of pH.

CONCLUSION

The shift in pK_a values (ΔpK_a up to 2.02) indicates that the investigated FQs interact with micelles of different charge and polarity, which directly involve their ionization centers. The anionic micelles expressed the most pronounced effect, especially on the ionization of carboxylic group. On the basis of these results it can be assumed that negatively charged biomolecules in plasma potentially may shift the equilibria toward the molecular form of carboxylic group especially at pH values 6 - 8.

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