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SPECTROSCOPIC INVESTIGATIONS OF FLUOROQUINOLONES METAL ION COMPLEXES

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Abstract: The complex formation reaction, between fluoroquinolones (FQ): ciprofloxacin (CPX), enoxacin (ENX), enrofloxacin (ENRX), lomefloxacin (LOMX), levofloxacin (LEVX), ofloxacin (OFX), norfloxacin (NFX), sparfloxacin (SPRX) and aluminum(III), iron(III), copper(II) and zinc(II) ions were investigated. The spectrophotometic titration method in a wide range of pH was utilized for estimation of complex formation equilibrium. The application of Bjerrum method allowed to estimate the complex equilibrium of analyzed species in the reaction mixture. The overall stability constants ($log\beta_{pqr}$) of fluoroquinolones complexes with metal ions were calculated using HYPRERQUAD program. The most stable complexes FQ were created with iron(III) and aluminum(III) and than copper(II) and zinc(II) ions, respectively. The highest values of calculated $log\beta_{pqr}$ were obtained for the $Me(FQ)_3H_3$ species and the lowest for the $Me(FQ)_2OH$ forms. Furthermore, an additional studies have been performed. The effect of the polyvalent metal ions on the complex structure has been investigated. The IR and ^{1}H, ^{13}C and ^{19}F NMR spectroscopy methods were used for the confirmation of the structure of the FQ-Me complex formations. The most significant shifts of signals of ^{1}H NMR spectra of the fluoroquinolones and their complexes were found for the protons substituted in the positions 2, 5 and 8, whereas the ^{13}C NMR spectra showed up the shifts changes for carbon atoms in positions 2, 3, 3a and 4.

Keywords: fluoroquinolones metal ion complexes, stability constants, UV, IR, ^{1}H, ^{13}C, ^{19}F NMR spectroscopy

Since 1962, when the nalidixic acid, a precursor of all fluoroquinolones was introduced into the medicinal care, a plenty analogues and highly potent derivatives against many bacteria strains has been discovered (1-3).

Despite the numerous clinical observations and the studies conducted *in vitro* to demonstrate the effects of metal-ion complexation on biological activity of this important class of antimicrobials, very little is known about the physicochemical basis of the interactions of the quinolones with metals or the structures of the possible complexes (4-6).

In the use of fluoroquinolones having a high affinity to metal cations it is necessary to prevent their complex formation in order to obtain the desired effect. The concurrent administration of magnesium – aluminum antacids drastically reduces the bioavailability of fluoroquinolones (6-8).

Multivitamins containing zinc decreased the bioavailability of the ciprofloxacin by an average of 24%. The low cation dosage (23.9 mg/day of zinc) may have accounted for the smaller degree of chelation than might be expected [1-6]. Also, a great number of studies have been performed to understand the physicochemical basis of interactions between fluoroquinolones and metal ions or structures of possible complexes (9-16).

Different methods, potentiometric, UV-VIS spectroscopy, polarography, fluorescence spectroscopy, NMR spectroscopy or even capillary electrohoresis method were used to evaluate the protolytic and complex equilibria of species in a solution (3,17-20).

Among listed methods, the most important role in such studies plays the potentiometric titration method. In our previous publication (21), we have described the potentiometric titration method utilized for the determination of overall stability constants of eight different fluoroquinolones with trivalent and divalent metal cations. These experiments were performed in a wide range of pH and allowed to establish numerous stability constants (21).

The spectrophotometric methods are also very important during the complexation studies. However, in most papers the spectrophotometric

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methods used for the estimation of complex equilibrium of fluoroqionolones with polyvalent metal ions are limited to the Job method (also called the continious variation method) or the mole fraction method, where the complexation experiments are carried in a constant pH [22]. In presented paper, Authors have used the Bjerrum method to describe the complex equilibrium of fluoroquinolones with polyvalent metal ions [22]. The analytical procedure in Bjerrum method differs from Job method and mole fraction method, because it can be performed in a wide range of pH. Moreover, in the reaction mixture the free ligand concentration exceeds the concentration of metal ions to make the complexation process complete.

EXPERIMENTAL

Reagents

The ciprofloxacin (CPX), enrofloxacin (ENRX), levofloxacin (LEVX) and sparfloxacin (SPRX) were obtained from Fluka Chemie GmbH (Buchs, Switzerland); enoxacin (ENX), lomefloxacin (LOMX), ofloxacin (OFX) and norfloxacin (NFX) were purchased from Sigma-Aldrich (St. Louis, USA). The aluminum(III) chloride hexahydrate (POCh, Gliwice, Poland), iron(III) nitrate nonahydrate (Loba Feinchemie, Austria), copper(II) sulfate pentahydrate (Standard, Lublin, Poland), zinc(II) sulfate heptahydrate (POCh, Gliwice, Poland), were utilized. All reagents used were of analytical and chromatography grade. The deuterated reagents such as D_2O (99.8 atom % D), NaOD (0.1 mol L^{-1} in D_2O) and DCl (0.1 mol L^{-1} in D_2O) were purchased in Armar Chemicals, Switzerland.

UV spectrophotometric titration and the system validation

The solutions of CPX, ENX, LOMX, OFX, SPRX (0.0015 mol·L^{-1}), ENRX, LEVX NFX (0.0016 mmol·L^{-1}), and metal salts Al^{3+} (0.337 mmol·L^{-1} and 0.250 mmol·L^{-1}), Fe^{3+} (0.376 mmol·L^{-1} and 0.250 mmol·L^{-1}), Cu^{2+} (0.376 mmol·L^{-1}) and Zn^{2+} (0.375 mmol·L^{-1}) were dissolved in deionized water. Deionized water was obtained by passing distilled water through a Millipore Simplicity UV water purification system (Waters Corporation, Milford, MA, USA). The FQ solution (1.0 mL) and the proper volume of metal ions stock solution was dissolved in deionized water, so that the final volume was 60.0 mL. The samples containing metal ions and fluoroquinolones were titrated with sodium hydroxide (0.1 mol·L^{-1}) or in the case of sparfloxacin with hydrochloric acid (0.1 mol·L^{-1}). The titration measurements were made using Mettler-Toledo DL 50 titrator (Switzerland) and were performed in the range of pH from 2.2 up to 10.5, under constant ionic strength (I = 0.1 mol·L^{-1} NaCl) and under gaseous nitrogen atmosphere at 22°C. The fluoroquinolones to metal cations ratio were (FQ:Me): 2:1 and 3:1 for aluminum(III) and iron(III), 2:1 for copper(II) and zinc(II), respectively.

The reaction mixture was simultaneously transferred into the UV spectrophotometer (HP 8452 Diode Array) using peristaltic pump (HP 890528). The UV spectra were collected in the range of wavelength 200-400 nm, whenever the titrant was added. The UV spectra of complexes were always compared with UV spectra of free fluoroquinolones.

The reproducibility of the results was assured by the repeated titrations and UV measurements. During the standardization of HCl and NaOH solutions the following parameters were evaluated: precision, accuracy and linearity, and whole validation process was performed according to the recommendations included in "Validation of Titration Methods" (23). The detailed analytical procedure validation data are available on the request.

The Hyperquad calculations of stability constants.

A series of UV spectrophotometric titration experiments concerning all analyzed FQ-Me systems were performed in order to verify that all overall stability constants were determined in the same analytical conditions. It is worth to emphasize, that in most publications the continuous variation method or mole ratio method at fixed pH was used for UV studies of FQ-Me complex formations (24-26). In the presented study, the UV spectrophotometric titration method was involved. The overall stability constants of the FQ-Me complexes were determined in the wide range of pH.

The calculation mode of overall stability constants based on the spectrophotometric titartion data was similar to those described in our previous paper (21).

Based on the Hyperquad calculations [27] the following complexes were analyzed for the aluminum(III) and iron(III) binary systems: Me(FQ)(OH), Me(FQ), Me(FQ)H, $Me(FQ)H_2$, $Me(FQ)_2(OH)$, $Me(FQ)_2$, $Me(FQ)_2H$, $Me(FQ)_3$, $Me(FQ)_3H$ and $Me(FQ)_3H_3$. For copper(II) and zinc(II) binary systems the following species were investigated: Me(FQ)H, $Me(FQ)H_2$ and $Me(FQ)_2$.

The 32 different ligand-metal systems were investigated using UV spectrophotometric titration method, and 16 of them were for the first time

described during the presented studies. A series of new species were evaluated for enoxacin, enrofloxacin, sparfloxacin with studied metal ions.

The UV spectra of all fluoroquinolones studied in the presence of the metal cations were always compared with the UV spectra of free FQ. To prove the correctness of the measurements, the dissociation constants of the free ligands were also evaluated. The obtained results were close comparable with those established in the literature [28-30].

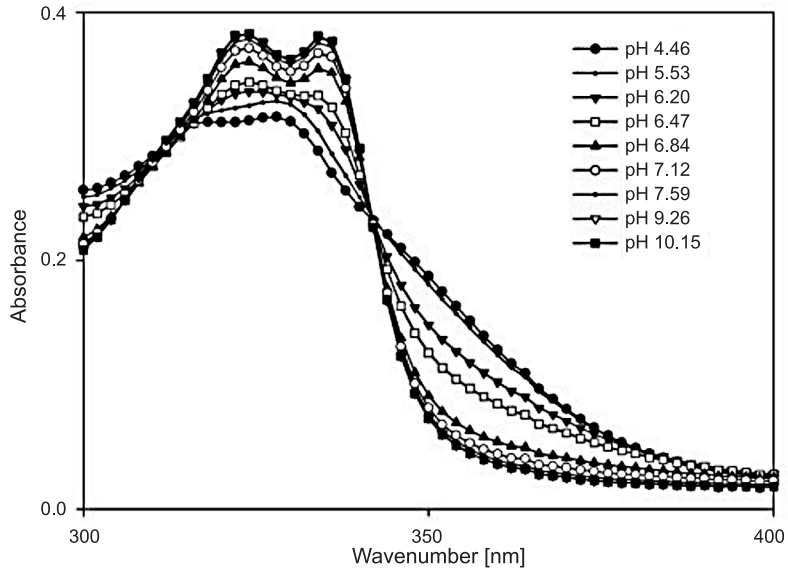

Figure 1. The UV absorption spectra of ENRX-Al (mole ratio 2 : 1) at different pH values

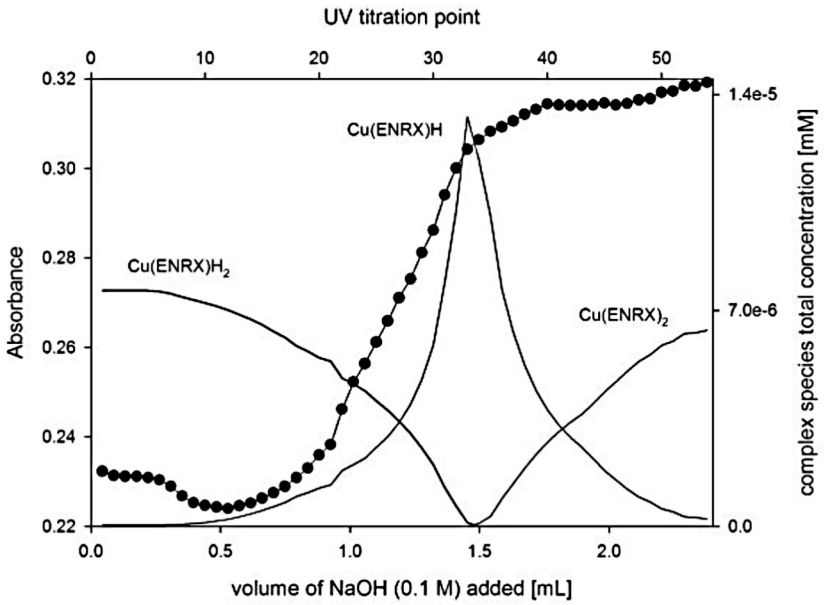

Figure 2. The enrofloxacin-Cu system (mole ratio 2 : 1). UV-titration curve and the determined pH dependent complex species (titrant NaOH (0.1 M), λ = 324 nm, I = 0.1 M NaCl, 22şC)

Table 1. The overall stability constants ($log\beta_{pqr}$) of fluoroquinolones and their complexes with aluminum(III), iron(III), copper(II) and zinc(II) ions.

p q r	CPX	ENX	ENRX	LOMX	LEVX	OFX	NFX	SPRX
Al (III)								
1 1 0	-	15.66 ± 0.01	-		13.18 ± 0.18	10.75 ± 0.04	-	11.44 ± 0.02
1 1 1	16.05 ± 0.05	17.99 ± 0.06	14.19 ± 0.09	18.26 ± 0.08	18.22 ± 0.19	-	14.82 ± 0.03	
1 2 -1	-	8.03 ± 0.07	5.37 ± 0.14	-	-	7.99 ± 0.09	-	11.65 ± 0.08
1 2 0	18.30 ± 0.08	-	14.36 ± 0.21	18.57 ± 0.18	-	16.44 ± 0.12	14.67 ± 0.16	-
1 2 1	27.19 ± 0.07	-	-	28.36 ± 0.18	27.76 ± 0.17	-	25.30 ± 0.17	21.14 ± 0.11
1 3 0	20.13 ± 0.10	16.51 ± 0.13	21.89 ± 0.13	18.53 ± 0.19	16.82 ± 0.25	16.12 ± 0.19	16.55 ± 0.38	19.81 ± 0.06
1 3 1	31.42 ± 0.06	27.06 ± 0.08	29.85 ± 0.12	29.18 ± 0.10	27.26 ± 0.23	26.28 ± 0.10	28.19 ± 0.16	
1 3 3	48.31 ± 0.04	45.16 ± 0.03	43.95 ± 0.02	47.18 ± 0.09	44.51 ± 0.19	43.51 ± 0.04	46.47 ± 0.14	48.22 ± 0.05
Fe (III)								
1 1 -1	-	-	9.88 ± 0.10	-	-	-	-	-
1 1 0	17.14 ± 0.01	16.33 ± 0.04	15.72 ± 0.03	15.76 ± 0.05	15.68 ± 0.17	15.24 ± 0.05	15.84 ± 0.02	17.45 ± 0.16
1 2 0	24.35 ± 0.08	23.75 ± 0.09	25.89 ± 0.03	21.84 ± 0.21	21.84 ± 0.21	25.74 ± 0.06	-	26.35 ± 0.20
1 2 1	-	32.99 ± 0.08	30.25 ± 0.04	31.29 ± 0.10	30.82 ± 0.20	-	31.71 ± 0.06	34.99 ± 0.21
1 3 0	29.01 ± 0.50	25.27 ± 0.07	25.70 ± 0.05	29.29 ± 0.17	25.27 ± 0.19	27.18 ± 0.09	25.69 ± 0.16	29.05 ± 0.17
1 3 1	39.43 ± 0.15	-	35.74 ± 0.07	37.62 ± 0.21	35.32 ± 0.10	36.10 ± 0.06	-	39.47 ± 0.16
1 3 3	47.84 ± 0.20	55.80 ± 0.07	44.32 ± 0.03	54.42 ± 0.10	44.78 ± 0.12	43.98 ± 0.10	54.64 ± 0.14	49.32 ± 0.12
Cu (II)								
1 1 1	17.26 ± 0.04	14.97 ± 0.09	14.58 ± 0.04	15.45 ± 0.06	15.01 ± 0.02	15.63 ± 0.09	18.24 ± 0.02	15.41 ± 0.11
1 1 2	20.58 ± 0.05	20.01 ± 0.03	18.95 ± 0.03	19.87 ± 0.10	19.46 ± 0.13	19.77 ± 0.10	-	19.85 ± 0.10
1 2 0	13.50 ± 0.10	9.82 ± 0.03	10.01 ± 0.04	9.81 ± 0.05	9.73 ± 0.02	9.19 ± 0.15	12.29 ± 0.04	11.84 ± 0.18
Zn (II)								
1 1 2	20.78 ± 0.04	20.21 ± 0.09	20.11 ± 0.14	19.92 ± 0.07	19.49 ± 0.06	21.16 ± 0.04	20.24 ± 0.50	20.48 ± 0.11
1 1 1	13.70 ± 0.07	15.33 ± 0.02	15.64 ± 0.13	15.21 ± 0.05	14.72 ± 0.02	16.67 ± 0.34	14.83 ± 0.05	14.85 ± 0.04
1 2 0	10.01 ± 0.06	9.61 ± 0.03	9.93 ± 0.09	9.50 ± 0.03	9.53 ± 0.02	10.78 ± 0.40	9.31 ± 0.06	11.88 ± 0.06

Spectroscopic measurements

The IR spectra of free FQ and their metal complexes were recorded on Bruker IFS 66v/S spectrometer, equipped with KRS-5 cuvettes (25 mm diameter and 23 μm space). The spectra were collected in the range from 4000 cm^{-1} up to 400 cm^{-1}.

The ^{1}H, ^{13}C and ^{19}F NMR spectra of fluoroquinolones and their metal complexes were recorded on a Varian Gemini 300 VT spectrometer. The spectra acquisition were made as follows: 300.4 MHz for ^{1}H, 282.3 MHz for ^{19}F and 75.5 MHz for ^{13}C NMR. The spectra were analyzed in the range from 0 ppm to 10 ppm for ^{1}H NMR, -150 ppm to 0 ppm for ^{19}F NMR and from 0 ppm to 240 ppm in the case of ^{13}C NMR. The DSS (3-(trimethylsilyl)-1-propanesulfonic acid) was used as an internal standard in the ^{1}H NMR and ^{13}C NMR investigations, and Cl_3CF (trichlorofluoromethane) for the ^{19}F NMR spectroscopy.

The concentration of all fluoroquinolones for IR and ^{1}H NMR was 0.02 $g \cdot mL^{-1}$, and for ^{13}C NMR it was 0.04 $g \cdot mL^{-1}$. All solutions for IR and NMR measurements were prepared in D_2O and at 22°C. For all spectroscopic measurements ENRX, ENX and SPRX were dissolved in NaOD (0.1 $mol \cdot L^{-1}$); CPX, LEVX., OFX and NFX were dissolved in DCl (0.04 $mol \cdot L^{-1}$). The LOMX was dissolved in NaOD (0.1 $mol \cdot L^{-1}$) for IR spectroscopic measurements and in DCl (0.04 $mol \cdot L^{-1}$) for NMR measurements.

RESULTS AND DISCUSSION

In the presented paper, the detailed quantitative behavior of the FQ – metal ions complexes were studied, using the UV spectrophotometric titration method (Fig. 1.).

The UV titration curves of the free fluoroquinolones and the FQ-Me systems were shifted dramatically (Fig. 2). These shifts were taken as evidence that all the metal ions studied have complexed with fluoroquinolones analyzed. All titration curves, both of free FQ and the FQ – metal ion systems, were titrated in the replication of three.

The changes of UV spectra of ENRX-Al (mole ratio 2:1) complexes at a different pH are presented in Figure 1. The UV spectra of the other FQ-Me complexes studied, possess two bands: the higher energy band centered at about 260-290 nm and a broad band with absorption maximum in the range of 330-360 nm. In comparison with the free FQ spectra, it indicates that the first band belongs to fluoroquinolone nucleus, while the second band may be attributed to the overlapping Me-carbonyl and Me-carboxyl bonds absorption (15). The presence of the isosbestic points proved that different complexes were formed.

The Hyperquad least-squares calculations were used for the determination of the overall stability constants of the fluoroquinolones and metal ion complexes. When the best possible fit was achieved, the non-negative non-linear least squares calculation of Hyperquad was used for the final calculation cycle.

Based on the Hyperquad calculations it was stated that all fluoroquinolones analyzed formed stable complexes (Table 1). The obtained data show, in general, the high affinity of the fluoroquinolones to the polyvalent metal ions resulting with the formation of the stable complex species. The highest values of the overall stability constants $log\beta_{pqr}$ were observed for the $Me(FQ)_3H_3$ species, while the lowest for the hydroxo-complexes with the following stoichiometry $Me(FQ)_2(OH)$ (Table 1). It was found that the high protonated species were more stable than the deprotonated ones.

Among all analyzed fluoroquinolones, the sparfloxacin, lomefloxacin, ciprofloxacin and enoxacin were prone to form the most stable species. Further, the most stable Al and Fe complexes among all, were found for protonated species: $Me(FQ)_3H_3$ ($log\beta_{pqr}$ ranged from 43.97 to 54.64), $Me(FQ)_3H$ ($log\beta_{pqr}$ 35.35 – 39.47) and $Me(FQ)_2H$ ($log\beta_{pqr}$ 21.14 – 34.99). In the case of copper(II) and zinc(II) ions, the most stable complexes were found for the $Me(FQ)H_2$ ($log\beta_{pqr}$ 18,95 – 21.16).

The enrofloxacin, ofloxacin, levofloxacin and norfloxacin formed the less stable complexes. The lowest values of the overall stability constants were evaluated for the species: $Me(FQ)_2OH$ ($log\beta_{pqr}$ 5.37 – 11.65), Me(FQ)H ($log\beta_{pqr}$ 13.70 – 18.26) and $Me(FQ)_2$ ($log\beta_{pqr}$ 9.31 – 18.30); with the aluminum(III), iron(III), copper(II) and zinc(II) ions. The calculations and results based on the UV spectrophotometric titration method were in a great agreement with those obtained using potentiometric titration method that Authors have applied earlier (21).

The coordination modes of fluoroquinolones to metal cations were confirmed by comparing the ^{1}H, ^{13}C, ^{19}F NMR and IR spectra of free FQ with that of FQ-Me complexes.

Figure 3 shows ^{1}H NMR spectra of free CPX and its complexes with aluminum ions. The addition of aluminum(III) ions in the mole ratio: 2:1 and 1:5 to the FQ solutions causes a significant change (Dd) in the spectral parameters in the environment of the

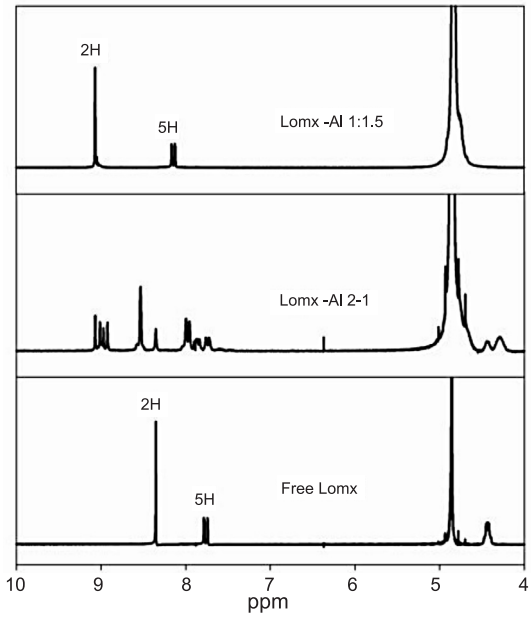

Figure 3. The ^{1}H NMR spectra of free CPX and CPX-Al in mole ratio 2 : 1 and 1 : 1.5

protons substituted at positions 2, 5 and 8, and an additional signals was also noticed, due to the increasing of concentration of metal ions. The concentration of CPX was always constant (0.06 mol·L^{-1}), while the concentration of Al^{3+} ions was varied from 0.03 mol·L^{-1} (CPX:Al more ratio 2:1) to 0.09 mol·L^{-1} (CPX:Al more ratio 1:1.5).

On the other hand, the resonance of H2 protons were significantly higher after addition of aluminum(III) in comparison with zinc(II) ions. It shows, that the aluminum ion is stronger bounded to the carboxyl group than zinc ion.

H2 proton of the ^{1}H NMR spectra for the analyzed free fluoroquinolones ranged from 8.35 ppm (ENX) to 8.73 ppm (SPRX) and for H5 proton for 7.06 ppm (OFX) to 7.81 ppm (ENX). The ciprofloxacin, enrofloxacin and norfloxacin exhibited an additional band of absorption due to the proton substituted in the position 8. This band was noticed in the range of 6.92 ppm (norfloxacin) to 7.53 ppm (enrofloxacin) (11, 31).

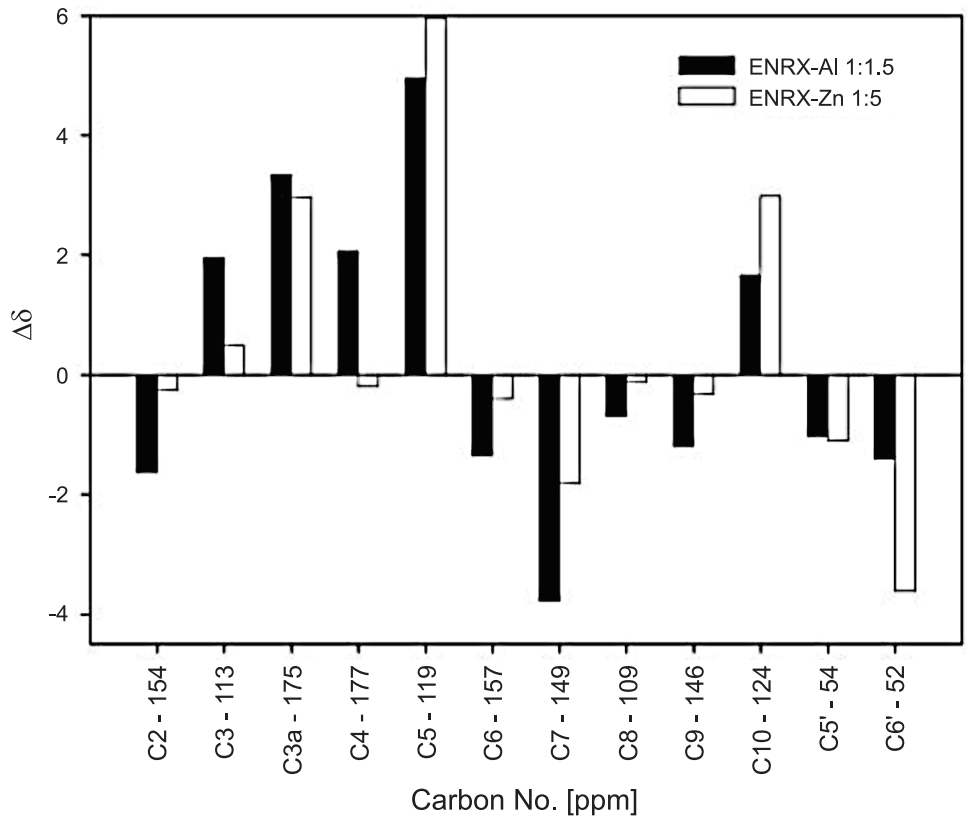

Figure 4. The difference of the ^{13}C NMR chemical shifts between ENRX-Al (mole ratio 1 : 1.5) and ENRX-Zn (mole ratio 1 : 5) complexes

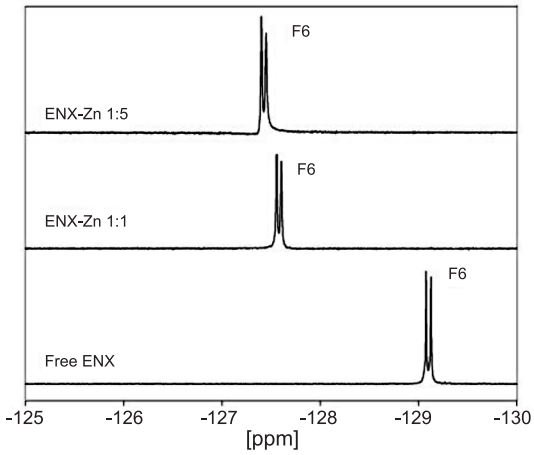

Figure 5. The ^{19}F NMR spectra of ENX and ENX-Zn systems in mole ratio 1:1 and 1:5

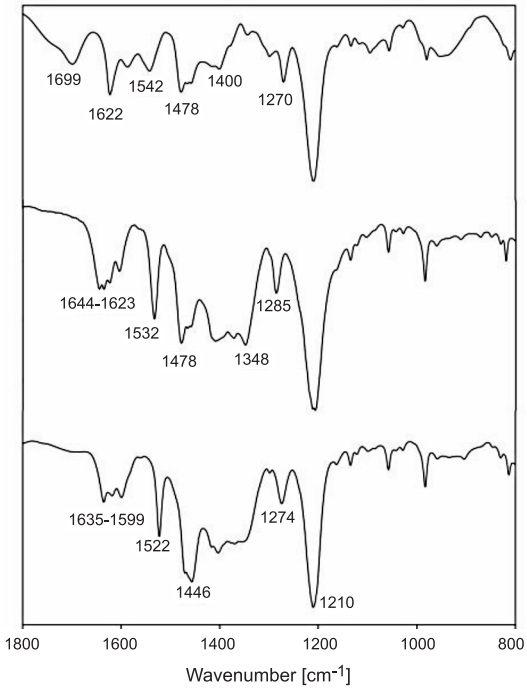

Figure 6. The IR spectra of LEVX, LEVX-Al and LEVX-Fe systems in mole ratio 1 : 1

Based on the analysis of the results obtained during the ^{1}H-NMR measurements, it was passible to identify that the aluminum(III) and zinc(II) ions were coordinated with the fluoroquinolones *via* the carboxyl and carbonyl groups substituted in the positions 3 and 4 of the quinolone basic structure (11, 31).

The ^{13}C NMR spectra of ENX, ENRX and SPRX with aluminum(III) and zinc(II) ions (Figure 4) show the differences (Dd) of carbon resonance between the ENRX-Al and ENRX-Zn complexes. The highest values of chemical shifts of the C5, C7, C3a, C3, C4 and C2 carbons were noticed for the ENRX-Al complex, and the highest values of the chemical shifts of the C5, C6', C3a and C10 carbons were observed in the case of the ENRX-Zn complex.

The ^{19}F NMR spectra of fluoroquinolones and its metal complexes show the highest chemical shifts due to the fluorine nucleus, and this makes these measurements sensitive to very weak interactions (32).

Fluorine NMR measurements, showed that the addition of aluminum(II) and zinc(II) ions to the fluoroquinolones (in the mole ratio: 3:1, 2:1, 1:1, 1:1.5, 1:2, 1:5 and 1:10) resulted with the significant changes of ^{19}F NMR spectra indicating the Me-FQ complex formation. Figure 5 shows, that the addition of zinc(II) ions (ENX:Zn 1:1 and 1:5) resulted with the significant chemical shifts of fluorine atom ranged from -129.077 ppm (free ENX) up to -127.404 ppm (ENX:Zn 1:5).

The IR spectra of free FQ and FQ-Me complexes were obtained in D_2O instead of H_2O, which allowed to avoid the influence of water absorption band at 1630 cm^{-1} (Fig. 6). The IR spectra of FQ and aluminum(III), iron(III), copper(II) and zinc(II) ions complexes showed the split of the bands present at the range of υ(O-C-O)s and υ(O-C-O)a vibrations. The absence of the band at 1700 cm^{-1} in the spectra of CPX, LEVX, OFX and NFX complexes could be explained by the deprotonation of carboxylic group due to the complexation reaction.

CONCLUSIONS

The presented study was designed to identify the quantitative behavior of fluoroquinolones metal ions complexes in aqueous solutions using the UV spectrophotometric titration method. Presented results obtained by the spectophotomertic Bjerrum method were in a great agreement with those based on potentiometric data (21).

Such wide and comparative spectroscopic studies of ciprofloxacin, enoxacin, enrofloxacin, lomefloxacin, levofloxacin, ofloxacin, norfloxacin and sparfloxacin and its aluminum(III), iron(II),

copper(II) and zinc(II) complexes has been done for the first time. There were established numerous of overall stability constants of FQ-Me complexes and their stoichiometry. During the Hyperquad calculations of the overall stability constants, it was assumed that the polyvalent metal ions were coordinated to the ligand molecule by the carboxyl and carbonyl groups substituted in the position 3 and 4.

The highest values of calculated stability constants among all analyzed complexes were established for the $Me(FQ)_3H_3$ ($log\beta_{pqr}$ ranged from 43.97 to 54.64) species; and the lowest for the hydroxo-complexes with the following stoichiometry $Me(FQ)_2(OH)$. It was found also that the high protonated species were more stable than deprotonated ones.

The most spectacular changes of the calculated values of the overall stability constants ($log\beta_{pqr}$) were observed according to the type of metal ion used for the complexation reaction. Moreover, it was observed, that the stability of the FQ-Me complexes strongly depends on number of the ligand molecules that bind the metal ions. It was also confirmed, that the stability of the complexes of analyzed fluoroquinolones with polyvalent metal ions follows the order: $Fe^{3+} > Al^{3+} > Cu^{2+} > Zn^{2+}$.

The ^{1}H NMR, ^{13}C NMR, ^{19}F NMR and IR spectroscopy methods have been used to study the behavior of fluoroquinolones and their metal complexes in solution. These extensive NMR and IR spectroscopic studies revealed also that fluoroquinolones drugs coordinate polyvalent metal ions to form stable complexes.

The authors believed, that the presented studies have not only the theoretical but also practical value. The presented UV spectroscopic studies significantly complete the knowledge about the complexation mechanism between the fluoroquinolones and polyvalent metal ions. Such information may be very useful for better understanding and interpretation of differences in bioavailability of fluoroquinolones and their interactions with antacids and other multimineral drugs. The concurrent administration of the metal ions containing drugs and multi-mineral supplements can reduce the bioavilability of the fluoroquinolones even by 80%; therefore, it is necessary to prevent the complex formation between FQ and metal ions in order to obtain the desired therapeutic effect (5, 6).

The equilibrium and the structural studies of FQ-Me complex species investigated in presented report, may be very helpful for the better understanding of the role of the metal ions during the inhibition of the DNA-gyrase enzymes by this group of antimicrobials.

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