

RESEARCH ARTICLE

A New Silver Complex with Ofloxacin – Preliminary Study

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Objective: Silver complexes of antibacterial quinolones have the potential advantage of combining the antibacterial activity of silver and fluoroquinolones. The objective of our study was the preparation and the preliminary physico-chemical characterization of a silver complex with ofloxacin. **Methods:** To achieve our goals several spectroscopic methods (ultraviolet spectrophotometry, mass spectrometry, and Fourier transform infrared spectroscopy) and thermal methods (differential scanning calorimetry and thermogravimetric analysis) were used in order to elucidate the chemical structure of the complex. **Results:** Using mass spectrometry we established the stoichiometric ratio silver:ofloxacin as 1:2. Experimental data suggest a particular coordination for ofloxacin, as a monodentate ligand, in the formation of a complex with silver, through the nitrogen atom from the methyl-piperazine cycle. **Conclusions:** The obtained complex has a chemical structure likely $[Ag(Ofloxacin)_2]NO_3$, requiring evaluation through other physico-chemical methods.

Keywords: fluoroquinolones, ofloxacin, silver, metalcomplex, silver nitrate

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Introduction

Due to the excellent chelating properties of quinolone antibacterial several metal complexes of these substances were synthesized and studied for their possible antibacterial and antifungal activities. The silver ion is known for its antibacterial and antifungal properties. Fluoroquinolones are synthetic antibacterial agents, with broad spectrum activity, good oral absorption and bioavailability. The 4-oxo and 3-carboxyl groups of fluoroquinolones offer excellent chelating properties for metal ions. Silver complexes of fluoroquinolone antibacterial have the advantage of combining the antibacterial activity of the silver ion with the one of the fluoroquinolone. There are a large number of studies on the complexation of antibacterial fluoroquinolones with metal ions using different metals [1]. Metal complexes have been synthesized with antimicrobial activity equal to or greater with the corresponding quinolone antibacterial. Research on the fluoroquinolone metal complexes has revealed also other biological effects: antifungal, antiparasitic, anticancer, anti-inflammatory, antioxidant and even insulin mimetic [2-4]. In the category of metal complexes with promising therapeutic effects are included those containing silver [5-10].

Complexation of antibacterial quinolones with silver combines the antibacterial activity of Ag (I) with the one of the quinolone. This complexation presents a particular coordination with the quinolone as the monodentate ligand

through the N4'-piperazine atom or possibly through a complex polymeric form, different from most other metal complexes of quinolone antibacterials. Although the silver bactericide potential is known from ancient times, only a few studies have used this metal ion to obtain quinolone antibacterial metal complexes [1, 11].

Antibacterial agents with new chemical structures are believed to be less susceptible to the occurrence of bacterial resistance mechanisms, consequently metal complexes of fluoroquinolone antibacterials can be promising therapeutic alternatives in the future.

Ofloxacin (OFL) (Figure 1) ((*RS*)-7-fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1-azatricyclo-trideca-5(13),6,8,11-tetraene-11-carboxylic acid), is a second generation fluoroquinolone, used in therapy as a racemic mixture. Ofloxacin is effective against aerobic Gram-positive microorganisms (*Staphylococcus aureus*, *Streptococcus pneumoniae*), aerobic Gram-negative microorganisms (*Escherichia coli*, *Haemophilus influenzae*,

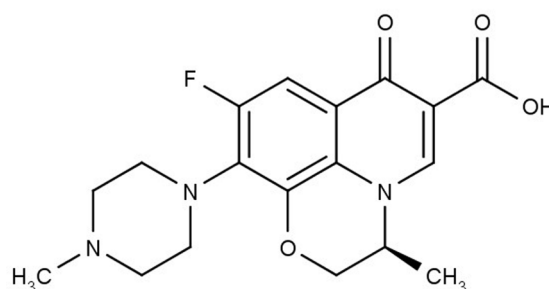


Fig. 1. The chemical structure of ofloxacin

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Klebsiella pneumoniae, and *Neisseria gonorrhoea*) and *Chlamydia*. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, which is an enzyme necessary to separate (mostly in prokaryotes, in bacteria in particular) replicated DNA, thereby inhibiting bacterial cell division. It is used in the treatment of urinary tract, skin and respiratory infections [12].

Due to the specific complexation ability of fluoroquinolones, in the case of OFL several metallic complexes (Mg^{2+} , Ca^{2+} , Ba^{2+} , Ni^{2+} , Zn^{2+} , Cu^{2+} , Co^{2+} , Pd^{2+} , Pt^{2+} , Bi^{3+}) have been studied before in terms of antimicrobial activity (including *Helicobacter pylori* and *Mycobacterium tuberculosis*), binding to DNA and to albumins [13-21]. At the moment only a few metal complexes with silver of antibacterial quinolones are known: nalidixic acid, piperidic acid (first generation), pefloxacin, norfloxacin, ciprofloxacin (second generation), moxifloxacin (fourth generation) [5,6,11,22-24].

The aim of this study was to obtain and characterize physico-chemically a complex with OFL with silver, metal ion which to date has not been studied in complexation with OFL. A synthesis method of the metallic complex was selected and adapted using silver nitrate and ammonia. The characterization of the metal complex was carried out by several methods: spectroscopic methods (ultraviolet spectrophotometry, mass spectrometry, and Fourier transform infrared spectroscopy) and thermal methods (differential scanning calorimetry and thermogravimetric analysis) in order to elucidate the chemical structure and to evaluate the behavior of the newly obtained compound in comparison with OFL.

Methods

Materials

The materials were purchased as follows: ofloxacin (OFL) from Ranbaxy Laboratories Limited (India) and silver nitrate ($AgNO_3$) from SC UTCHIM SRL (România). Both substances were of pharmaceutical grade. Other reagents used were: methanol (GR p.a., Lach-Ner, Czech Republic), and ammonia 25% CP (Microchim, Romania). All reagents and solvents were of analytical grade.

Synthesis of the silver complex

1 mM OFL and 0.5 mM $AgNO_3$ were dissolved in 50 mL concentrate ammonia and 100 mL distilled water, and maintained on a boiling water bath with reflux condenser for 8 hours. The resulting yellow solution was concentrated on a boiling water bath and the obtained substance was dried in an oven at 80 °C for 3 hours, and then kept in the desiccator for 3 days with $CaCl_2$ dehydrated protected from light. The synthesis method of the metal complex was adapted after the method described by Li YX et al [6].

Analysis Methods and Apparatus

Ultraviolet (UV) spectrophotometry. UV spectra were recorded on a spectrometer UV-VIS Specord 210 spec-

trometer (Analytik Jena, Germany) and processed using WinASPECT software (Analytik Jena, Germany). We recorded the spectra of the following solutions: 0.002 mM OFL compared to [0.002 mM OFL + 0.001 mM $AgNO_3$] dissolved in methanol. Also the UV spectrum of OFL was registered in comparison with the obtained silver metal complex; both substances are dissolved in distilled water.

Mass spectrometry (MS). Mass spectra were determined with an Agilent 6410 Triple Quadrupole detector (Agilent Technologies, USA) with electrospray ionization (ESI) and vacuum pump. The recorded data were processed using MassHunter software. Conditions of the ionization source were: gas flow 10 L/min, 50 psi, 350°C, 4000 V, ESI +, with a full scan on the field 100-1500 amu data acquisition module.

Fourier-transformed infrared (FT-IR) spectroscopy. FT-IR spectra were recorded on a spectrometer FT-IR Thermo Nicolet (USA) and processed using Omnic V.6 software, in the range of 400-4000 cm^{-1} .

Differential Scanning Calorimetry (DSC) analysis. DSC curves were recorded on a DSC 60 Shimadzu apparatus, in the range of 30 - 350°C, with a temperature increase rate of 10°C/min. The weight of the samples was 3 mg.

Thermogravimetric analysis (TGA) and Derivative Thermogravimetric (DTG) analysis was carried out using a Mettler Toledo TGA/DSC Thermogravimetric Analyzer. The temperature range was 30-350 °C with an increase rate of 10°C/min. The weights of the samples were between 4 - 7 mg. The sample was purged with nitrogen at a rate of 40 mL/min. Aluminum crucibles were used as standard.

Results

Synthesis of the complex

The obtained compound was a solid crystalline substance with bright brown crystals, soluble in concentrated ammonia, in hot water, slightly soluble in HCl 10%, very slightly soluble in dimethyl sulfoxide, dimethylformamide, insoluble in 10% NaOH, ethanol, methanol, and acetone.

UV spectrophotometry analysis

Preliminary possible changes in UV spectrum of OFL in the presence of silver ions were studied (*Figure 2*).

Two absorption maxima can be observed, both in the case of OFL (0.002 mM) and OFL with $AgNO_3$ solution (0.002 mm / 0.001 mm), the values are shown in *Table I*.

After obtaining the metallic complex the UV spectra of this was registered in comparison with the UV spectra of OFL. As solvent we used distilled water, solvent in which we were able to dissolve both substances in the same concentration ($3.6 \cdot 10^{-4}g\%$). Absorption UV maxima of OFL and of the obtained complex were very similar (*Figure 3*).

MS analysis

During MS analysis the capillary voltage was changed in the 3000-4000 V domain, the temperature in the ionization source were in the 300-350 °C domain without sig-

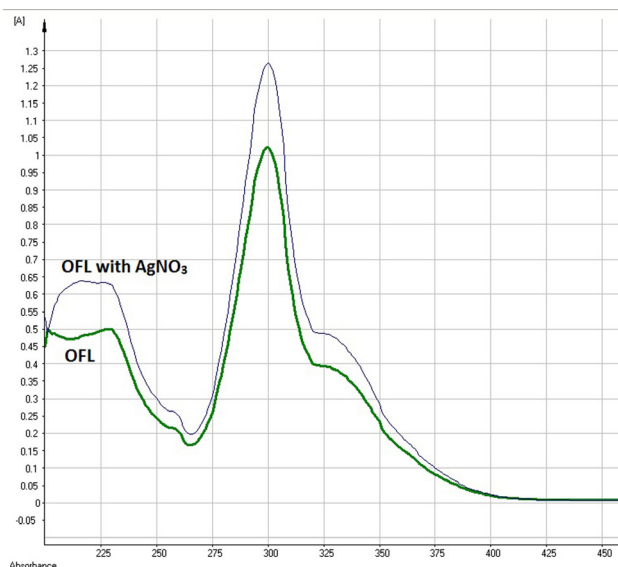


Fig. 2. UV spectra of OFL (0,002 mM) and OFL with AgNO3 (0,002 mM / 0,001 mM) in methanol

Table I. Absorption UV maxima of OFL and OFL + AgNO3 (dissolved in methanol)

Substance	λ_1 (nm)	Absorbance (1)	λ_2 (nm)	Absorbance (2)	Concentrations [mM]
OFL	228	0,500	300	1,023	0,002
OFL + AgNO ₃	226	0,633	300	1,264	0,002 / 0,001

nificant changes in the spectrum. The full scan type mass spectrum at 4000 V and 350 °C of the sample analyzed was identified m/z 830.9 corresponding to a ratio molecular silver ion:OFL of 1:2.

FT-IR spectroscopy analysis

The FT-IR spectra of OFL and of the obtained complex were registered and compared (Table II).

Table II. The different registered IR frequencies (cm⁻¹) – OFL and complex with silver

Band position (cm ⁻¹)	OFL-silver complex	Assignments
OFL		
-	3650-3750	ν (-OH)
2785	-	ν (N-H)
1712	1708	ν (C=O) _{carb}
1621	1621	ν (C=O) _{py}
-	1395	ν (NO ₂)
1288	1288	ν (C-F)
-	1033	ν (NO ₂)

DSC analysis

We registered and compared the DSC curves of OFL, AgNO₃ and of the obtained complex (Figure 4).

TGA and DTG analysis

TGA of the investigated metal complex is useful to gather information about the stability of the complex. Thermodegradation of the complex had a first decomposition stage only in the temperature range 230-260°C with a loss of

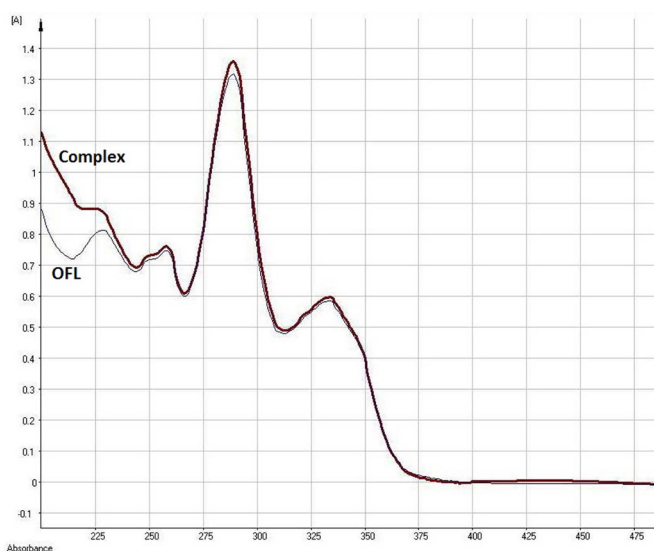


Fig. 3. The UV spectra of the obtained complex in comparison with OFL

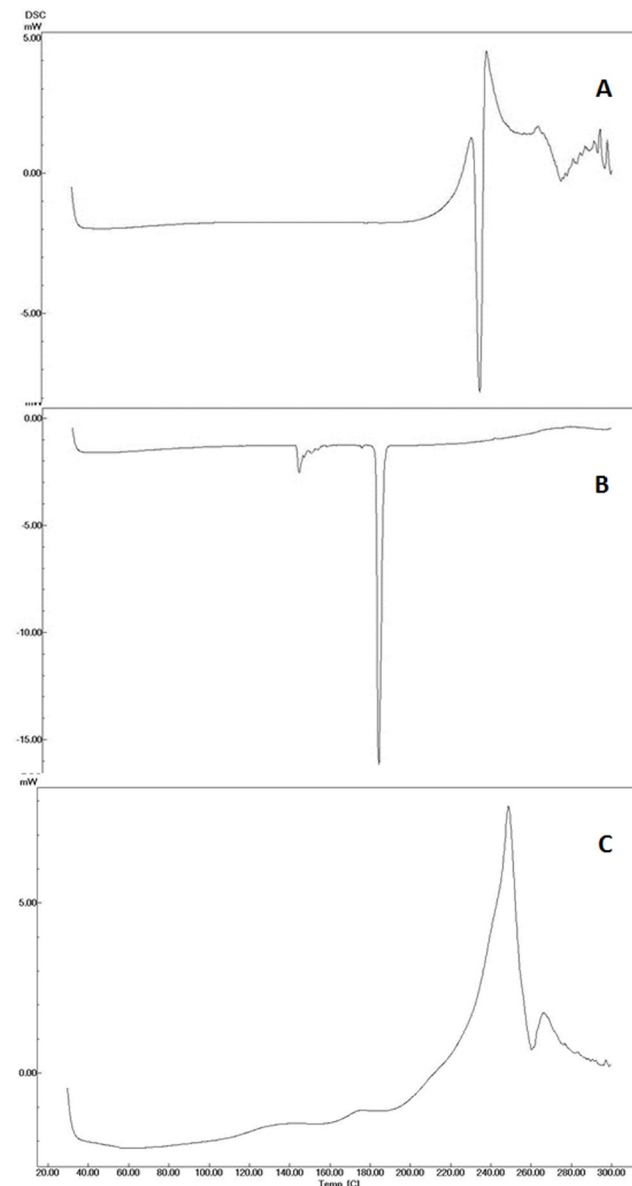


Fig. 4. DSC curves of OFL (A), AgNO3 (B) and obtained complex (C)

approximately 8.81% of the weight, and a degradation constant up to 350°C, with a weight loss of 21%. DTG analysis exhibit an endothermic peak and two exothermic peaks, different from the OFL and AgNO₃ records (Figure 5).

Discussion

Synthesis of the complex

Obtaining a homogeneous silver complex with ofloxacin is difficult because it is necessary to find a suitable stoichiometric formula. The majority of variants suggested by the literature, started from the premise of ratio silver:OFL 1:2, where OFL is a monodentate ligand, suggested by Li Y.-X. et al, without excluding the possibility of 1:1, 2:1 ratios or other variations [6, 22]. The ammonia environment seems to positively influence the formation of the metal as Ag⁺ ion is included in the initial complex [Ag(NH₃)₂]NO₃. We tried a variant without ammonia solution, but without obtaining a complex. In addition the stability of the complex is influenced by the working conditions: temperature, oxygen from the atmosphere, which can generate potentially Ag₂O formation (cubic crystals, black-brown) relatively easily decomposed to Ag and O₂ (Ag₂O → 2Ag + 1/2O₂). The formation of AgO (black powder containing Ag⁺ and Ag³⁺), in which +1 and +3 the silver oxidation state it is unlikely.

The final compound obtained is a crystalline solid substance with slightly bright brown crystals, with an indicative solubility in various solvents previously presented.

The aqueous solution obtained by dissolving 1 mg substance in 5 ml of the solvent has a neutral pH (universal indicator strips Merck). The greatest difficulty of this stage is to obtain a homogeneous compound, with a crystalline structure, soluble in different solvents.

UV spectra analysis

The UV spectra of OFL recorded in acidic and basic medium, show hypsochrome shifts of absorption maxima in comparison with the spectrum recorded in methanol. In basic medium occurs an increase in the absorption band of the third absorption maximum (due perhaps to the formation of a sodium salt). The tricyclic chemical structure (quinoline nucleus condensation with a heterocycle containing an oxygen atom) brings the possibility of transitions. The absorption maximum of OFL corresponds to the chromophore which includes the nitrogen atom (position 4) and 6-carboxyl group (the numbering of the atoms according to the monograph of the European Pharmacopoeia). The UV absorption maxima of OFL correspond with those from the literature (Table III) [25,26].

There is a slight hyperchromic shift in the case of the UV spectrum of the OFL with silver nitrate solution in methanol in comparison with the OFL spectrum, but the modification of the UV spectrum cannot be considered significant. This shows that no major structural changes occur in the presence of silver ions. The compound synthesized was dissolved in hot water; therefore, we preferred to compare the absorption peak with the one of OFL in this

Table III. The absorption maxima of OFL

Ofloxacin	Comparative values of absorption maxima							
	Experimental				References [25,26]			
	0.1M HCl	Methanol	Water	0.1M NaOH	0.1M HCl	Methanol	Acetone	0.1M NaOH
λ ₁ (max)	295	298	289	289	294	298	300	288
λ ₂	327	327	333	334				

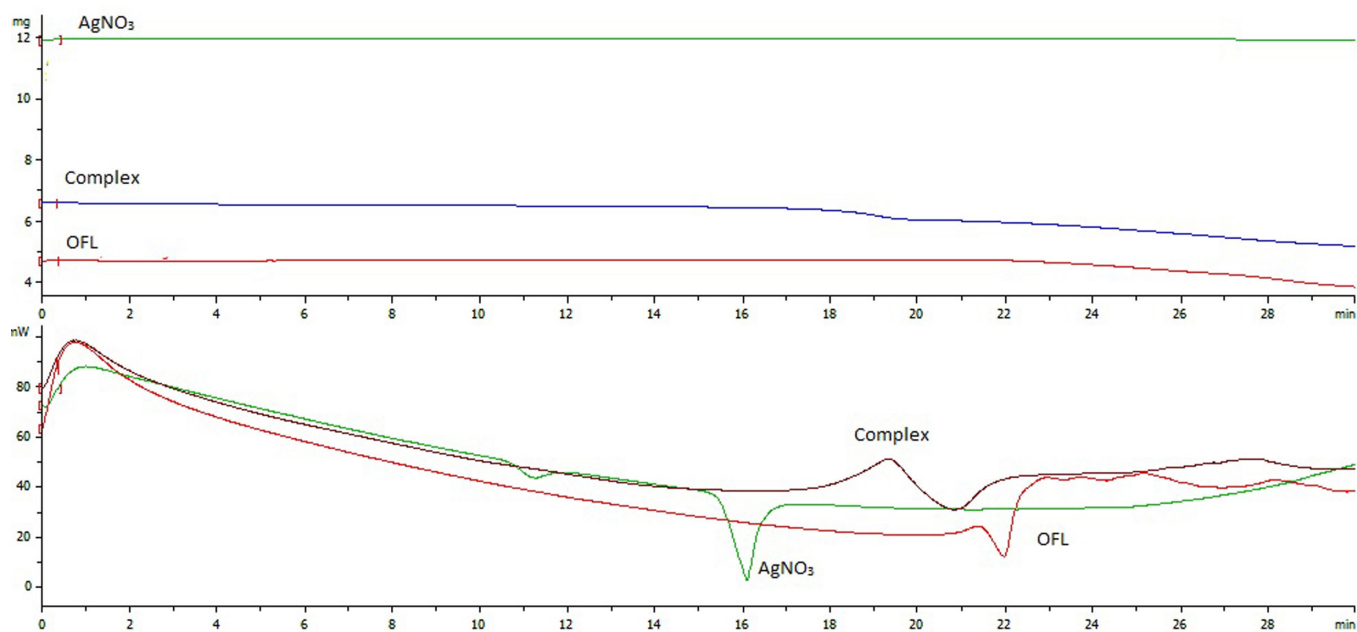


Fig. 5. TGA/DTG curves of OFL, AgNO₃ and complex

solvent. No changes of the UV spectra of the complex were observed in comparison to OFL. Anyway, even if OFL became a monodentate ligand in the studied complex, this is not visible in the UV light, as silver ion does not absorb in the UV domain.

MS spectra analysis

In general, antibacterial quinolones may become ligands for divalent and trivalent cations, with 3-carboxyl and 4-oxo as chelating groups (in a stoichiometric ratio of metal:ligand of 1:1, 1:2 or less frequent, 1:3, 1:4), but also through N⁴ nitrogen atom from the piperazine substituent. The structure of a metal complex of silver with OFL has not been published yet. By association with patterns obtained so far using OFL, in this study, it is possible to obtain a compound with a stoichiometric metal: ligand of 1:2 or 1:1 while ratio of 1:3 is unlikely [13-21,27]. In the mass spectrum (*m/z* 830.9) is highlighted the molecular ion $\text{Ag}(\text{OFL})_2^+$, corresponding to ratio metal:ligand of 1:2 combination, and *m/z* 362.1 corresponding to the molecular ion of the free OFL. Metal complex is formed in this ratio, but not the entire amount of OFL has been included in the complex and obviously the Ag^+ ions from AgNO_3 have not been fully complexed.

FT-IR Spectroscopy analysis

FT-IR band assignment for the compound was compared to that of OFL (Table II). In the literature, OFL shows characteristic absorption bands for stretching vibrations of the carboxyl groups $\nu(\text{C}=\text{O})_{\text{carb}}$ at 1720 and the pyridone $\nu(\text{C}=\text{O})_{\text{py}}$ at 1621 cm^{-1} . Absorption bands attributed to carboxyl group $\nu(\text{C}=\text{O})_{\text{carb}}$ can be found both in the complex spectrum (1708 cm^{-1}) and in the one of OFL (1712 cm^{-1}) without noticeable changes in [24,28-30]. The stretching vibration for the pyridone group $\nu(\text{C}=\text{O})_{\text{py}}$ mentioned in the literature are assigned to 1621 cm^{-1} (moxifloxacin) and 1630 cm^{-1} (norfloxacin) [11,29]. The stretching vibration for the pyridone group $\nu(\text{C}=\text{O})_{\text{py}}$ are identical for both the OFL and the complex obtained at 1621 cm^{-1} [13]. From the assigned comparative values of the FT-IR spectra of the complex and OFL, we can conclude that the carboxyl group is not involved in the formation of the silver complex. OFL shows an average value of absorption band of 2785 cm^{-1} , attributable to the stretching vibration of the nitrogen atom (N⁴) from the piperazine substituent [29]. This band is missing from FT-IR spectra of synthesized complex and can suggest involvement in silver ion complexation. Fluorine substitution of the aromatic ring (Ar-H) has an absorption band between 1270 - 1100 cm^{-1} representing the vibrations of tension C-F [31]. Both OFL and the synthesized complex have a mean absorption band at 1288 cm^{-1} , which can be assigned to the connection C-F of the tricyclic ring. The metal complexes of antibacterial quinolones, exhibit in general, very broad bands between 3400 - 3600 cm^{-1} assigned to $\nu(\text{-OH})$, respectively to water molecules coordinated or bound by hydrogen bonds. Spec-

trum of the obtained compound exhibits a broad band in the area 3650 - 3750 cm^{-1} , which can be attributed to the water from the structure of the complex [11,29]. Characteristic bands of the bidentate nitrate group (NO_3^-), in the case of complex $[\text{Ag}_2(\text{norfloxacin})_2](\text{NO}_3)_2$, are observed at 1384 and 1031 cm^{-1} , assigned to $\nu_{\text{as}}(\text{NO}_2)$ and $\nu_{\text{s}}(\text{NO}_2)$ [32].

In the case of our complex, values of 1395 cm^{-1} and 1033 cm^{-1} can be attributed to vibration strength for this group, suggesting that the nitrate group is part of the target metal complex. A strong band is observed at 1456 cm^{-1} corresponding to the stretching vibration $\nu(\text{N}=\text{O})$.

DSC/TGA analysis

OFL it's a racemic mixture with a melting point of 225-227 °C [12]. Determination of the melting point by DSC method (30 - 350°C) revealed a melting point for OFL of 270.4°C higher than the values found in the literature. The melting point of AgNO_3 is 211,91°C corresponding with the data from literature [33]. The synthesized compound melted at 211.91 °C, but with an exothermic curve, with a high peak, very different from the one obtained for OFL and AgNO_3 . The synthesized compound proved to be stable up to 230°C when it started to decompose. Decomposition profile is similar to that of other metal complexes of antibacterial quinolone agents. In the first stage there is a possible loss of hydration water molecules (4 molecule), which are not present in the mass spectrum analysis, probably as a consequence of the rapid removal of the ionization chamber. This suggests that these are weakly bound water molecules [13,32]. After 260°C the degradation continued steadily up to 350°C. DTG shows an endothermic peak and two exothermic peaks different from the one of OFL and AgNO_3 . Linked with the decomposition profile of other metal complexes of FQ, this stage can be considered the step in which AgF and Ag (fluoroquinolone) complex are formed, which at much higher temperatures (above 500°C) continues until the formation of AgF [32].

The Ag^+ ion (which is a d^{10} ion) can form a linear complex with two ligands (classic example is NH_3 , in the $[\text{Ag}(\text{NH}_3)_2]^+$). Most of Ag^+ complexes have a coordination number of 2, and a linear structure as the Ag^+ ion has a relatively large mass and a low electric charge, resulting in low electron density. Such an ion doesn't assimilate electronic density of the ligands as easy as those ions that have a high electron density [34]. We can state that the ammonia environment favors the complex formation with OFL. In the absence of ammonia the complex does not form, the mass spectrum showing only the specific free OFL molecular ion. The mass spectrum correlated with the data presented above, suggested that the chemical structure of the complex correspond most likely to a $[\text{Ag}(\text{Ofl})_2]\text{NO}_3$ structure that functions as a monodentate ligand and complexation occurs at the C-nitrogen N⁴-methyl-piperazine (Figure 6), a structure similar to the silver complex obtained Li Y.X. et al for norfloxacin [6].

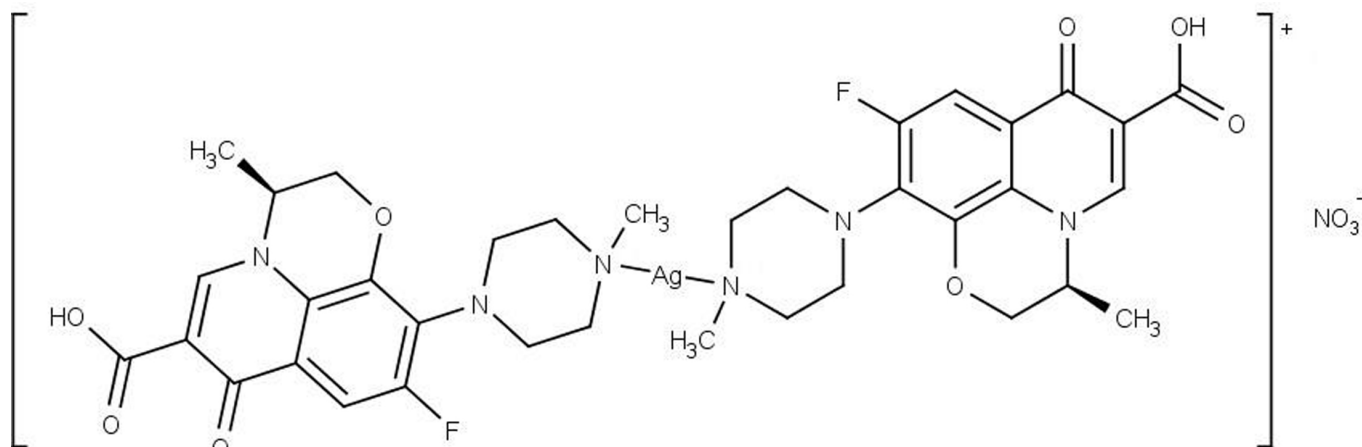


Fig. 6. The proposed structure for the synthesized complex

Conclusion

During the current study we obtained a silver complex with OFL which was characterized preliminary by several methods: spectrometric methods (UV spectrophotometry, FT-IR spectroscopy, mass spectrometry) and thermal methods (DSC and TGA) in order to elucidate the chemical structure. The proposed structure of the complex obtained from the results of physico-chemical analysis is $[Ag(OFL)_2]NO_3$. Since the synthesis of new molecules with antibacterial activity is an absolute necessity and also a permanent challenge for the medical world due to the alarming increase in bacterial resistance, a metal complex of the silver and OFL may be a promising therapeutic alternative in the future.

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Conflict of interest

None to declare.

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