New Perspectives: Quinolones as Complexation Agents

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Background: Quinolones are synthetic antibacterial agents, with a 4-oxo-1,4-dihydroquinolinic structure, which is based on the nalidixic acid model. The 4-oxo and 3-carboxyl groups confer quinolones excellent chelatation properties with metallic ions.
Aim: To highlight a few theories regarding the complexation phenomenon of quinolones.
Methods: Complexes with metallic ions have been characterized (stoichiometry, in vitro physical-chemicals properties, stability studies, and behavioral studies in different biological mediums).
Results: New availabilities have been identified: bioavailability of the complexed quinolones and formulation of new pharmaceutical products with a superior bioavailability and therapeutic effect; the antimicrobial activity of quinolone complexes; quinolone complexes as antitumor drugs with the aim of obtaining less toxic compounds; understanding the mechanism of action of quinolones, which is a challenge especially regarding their selectivity at the bacterial DNA level; development of new determination methods, based on the complexation of quinolones with metallic ions.
Conclusions: The 21st century may provide new useful therapeutic aspects on the basis of complexation between quinolones and metals.

Keywords: quinolones, fluoroquinolones, metallic complexes, complexation

Introduction

Quinolones are synthetic antibacterial agents based on the nalidixic acid model, a naphthyridine derivative, introduced in the treatment of urinary tract infections since 1963. Initial clinical uses of quinolones were limited to the treatment of urinary tract infections because they present good absorption after oral administration and potent activity against common Gram-negative pathogens.

Following extensive research regarding the chemical structure – therapeutic activity relationships, compounds with high potency and expanded spectrum of activity, improved absorption and distribution properties were synthesized and introduced in the therapy. This new quinolones proved to be useful not only in urinary tract infections but also in the treatment of serious systemic infections [1, 2, 3].

Since 1977, these synthetic antibacterial agents have been widely used in therapy. The major qualitative leap occurred with the introduction of a fluorine atom in the 6th position of the quinoline cycle, resulting in fluoroquinolones, compounds with an increased chemotherapeutic potential (Table I).

Three important factors contributed to the therapeutic explosion of quinolones:

- unprecedented mechanism of action based on the inhibition of the microorganisms ability to replicate and transcribe their DNA;
- their potency and activity spectrum - comparable with those of the semisynthetic antibiotics;
- their relatively simple chemical structure, which led to a large number of analogues synthesized with minimal costs [2, 3].

1) The ability of quinolones to chelate metal ions

If we look upon the chemical structure of these compounds, we can observe that a hexa-atomic heterocyclic nucleus is attached to the core of pyridine-4-one (Figure 1). The 4-oxo and 3-carboxyl groups of quinolones give them excellent chelating properties with metal ions (Figure 1).

The chelating ability may influence the quinolones in vivo antimicrobial activity, but can also interfere in the cases when co-administration of drugs that contain metal ions (antiacids, antianaemic drugs etc.) is required, or foods rich in metal ions are consumed. In the last twenty years, numerous studies and researches have advanced interesting theories about this phenomenon specific to quinolones [3, 4, 5, 6] (Table I).

2) Characterization of metal ion complexes with quinolones

Studies regarding the complexation with metal ions have focused on many chemical elements from the following groups of the periodic table:

- Group II – alkaline earth metals: Mg, Ca, Ba
- Groups I–VIIIB: Cr, Mo, Mn, Fe, Ru, Co, Ni, Pd, Pt, Cu, Ag, Zn, Cd, Hg, V (VO^{2+})
- Group IIIA: Al
- Group IVA: Sn, Pb
- Group VA: Bi
- Actinoid: U (UO_2^{2+})

2.1. Stoichiometry – structure

Chelated quinolones forms with metal ions are 1:1, 2:1 or 3:1 [1, 7]. The stoichiometry of chelated forms depends on several factors: the relative concentrations of the chelated

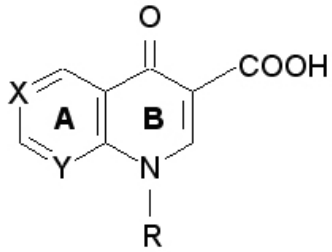


Fig. 1. General structure of quinolones
X = Y = CH Ring A = benzene
X = CH, Y = N Ring A = pyridine
X = Y = N Structure A-B = pyrimidine

agents (quinolones) and metal ions, metal ion valence and pH. For example, the complex between ciprofloxacin and magnesium ion is a 2:1 chelate (Figure 2).

Spectral studies suggest that norfloxacin and ciprofloxacin behave like bidentate ligands in these complexes, the carboxylic oxygen and carbonyl exociclic oxygen atoms participating in these links. The results obtained indicate the formation of complexes like: $[M(Ciprofloxacin)_2](ClO_4)_2.xH_2O$ and $[M(norfloxacin)_2](ClO_4)_2.xH_2O$, where M = Mg^{2+}, Ca^{2+} and Ba^{2+}. It seems that the N1-piperazine nitrogen atom is also involved in some complexion [8, 9, 10].

Efthmiadou et al. [11] studied metal complexes of enrofloxacin with Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd2+ and UO_2^{2+}, in which each metal has six coordinative links and the complex can be described as a distorted octahedron. The proposed structures are the following ones: $Mn(enrofloxacin)_2(H_2O)_2$, $Fe(enrofloxacin)_3$ and $UO_2(enrofloxacin)_2$. Efthmiadou et al. [12] also studied complexes of pipemidic acid with various metal ions.

Vieira et al. [13] have synthesized complexes of Pt^{2+} and Pd^{2+} with some fluoroquinolones (ciprofloxacin, levofloxacin, ofloxacin, sparfloxacin and gatifloxacin) as ligands. Coordination to Pt^{2+} occurs in a bidentate fashion via the piperazine nitrogen atoms, this type of coordination being considerably rare.

Formation of complexes with some divalent cations such as Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+} and transition metals Mn^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+} was also studied. The formation constants (Kf) values of complexes with ofloxacin, norfloxacin and flumequine proved that from the list of transition metals mentioned above only Ni^{2+} and Co^{2+} have the ability to form stable complexes. The K_f values of Mn^{2+} and Zn^{2+} compared with those of Ni^{2+} and Co^{2+} are relatively small. For cations belonging to the alkaline earth metals, the Kf values decrease going down in the group in the periodic table. The composition of the complex is 1:1 for all the cations [14].

Athanasellis and al. [15] studied the structure of complexes between Mn^{2+}, Zn^{2+} and Ba^{2+} with quinolones (N-methyl-3-acetyl-4-hydroxyquinolinium-2-one and N-H-3-acetyl-4-hydroxyquinolinium-2-one).

The reaction between norfloxacin and $AgNO_3$ leads to a particular mononuclear complex $[Ag(norfloxacin)_2]NO_3$, in which the coordination of the Ag^+ ion is approximately linear [16] (Figure 3, Figure 4).

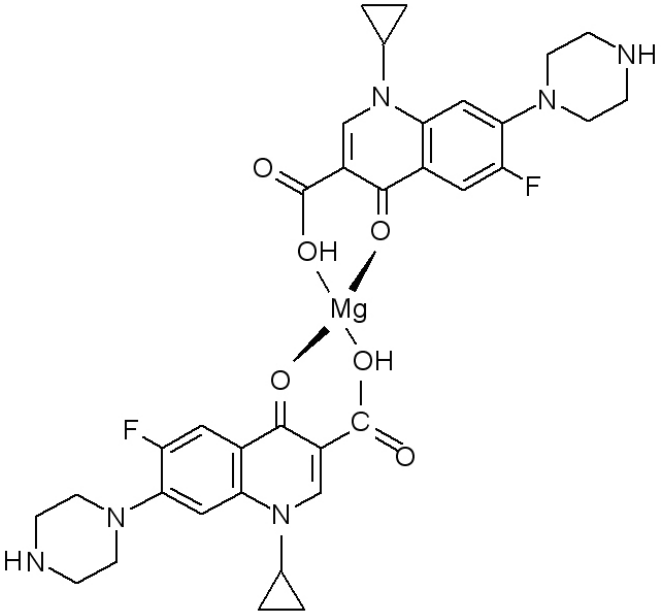


Fig. 2. The 2:1 complex between ciprofloxacin and magnesium ion [1]

Coordination of the second ligand (for example 2,2-bipyridil-glycine or 2,2-bipyridil glycine-tyrosine) is more favored than the first ligand and suggests distortion of the 1:1 complex [17, 18].

2.2. Effect of pH

Stoichiometry of the complexes is influenced by the pH values of the environment. Thus, in an acid environment a complex formation between Cu^{2+}-ciprofloxacin in a 1:1 ratio is favored but in a basic environment a complex formation in a 1:2 ratio is favored [1].

Urbaniak B. et al. [19] used a capillary electrophoresis method to investigate the complex formation of several fluoroquinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, lomefloxacina, enrofloxacin and sparfloxacin) with ions of Mg^{2+}, Al^{3+} and Fe^{3+} at two different pH values. It was established that the optimal values for the formation of complexes with Al^{3+} and Fe^{3+} are between 3 and 5.5. Al^{3+} and Fe^{3+} precipitated over the value of 5.5. In addition, the optimum pH for the formation of complexes between Mg^{2+} and fluoroquinolones is of 8.02. The constants obtained for the studied metal ions studied increased in the order $Mg^{2+} << Al^{3+} < Fe^{3+}$.

2.3. Solubility

At the most physiologically relevant pH values, quinolones show significant dissociation at both the 3-carboxylic group and also at the alkaline group 7-(1-piperazine). The trend of fluoroquinolones (eg norfloxacin and ciprofloxacin) to cause in high dose crystalluria in alkaline urine is in part due to the predominance of the less soluble zwitterionic form. Solubility of quinolones in water and other polar solvents is changed by complexation with metal ions. It depends on the structure of quinolones, metal ion and pH conditions [1, 6, 8, 10, 20].

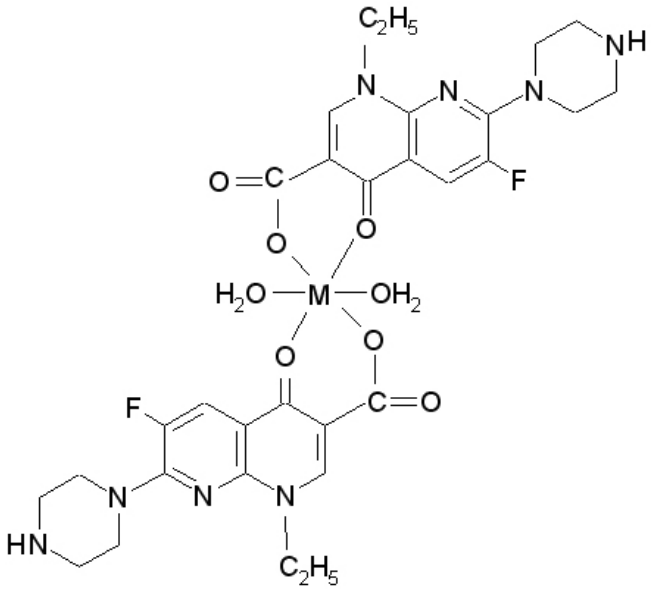


Fig. 3. Proposed structure for enoxacin complexes with ions Cu^{2+}, Mn^{2+} and Ni^{2+}, M representing metal ion [21]

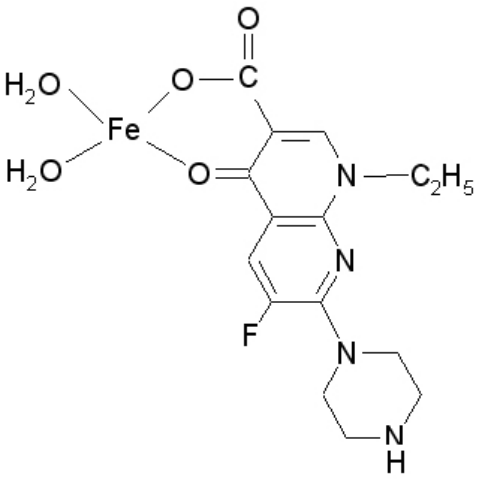


Fig. 4. Proposed structure for enoxacin complex with Fe^{2+} ion [21]

Although in the literature [1] it is mentioned that, in general, chelated forms of fluoroquinolones are often insoluble in water, Upadhyay et al. [10] have investigated the complexes formed by ciprofloxacin and norfloxacin with Mg^{2+}, Ca^{2+} and Ba^{2+} perchlorate and concluded that the phenomenon of complexation of the two fluoroquinolones increased their solubility in water and other polar solvents. Increased solubility of quinolone complexed with Mg^{2+} is mentioned in several registered patents [20]. Complexes of enoxacine with Mn^{2+}, Fe^{3+}, Ni^{2+}, Cu^{2+} were insoluble in hot water but soluble in methanol, ethanol and chloroform at different temperatures [21].

3. Bioavailability of quinolones complexes with metals

Oral co-administration of quinolones antacids, antianaemic or mineral supplements can significantly reduce the oral bioavailability of quinolones, because of chelates formation, which are often insoluble in water [1].

Oral absorption of quinolone is reduced by co-administration of preparations containing metal ions. Kawai Y. et al. [22] established that the stability constants decreased in the following order, for trivalent metal cations Fe^{3+}> Al^{3+}, respectively for divalent metal cations Cu^{2+}> Fe^{2+}> Zn^{2+}> Mg^{2+}> Ca^{2+}. Quinolones interact in the stomach with Al^{3+} and in the intestine with Mg^{2+} when are co-administered antacids containing Al^{3+} and Mg^{2+}. These results suggest that the formation of quinolone complexes with metal cations is an important phenomenon affecting quinolone absorption in the gastrointestinal tract. The presence of divalent ions in urine (for example Mg^{2+}) can also contribute to lower solubility of fluoroquinolones in urine in comparison with plasma [1].

Sodium bicarbonate, potassium citrate, ferrous sulphate, magnesium trisilicate, calcium carbonate and aluminum hydroxide co-administered with ofloxacin and pharmacokinetics of ofloxacin in healthy human volunteers have been investigated in saliva and urine. Administration of Al^{3+} (aluminum hydroxide) decreased the values of these parameters. Al^{3+} also influenced negatively the absorption of ciprofloxacin. In vitro studies in an artificial gastric juice indicate that Fe^{3+}, Al^{3+} and Ca^{2+} reduce the bioavailability of ofloxacin. This effect was explained by its complexation with the metal ions in question [4].

Sometimes metal ion complexation of a quinolone may lead to compounds more soluble in water and other polar solvents than the free quinolones. Because Mg^{2+} complexes with quinolones are more soluble than the free quinolones, complexes can be administered by injection both subcutaneously and intramuscularly, with low local irritative effect and a rapid absorption in the circulation stream [10, 20].

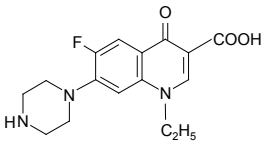
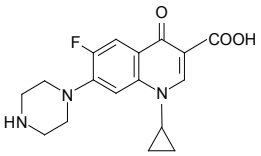
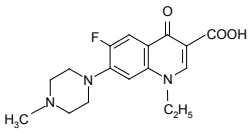
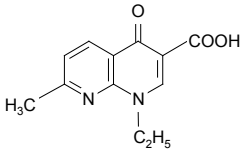
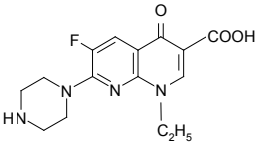
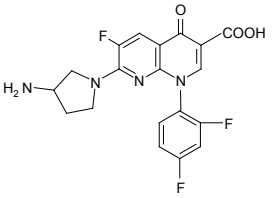
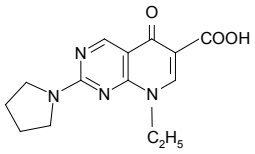
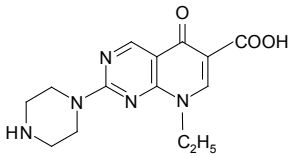
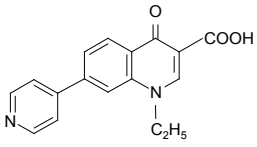
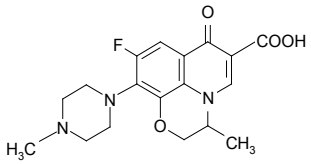
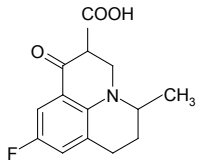
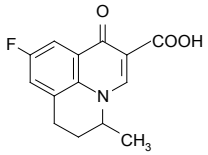
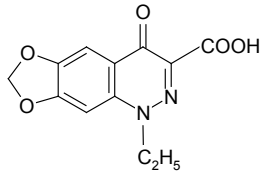
4. Activity of quinolone complex forms

Some complexes between metals and quinolones have been successfully tested for their antibacterial activity:

Ciprofloxacin. Dilip KS et al. [23] studied the mixed complex of Cu^{2+} with ciprofloxacin and phenantroline, and found out that it presents a significant increase in antibacterial activity against the species Mycobacterium smegmatis in comparison with the free ciprofloxacin. This effect is explained by facilitation of the intracellular transport of the complex, while Cu^{2+} can be easily reduced to Cu^{+}, which is lethal to microorganisms.

LMM Vieira et al. [13] studied complexes of Pt^{2+} and Pd^{2+} with several fluoroquinolones including ciprofloxacin. These complexes presented good activity on the species Mycobacterium tuberculosis $H_{37}Rv$. Complexes of Fe^{3+} with ciprofloxacin were also synthesized, their antimicrobial activity was tested and found to be comparable to the free ciprofloxacin. The advantage is that these metal complexes showed no toxicity on experimental animals [24]. Patel et al. proved that complexes of ciprofloxacin with metal ions increase the antibacterial activity against the species Escherichia coli, Pseudomonas aeruginosa, Streptococcus aureus, Bacillus subtilis, Serratia merscences, this phenomenom being closely related to the interaction with bacterial DNA [25].

Table I. Representatives of the quinolones class

Quinolones		Representatives		
		Norfloxacin	Ciprofloxacin	Pefloxacin
Group I	I a. Quinoline			
	I b. Naphtiridine	Nalidixic acid	Enoxacin	Tosufloxacin
				
	I c. Pyrimidine-pyridine	Piromidic acid	Pipemidic acid	Rosoxacin
				
Group II		Ofloxacin	Flumequine	Ibafloxacin
				
Group III		Cinoxacin		
				

Norfloxacin. Complexes of norfloxacin obtained with Fe^{3+} and Zn^{2+} showed an increase antibacterial activity against Escherichia coli and Bacillus dysentheriae comparatively to free norfloxacin [13]. The complex formed between norfloxacin and Ag^{+} ions can be used to treat bacterial infections in severe burns [16].

N-propyl-norfloxacin and propyl-norfloxacin. Nine metal complexes were obtained between N-propyl-propyl-norfloxacin, propyl-norfloxacin and VO^{2+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Mo^{2+}, Cd^{2+}, UO_2^{2+}. Antimicrobial activity of the complexes did not improve when tested on three different microorganisms in comparison to the free propyl-norfloxacin, with one exception UO_2(propyl-norfloxacin)$_2$, which proved to be more potent against Staphylococcus aureus [26].

Sparfloxacin. The product obtained by complexation between Co^{3+} and sparfloxacin has a higher antimicrobial activity on some pathogenic bacteria in comparison with free sparfloxacin. Also the compound obtained by complexation between Pt^{2+} respectively Pd^{2+} and sparfloxacin showed a good activity against Mycobacterium tuberculosis H_{37} Rv [13, 27].

Enrofloxacin. In general, metal complexes of enrofloxacin present an equal or increased antimicrobial activity then the free enrofloxacin. The best antimicrobial activity of the studied complexes was exhibited by the complex Fe(enrofloxacin)3 against Eserichia coli and Pseudomonas aeruginosa. [11, 28]

Enoxacin. Antimicrobial activity of the complex between Fe^{3+} and enoxacin decreases, which attracts lower therapeutic efficacy. The Ni^{2+} complex exhibited an increase of the antimicrobial effect against all the test strains except Staphylococcus aureus. The Mn^{2+} complex showed improved activity against Staphylococcus aureus and Bacillus subtilis,while the Cu^{2+} complex proved to be more active against Citrobacter and Staphylococcus aureus. Mn^{2+} and Cu^{2+} complexes exhibited potential to mediate antiinflammatory response [21].

Pipemidinic acid. Pipemidic acid complexes with $^{+}$, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Mo^{2+}, Cd^{2+}, UO_2^{2+} have shown diverse biological activities compared with the free pipemidic acid. The best antimicrobial activity was provided by UO_2(pipemidic acid)$_2$ against the three tested microorganisms (E. coli, P. aeruginosa and S.aureus) [12].

5. The research of the antitumor effect of quinolone complexes with metals

The clinical use of platinum compounds was limited by the development of tumor resistance to the drugs and by their side effects that occur following administration. These limitations have led to research in order to find non-platinum anticancer agents, more active, less toxic, containing other transition metals. Complexation with ruthenium was found to be very promising, with pharmacokinetic properties similar to platinum anticancer agents, but with less toxicity. A number of ruthenium complexes with quinolones have been synthesized and characterized (oxolinic acid, pipemidic acid, enoxacin, levofloxacin) [29].

A complex of Cu^{2+} with N-propyl-norfloxacin in the presence of 1,10-phenantroline was also synthesized and characterized, and its biological properties as antitumor and antimicrobial agent were studied. The results obtained are encouraging for cancer chemotherapy [30].

6. Metal complexes role in the mechanism of action of quinolones

The formation of complexes between quinolones and divalent cations play an important biological role. The ability of these substances to interact with some cellular components is mediated by the complexation. It appears that DNA-gyrase cannot bind quinolones in the absence of DNA and the concentration of quinolone bound to DNA is modulated by the Mg^{2+} ion concentration. In addition, some studies have indicated that a bridge with Cu^{2+} or Fe^{2+} [7] complemented the link between fluoroquinolones and DNA.

The interaction with DNA was studied by UV and CD spectroscopy. DNA can provide three distinct sites link (may be a common link, a connection through a phosphate group or interleaved). This behavior is of great importance regarding the role of quinolone in the human body [11].

Co^{2+} complexes with ciprofloxacin were studied in terms of bacterial DNA binding and its cleavage, aiming to understand their mechanism of action and their antibacterial activity [25].

7. Developing new analytical methods based on complexation of quinolones with metals

Complexations with metals show interest in developing new analytical methods for quinolones analysis:

- several methods were developed for determination of six quinolones (ciprofloxacin, norfloxacin, ofloxacin, levofloxacin, sparfloxacin and lomefloxacin) based on complexation with Cu^{2+} and erythrosine. The most sensitive investigated method proved to be RRS (Resonance Rayleigh Scattering) [31].
- Ciprofloxacin can be determined using a spectrophotometric method in visible based on its complexation with Fe^{3+}, from the nitrate salt of iron (III) [32].

Conclusion

The research of quinolone complexes with metal ions has made important steps towards the selection of compounds, which exhibit superior bioavailability and minimum side effects. Many studies are focused on explorations of the antimicrobial effect shown by many quinolone complexes with metals and on the identification of new therapeutic utilizations (anti-inflammatory effect, anticancer). At the same time, these studies have helped to decipher the intimate mechanism of action of quinolone on the bacterial DNA. New, simple, cheap and accessible methods have been developed for the determination of quinolone, based on the phenomenon of complexation with metal ions. The 21st century may provide new useful therapeutic aspects on the basis of complexation between quinolones and metals.

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