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# Complex Formation of Gatifloxacin Drug Belongs to Flouroquinolone Family for Biological Study

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IN THIS work, the complexation reaction between La(III) ion and gatifloxacin drug belongs to flouroquinolone family was studied in an ethanolic solution. The coordination behavior of the formed complex was investigated by different techniques. The elemental analysis shows that the metal to ligand ratio of 1:1. The molar conductance measurement display the none electrolytic nature of the complex. The thermal behavior of the complex was investigated and the thermal decomposition pathways have been postulated showing that the final product is metal oxide and eight carbon atoms. Antibacterial and antifungal properties of the metal complex has also been examined against Gram positie bacteria (*Bacillus Subtilis*, and *Staphylococcus aureus*) and Gram negative bacteria (*klebsiella* pneumoniae, and *Escherichia coli* in addition to fungai (*Candida albicans*, *Candida tropicalis*, *Aspergillus flavus*, and *Fusarium oxysporum*). Gatifloxacin drug and its complex were found to be have variable degree of a remarkable biological activity.

**Keywords:** Gatifloxacin; Metal complex; Spectrophotometry; Antimicrobial activity.

## Introduction

Fluoroquinolone family (FQs) is one of the most common pharmaceutical compounds that are gaining increasing interest in the medical and biological fields due to its high efficiency as one of the synthetic anti-microbial agents that are widely used in many therapeutic purposes [1-4]. Among the medicinal applications of this family, strong immune effects as well as its use as an antimalarial and anticancer agent [5-7]. Depending on the antibacterial activity, and clinical indications, FQs can be classified into four generations [8]. Among the members of the fourth generation group, Gatifloxacin antibiotic with the IUPAC name 1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid (Fig.1) has many distinct properties and applications that qualify it to be one of the most important fluoroquinolone drugs [9-12]. The superior characteristics include the highly activity against gram positive and gram negative bacteria compared with other fluoroquinolones and treatment of respiratory problems such as chronic bronchitis, community acquired pneumonia and acute sinusitis [13-16]. Moreover, gatifloxacin is used very efficiently in the treatment of urinary tract infections, urethral and cervical gonococci infections [17]. The excellent biological applications of The HGAT attributed to presence of the substituted piperazine ring at C7-position and methoxy group at C8-position [18]. The recent studies indicate that the ability of gatifloxacin antibiotic to complexation with several metal ions contributes to enhancing its biological activity [19,20]. Carbonyl and carboxyl groups of the Gatifloxacin ligands are the effective sites to chelation with metal ions to complex formation [21]. List of metal ions that

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contributed to the formation of complexes with Gatifloxacin drug contains as example, Zn(II). Co(II), Cd(II) and Cu(II) [22-24]. Despite the tremendous importance of the lanthanide metal ions, no studies were found regarding its complex formation with Gatifloxacin antibiotic ligand. The lanthanide compounds are widely used as antiemetic and effective treatment for various types of cancer [25-27]. According to previous points, in the present paper, we describe the syntheses La(III)- complex with gatifloxacin antibiotic drug. The prepared complexes have been characterized by different analytical techniques such as IR, UV, mass spectra, and thermal analysis. The Activity of metal complex against several types of bacteria, and fungi was investigated.

## Experimental section

*Chemicals used*

All used materials were bought from Fluka, Prolabo and Sigma Aldrich Companies and are used without further purification.

*Apparatus*

UV-vis spectrophotometer, model UNICAM used for the absorbance measurements in the range 200–800 nm, Infrared spectra were recorded as KBr disc use a FTIR-IR prestige 21 covering the frequency range 400-4000 $cm^{-1}$. Perkin Elmer analyzer equipment's-Shimadzu was used for thermal study from 50 to 1000 $^{O}C$ under a nitrogen air flow of 50 mL $min^{-1}$ and a heating rate of 10 $^{O}C$ $min^{-1}$. Melting point measurements were recorded using GALLENKAMP melting point apparatus.

## Experimental part

*Synthesis of lanthanum (III) complex*

An equal ratios of ethanolic solution of $LaCl_3.6H_2O$ was added slowly to an ethanolic solution of Gatifloxacin followed by gently stirring with a magnetic stirrer and allowed to reflex for 3 h on water bath where a precipitate was obtained. The precipitated complex was filtered, washed several times with ethanol followed by diethyl ether and dried in vacuum desiccators over anhydrous $CaCl_2$.

*Microanalytical technique*

Elemental analyses (Elemen. Analy. -Vario EL Fab. CHNS Nr.- 11042023) was used to determine the content of carbon, hydrogen, and nitrogen while La - content was determined complexometrically [28].

*Molar conductance measurement*

Molar conductance measurement of the prepared La (III) complex ($1x10^{-3}$ M in DMF solvent) was measured at ambient temperature by JENWAY 3450 pH & Conductivity meter (JCM-3450).

*Anti-microbial study*

The evaluation of the fourth generation-gatifloxacin antibiotic and its lanthanum complex as anti-microbial compounds is done using agar well diffusion technique (AWDT) [29,30] by testing their effect and activity against selected types of bacteria of both types (*Bacillus Subtilis* and *Staphylococcus aureus* as a gram positive type and *klebsiella pneumoniae* and *Escherichia coli* as a gram negative type), as well as by studying the extent of their activity against some types of fungi (*candida albicans, candida tropicalis, aspergillus flavus* and *fusarium oxysporum)*. The activity of the samples under study were estimated by measuring the diameter inhibition compared with the standard antibiotic *gentamicin and amphotericin* as a standard for bacteria and fungi, respectively. An inhibition zone diameter over 6 mm indicates that the tested compound is active against the organism under investigation.

## Results and Discussion

*Molar conductance measurement*

A freshly prepared complex solution in DMF indicated that the complex is nonelectrolyte [31]. The conductance value with some physical properties of the complex were tabulated in Table 1.

**TABLE 1. Analytical data and some physical properties of the synthesized metal complex**

| Compound | Color (Yield %) | M.P. (°C) | Elemental analysis, Found (Calcd.) | | | | Λ(μs cm$^{-1}$) |
|---|---|---|---|---|---|---|---|
| | | | C% | H% | N% | M% | |
| **La(III) complex** | Yellow (71) | 227ºC | 37.34))31.71 | 3.46))4.03 | 6.87))6.47 | 22.73))22.4 | **0.77** |

***IR spectra studies***

For the prepared La (III) complex, several observations indicate the occurrence of the coordination bond between lanthanum ion and the carboxylate oxygen of the ligand. First, absence of the characteristic frequency of the carboxylic group of the antibiotic ligand which lie at 1715 cm$^{-1}$and replace it by two very strong distinctive bands at 1568 and 1382 cm$^{-1}$ which can be assigned as asymmetric and symmetric ν ($CO_2$) stretching vibration of ν (O-C-O) s, respectively [32]. Further, shifting the frequency mode of ketone group of the ligand from 1633 to 1620 cm$^{-1}$ in the complex. In addition, a monodentate coordination mode of the carboxylate group can be demonstrated by presence the difference between the frequency of symmetric and asymmetric (O-C-O) (1382- 1568 cm$^{-1}$). Also, the prepared lanthanum complex exhibit a characteristic broad band at 3410 cm$^{-1}$ due to ν (-OH) of coordinated water molecules. Finally, a new characteristic IR band was observed at 445 cm$^{-1}$ corresponded to ν (Li-O) vibration [33-35].

*Electronic spectra*

In the ultraviolet- visible region (200- 800 nm), the electronic spectra of the solutions of antibiotic-HGAT ligand and its complex display presence of the electron transitions π → π* and n → π * for the rings of aromatic hydrocarbons and the groups of (ketone, -NH imine and carboxylic at 220, 290, and 340 nm, respectively [36].

*Thermal analysis*

Thermogravimetric analysis and differential thermogravimetric (TGA and DTG), respectively were performed under nitrogen atmosphere and the heating rate was suitably controlled at 10 °C / min. The results of TG/DTG of the prepared sample showed in Fig.2 and listed in Table 2. For the lanthanum complex, four degradation steps were appeared in the range 33-737 ºC. The maximum temperatures occurred at 75, 281,309 and 344 ºC in the first, second, third and fourth step, respectively. The weight loss in the first step give 18.33 % (18.50% calc.), 9.32% (9.69% calc.), 14.15% (14.05 calc.%) and 19.42% (19.70 calc.%) for the first, second, third and fourth step, respectively. The lost species are ($CO_2$ and $Cl_2$), (HF and $C_3H_5$), ($2H_2O$ (coordinated water) and $3NH_3$ and ($3C_2H_2$ and $CO_2$) for the (First, second, third and last step), respectively. After the deterioration, it was found that the weight loss of the residual is 38.78 % (38.06% Calc,) belonged to presence of lanthanum metal and 8C.

**TABLE 2. Thermal decomposition data of La (III) complexes**

| Compound | steps | temperature / ºC | Degradation range/ ºC | Mass loss% Obs (calc.) | Total mass loss % Obs (calc.) | Assignment | Residue |
|---|---|---|---|---|---|---|---|
| **La(III) complex** | 1 | 75 | 33-243 | 18.33 (18.50) | 61.22 (61.94) | $CO_2$ and $Cl_2$ | La +8C |
| | 2 | 281 | 243-289 | 9.32 (9.69) | | HF and $C_3H_5$ | |
| | 3 | 309 | 289-344 | 14.15 (14.05) | | $2H_2O$ and $3NH_3$ | |
| | 4 | 344 | 344-737 | 19.42 (19.70 | | $3C_2H_2$ and $CO_2$ | |

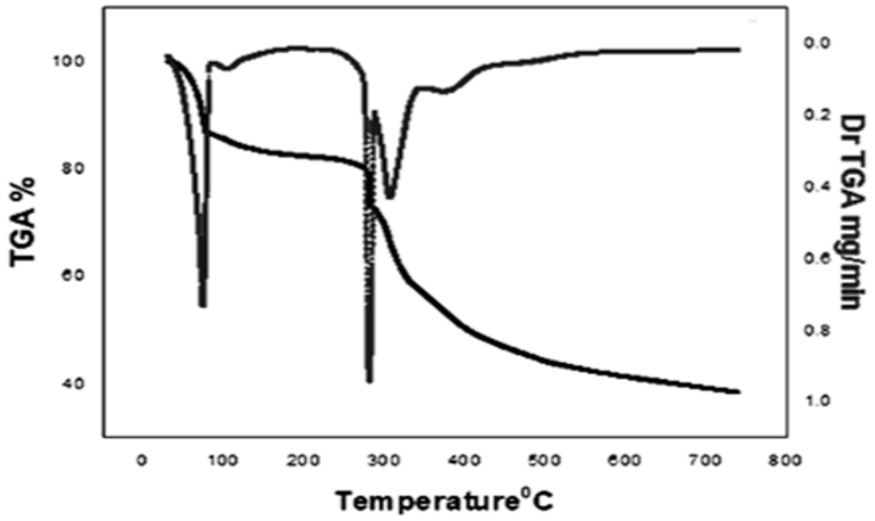


**Fig. 2. TG and DTG curves of La(III) complex**

*Anti-microbial activity*

The biological performance of the gatifloxacin antibiotic drug and its complex with lanthanum ion was evaluated by studying their activity as an anti-microbial against selected types of bacteria and fungi. Anti- bacterial activity was studied against *Bacillus Subtilis* (Gram +ve), *Staph.aureus* (Gram +ve), *klebsiella pneumoniae* (Gram -ve) and *E. Coli* (Gram -ve). While *Candida albicans*, *Candida tropicalis*, *Aspergillus flavus*, *Fusarium oxysporum* were used as types of fungi to examin the prepared compounds as anti-fungal. From the results and obtained values we can observe the higher activity of the prepared complex aginest all types of bacteria, where the values of inhibition zone are (49 mm, 37 mm, 50mm and 29 mm) for the (*Bacillus Subtilis* (Gram +ve), *Staph.aureus* (Gram +ve), *klebsiella pneumoniae* (Gram -ve), and *E. Coli* (Gram -ve)), respectively. On the other hand , the HGAT ligand showed the highest antifungal performance against *Candida albicans* (17 mm) and *Candida tropicalis* (14mm) , while the La(III) complex did not show any noticeable activity against all fungal species. The results of anti-microbial activity are presented in table 3 and displayed in Fig. 3 and 4.

**TABLE 3. Antimicrobial screening results of La(III) complex**

| Compound | Gram – Positive bacteria | | Gram – negative bacteria | | Fungi | | | |
|---|---|---|---|---|---|---|---|---|
| | Bacillus Subtilis | Staph. aureus | K. pneumoniae | E.coli | Candida albicans | Candida tropicalis | Aspergillus flavus | Fusarium oxysporum |
| La(III)- complex | 49 | 37 | 50 | 29 | NA | NA | NA | NA |
| Gentamycin | 26 | 15 | 16 | 22 | - | - | - | - |
| Amphotericin | - | - | - | - | 19 | 21 | 15 | 27 |

***NA : No activity**

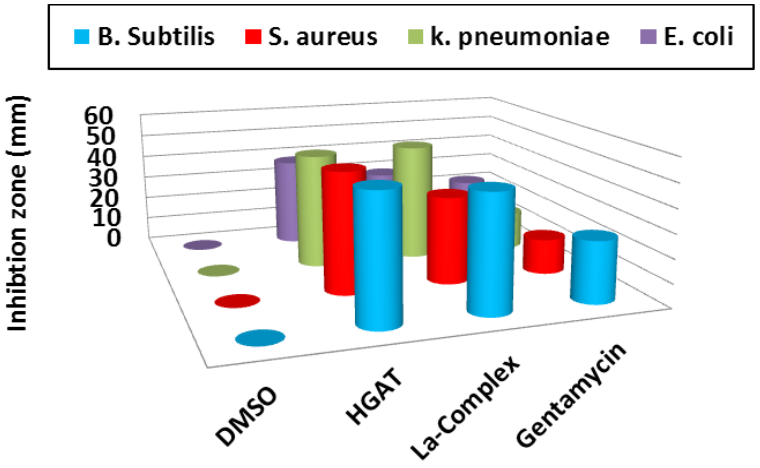


**Fig. 3. Antibacterial activity of HGAT antibiotic ligand and La(III) complex**

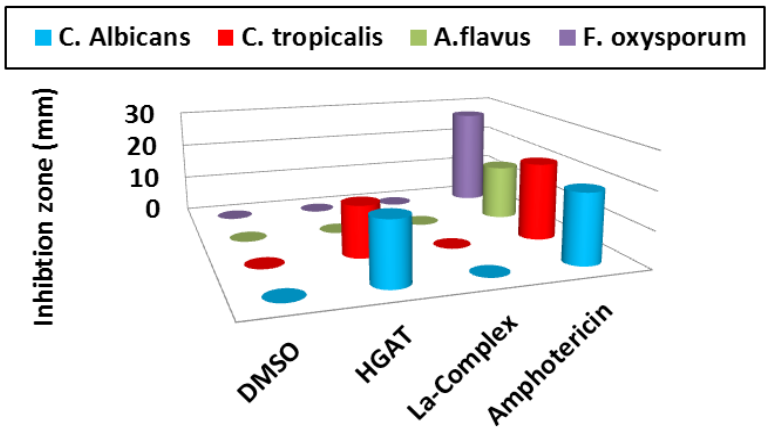


**Fig. 4. Antifungal activity of HGAT antibiotic ligand and La(III) complex**

*Gatifloxacin investigation based on colorimetric assay*

Due to the successful interaction between gatifloxacin and La(III) ion giving La(III) complex, the use of complex formation idea is very useful in estimation of gatifloxacin in its formulations. The earlier studies show that the colorimetric method is based on formation of a colored complexes and hence, this technique can be applied in gatifloxacin investigation. The test of the interaction between gatifloxacin and Fe(III) ion resulted in formation of Fe (III) complex characterize with an orange color. Uv-vis spectroscopy study confirm Fe (III) complex formation. In future, a more work is needed to further study including some factors affecting on complex formation.

## Conclusion

Flouroquinolone family has been highly considered due to its high activity against Gram positie and Gram negative bacteria. Mainly, there are four different classes of Flouroquinolone family. Among the members of the fourth

generation group, Gatifloxacin antibiotic. Gatifloxacin has the ability to form the metal complexes because it has different coordination sites. The utilization of Gatifloxacin as an organic ligand in interaction with La(III) ion is an example of Gatifloxacin metal complexes which allows the progress of metallodrugs. The coordination behavior of the formed complex was investigated by different techniques. Antibacterial and antifungal properties of the metal complex has also been examined against different species of Gram positie and Gram negative bacteria in addition to fungi

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*Conflicts of interest*
The author declares no conflict of interest.

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# تكوين متراكب عقار الجاتيفلوكساسين الذى ينتمي الى عائلة الفلوروكينولون للدراسة البيولوجية

**منى محمد مصطفى[1]، زينب حلمى عبد الوهاب[2]، عايده عبد العال سلمان[2] و وليد محمد عبد الباسط[1]**
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يتضمن هذا البحث استخدام عقار جاتيفلوكساسين الذى ينتمي إلى عائلة الفلوروكينولون في تحضير متراكب اللانثنيوم الثلاثى . تم اثبات السلوك التناسقى لعامل التراكب العضوى فى تكوين متراكب اللانثنيوم الثلاثى بواسطة تقنيات مختلفة. أوضح التحليل العنصري أن نسبة الأيون الفلزي إلى عامل التراكب العضوى هى 1: 1. دلت نتائج التوصيل المولاري أن متراكب اللانثنيوم ذات طبيعة غيرمتأينة أى طبيعة غير الكتروليتية .تم فحص السلوك الحراري لمتراكب اللانثنيوم وتم افتراض مسارات التفكك الحراري التي توضح أن المنتج النهائي هو أكسيد فلز وثماني ذرات كربون. تم أيضًا فحص الخصائص المضادة للبكتيريا والفطريات لمتراكب اللانثنيوم ضد البكتيريا موجبة الجرام (Bacillus Subtilis ، و Staphylococcus aureus) والبكتيريا سالبة الجرام (klebsiella pneumoniae ، و Escherichia coli بالإضافة إلى الفطريات (Candida albicans ،، Aspergillus flavus، Candida و Fusarium oxysporum) وقد وجد أن عقار جاتيفلوكساسين ومتراكب اللانثنيوم يمتلكان درجات متعددة من النشاط البيولوجي الملحوظ.