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NOVEL QUINOLONES METALS COMPLEXES AS IMPROVED MEDICINAL AGENT

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ABSTRACT

Due to the global usage of quinolones, many different bacteria have become resistant to quinolon es. Then, due to the combination of metals, their derivatives need to be prepared and their biologi cal activity against bacteria needs to be improved. In this study, quinolones reacted with essential elements to form metal complexes and thus their activity was increased.

Different spectroscopic techniques, including FTIR, UV, and AAS (atomic absorption spectroscopy), were used to identify new substances. Novel compounds were effectively screened biologically against a range of pathogen groups. After analysis, some of our new compounds were shown to have better anti inflammatory properties compared to the parent compound. These complexes were also found to be less toxic at the same dose.

KEY WORDS: Quinolones; Synthesis; Characterization; Biological activities

INTRODUCTION

Quinolones are commonly employed as antibiotics because broad-spectrum antibiotics are effective against both Gram-positive and Gram-negative bacteria (Psomas & Kessissoglou, 2013).

Since 1962, products containing nalidixic acid have been manufactured.This chemical, which is patented by the American pharmaceutical company Sanofi-Aventis, was initially used to treat urinary tract infections.Broad-spectrum antibiotics are a type of antibiotic.George Lesher discovered the first quinone, nalidixic acid.1-ethyl-1,4-dihydro-methyl-4-oxo-1,8-naphthyridine-

3-carboxylic acid is the property of naphthyridine acid, as shown in Figure 1. It was applied for the first time in 1964 (Buchbinder, Webb, Anderson, & McCabe, 1962).

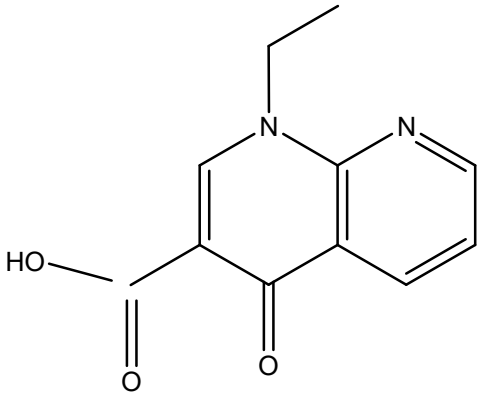


Figure 1 Nalidixic Acid

The most common type of quinolone used nowadays is flouro quinolone. Depending on their antibacterial range and pharmacokinetic characteristics, they are further separated into second, third, and fourth generation categories.

Second Generation
Ciprofloxacin, Lomefloxacin, Norfloxacin, and Ofloxacin are present in this generation. Additionally, it works rather well against Gram-negative bacteria.

Third Generation
Balofloxacine, Goutifloxacine and Levofloxacine are present. Both gram positive and gram negative bacteria are actively opposed by it.

Fourth Generation
These include Moxifloxacin and Saitafloxacin. Both gram positive and gram negative bacteria are susceptible to the long-term effects of these medicines.

The two primary metal chelation sites in quinolone molecules are represented by the carboxyl and carbonyl groups of neighboring functions, which are the most prevalent coordination types in quinolone chelates.Quinolones have the ability to interact with various cations to create organic metallic complexes with special characteristics.M Cu2+, Zn2+, Fe2+, and Co2 (Uivarosi, 2013).

EXPERIMENT

- All of the metal salts were acquired from Merck and are of analytical quality. We didn't purify these salts further before using them. Quinolone was obtained and utilized as such from Welwrd Pharmaceuticals Hattar.
- Under carefully monitored circumstances, reactions were conducted using reflux condensation.
- SENsir IR spectrophotometer's IR spectra
- UV spectra noted at solo beam Germany IRMICO.

- Melting point at gallon kamp apparatus.
- Atomic absorption at shimatzoo 300.
- By using the disc diffusion approach, biological activities under LFC have an efficiency of 99.99%.
- A toxicological investigation was conducted on albino rats.

Syntheses of Quinolone complexes:
Quinolone and metal salt were dissolved in methanol at a 2:1 mmol ratio, then refluxed to generate quinolonemetal scomplexes (Turel, Bukovec, & Farkas, 1996).
After being refluxed for 30 minutes at room temperature, the reaction mixture was left to stand overnight.The precipitated complex was filtered, cleaned with diethyl ether, and allowed to air dry at room temperature with reduced pressure.The union was maintained under typical circumstances.In water and other organic solvents including ethanol, phenylacetone, acetonitrile, and diethyl ether, this chemical is colorful and indecipherable; nevertheless, it may be understood in dimethylformamide (DMF) and dimethyl sulfoxide.

Synthesis of Iron Complex with Norfloxacin
1 millimol of norfloxacin (319 mg) should be dissolved in fifty milliliters of HPLC-grade methanol by means of constant heating and stirring. Similarly, 0.5 millimol of FeCl3.4H2O salt (198 mg) should be dissolved in fifty milliliters of methanol. This mixture should then be supplemented with the above dose of norfloxacin. The solution turns red-yellow right away as a result of complex formation. The product is obtained in powder form by evaporating the solvent at room temperature.

Synthesis Of Copper –Norfloxacin complexes
Norfloxacin (319 mg) mmole was dissolved in 50 ml of HPLC-grade methanol by boiling and stirring the mixture continuously. 0.5 mmol CuNO3.3H20 salt (89 mg), separately dissolved in 50 ml of methanol, was added to this solution. The complex's rapid production caused the solution's color to shift to a light green. Solvent was allowed to evaporate at normal temperature, yielding a powdered product.

Synthesis of Zinc- Norfloxacin Complexes
50 cc of HPLC grade methanol was heated and stirred to dissolve 1 mmol of Norfloxacin (319 mg). This solution was supplemented with 0.5 mmol ZnNO 3.61-120 salt (148 mg) that had been separately diluted in 50 ml of methanol. The complex's evolution caused the result's color to instantly change to white. Solvent was allowed to evaporate at room temperature to produce the product in powder form.

Synthesis Of zinc-levofloxacin complexes
(Weight in Levo mol = 361.36)
One mole of zinc chloride (136 mg) and seventy-four milligrams (two moles) of levofloxacin hemihydrates interacted during an overnight methanol reflux.

Synthesis Of zinc-Gemifloxacin complexes
Levofloxacin hemihydrates (MW = 389.381 g/mol) and zinc chloride (MW = 136 mg) interacted over night in methanol reflux. At first, a brown solution developed. Yellow crystals developed after drying.

Synthesis Of zinc-ciprofloxacin complexes

331.34 g/mol
1.326 gm (four mole) of ciprofloxacin reacted with two mole of zinc chloride 272.4 mg in water (as slightly soluble in methanol) reflux overnight. Complex is soluble in water got concentrated by evaporation of water.
Complex is more soluble then the parent ciprofloxacin

RESULTS AND DISCUSSION

Infra-Redspectrophotometry(IR)

The IR spectra of novel metal complexes that differ from their parent component were confirmed. Using a SENsir IR spectrophotometer, IR spectra were captured between 4000 and 1000 cm-1. The Norfloxacin FTIR spectra. Evidence demonstrating the band located at 1731 cm"' and 1250 cm-' has been assigned to the carboxylic group (C=0) and v(C-O) (Macías, Villa, Rubio, Castiñeiras, & Borrás, 2001). There are no symmetric and a-symmetric vibration frequencies produced by the carboxylic free group. In the field of norfloxacin, the carbonyl group of ketone has the highest value at 1620 cm. Figure 2 (Macías et al., 2001; Perez, Bustos, Taranto, Frías, & Ledesma, 2018).

The Iron-Norfloxacin spectrum is displayed in Fig. 3. The peaks at 1731 cm"' and 1250 cm"' that cause carboxylic group stretching have vanished, as seen by this spectra. Similar to a loaded spring, the free carboxylic group to which metal is bound now exhibits symmetric and asymmetric vibration frequencies. Accordingly, the new ultimate rises at 1464 cm"' in the iron-norfloxacin spectrum. This band can be attributed to the symmetric stretching (ύ) of the ligated (C00)" and is absent in free Norfloxacin (Perez et al., 2018). Another additional peak in this spectra, located at 1630 cm"', is similarly lacking in parent Norfloxacin and is likely due to the ligated carboxylic group's asymmetric stretching (ύ) vibration. Additionally, a new signal at 1516 cm"' in this spectrum is attributed to ligated ring carbonyl v (C=0), (Macías et al., 2001).

Fig 5 shows the spectrum of Zn-Norfloxacin. This spectrum also shows that the peaks responsible for carboxylic group stretching (at1731cm-I and 1250cm-') are disappeared. The original crowning arises at 1479cm-I in this spectrum. This band is absent in the free Norfloxacin and can be assign to symmetric stretching (v,) of the ligated (COO-) (Perez et al., 2018). There is another new peak at 1630 cm-'in this spectrum which is also absent in parent Norfloxacin and can be reasonably assign to asymmetric stretching (va) vibration of the ligated carboxylic group (Perez et al., 2018). This spectrum also shows another new peak at 1528cm-I and is assign to ligated ring carbonyl v (CO) (Macías et al., 2001).

The peaks at 1731 cm-1 and 1250 cm"' that are responsible for carboxylic group stretching have vanished, according to the Chromium-Norfloxacin spectra. At 1479 cm^2, the new peak appears in this spectrum. This band can be attributed to the symmetric stretching (vs) of the ligated (C00)-, as it is absent in free Norfloxacin (Perez et al., 2018). This spectrum shows an additional new peak at 1631 cml, which is also absent in the parent drug norfloxacin and which is plausibly related to the ligated carboxylic group's asymmetric stretching (va) vibration (Perez et al., 2018). Additionally, a new peak at 1520 cm' that is assigned to ligated ring carbonyl v (C=0) is visible in this spectrum (Macías et al., 2001).

Comparison of ciprofloxacin bas spectra with Zn- ciprofloxacin shows peaks that are assigned for carboxylic group stretching at1700cm as in ciprofloxacin is missing in Zn-Ciprofloxacin spectra. The peak responsible for υ (COO) sym at 1300 in Ciprofloxacin spectra has been shifted to some higher value at 1400. Fig 7.

Levofloxacin-Zn complexes spectra also shows that the peaks at 1720 and 1250 cm are missing. Similarly Gemifloxacin zinc complexes the peaks at 1720 and 1250 cm are also missing.

Ultra violet and visible spectroscopic study

The range of wavelengths for the UV spectra was 200–400 nm. A spectrum shows that the ligand and metal complex spectra have not changed significantly. This illustrates that the ligand's structure remains unchanged during complex formation. Fig. 11–14 (Efthimiadou et al., 2006).
When legend attaches to the zinc metal, there are no d-d transitions of electrons observed in the UV scan of the zinc complexes in DMF. Because zinc's d orbital d10 is completely filled, it is therefore impossible to determine the bonding using UV spectrophotometry (Fig).Even though we utilize the exact same concentration, the spectrum only differs in the peak's strength. The variation in the molecular weight of the ligands and complex is the cause of the intensity difference. Ale et al.'s thermal and photochemical analysis of a few zinc-cephalosporin complexes finds similar spectra (Aly, Osman, El-Maali, & Al-Hazmi, 2004).

Atomic absorption analyses

The atomic absorption metal analysis Shimatzoo 300 approved the measurable research.
The comparison of the experimental and theoretical data reveals that all of the metals calculated empirically agree with the theoretical predictions (Table 3).

Antibacterial Activities

Using disc diffusion techniques and a digital Vernier caliper, the zone of inhibition was determined. According to reports, cephalexin ligand exhibits modest efficacy against *Klebseka pneumonia*, but zinc complexes exhibit better activity (Auda, Mrestani, Fetouh, & Neubert, 2008).
Table 2 demonstrated that certain metal complexes are more effective than the original quinolone. The fact that metal campuses are not very soluble in water may account for their reduced efficacy.
Greater activity against *Klebsela pneumonias* is shown by Zn complexes with gemifloxacin and Iron complexes with ciprofloxacin. Fe-Ciprofloxacin also has an effect on *E. coli.*

Toxicity study

Research revealed that metal complexation reduces a drug's toxicity (Auda et al., 2008). Doses are increased from 50 mg/kg body weight given intravenously to determine the fatal dose (LD50). Table 3 data demonstrated that metal complexes are less hazardous than their parent quinolone after administration rates were monitored.

Table 1: Principal vibrational frequency of quinolone metal complexes, υ (cm^{-1})

Compound	υ(C=O)	υ (C-O amide)	υ(COO) Asym	υ(COO) sym	C=O
Ciprofloxacin Zn			1610	1415	1499
Ciprofloxacin	1710		1650	1301	1502
Gemifloxacin Zn			1615	1445	
Gemifloxacin	1720	1260	1510		1510
Levofloxacin zn			1610	1409	1510
Levofloxacin	1719	1249	1619	1411	
Norfloxacin-Fe			1629	1466	1515
Norfloxacin	1733	1252			1621
Norfloxacin Zn			1633	1490	1569

Table 1

(IR spectral data for Quinolone and their metal complexes.)

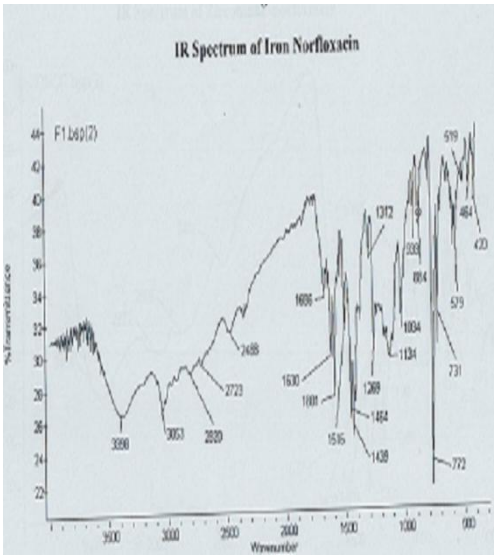


Figure 1 (IR spectra of norfloxacin)

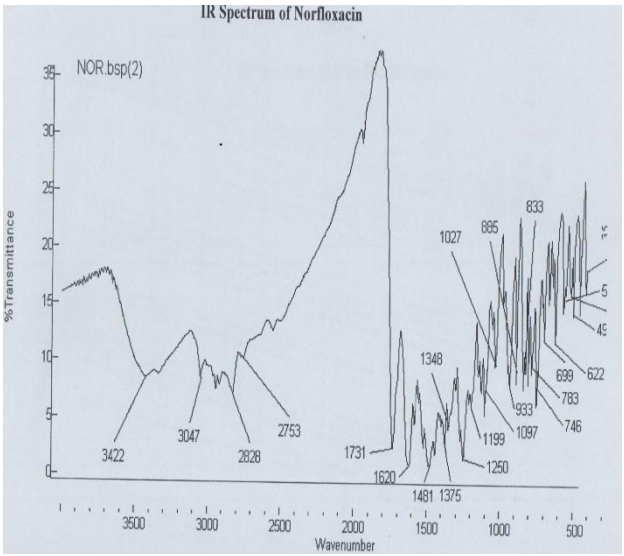
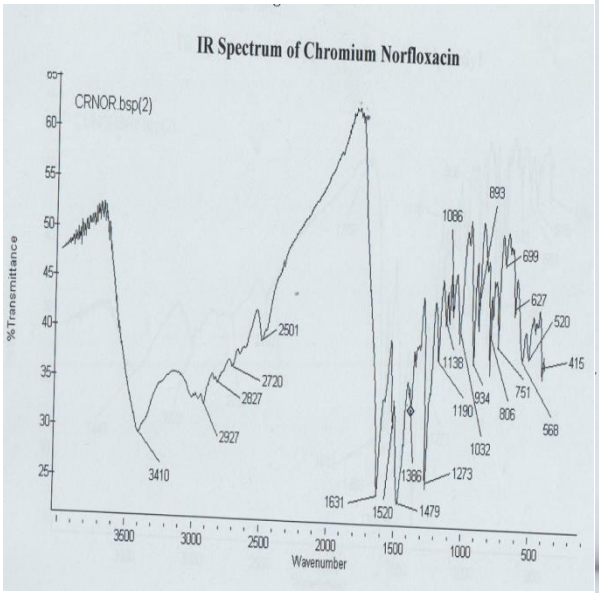


*Figure 2 (**IR spectra of Fe-norfloxacin**)*



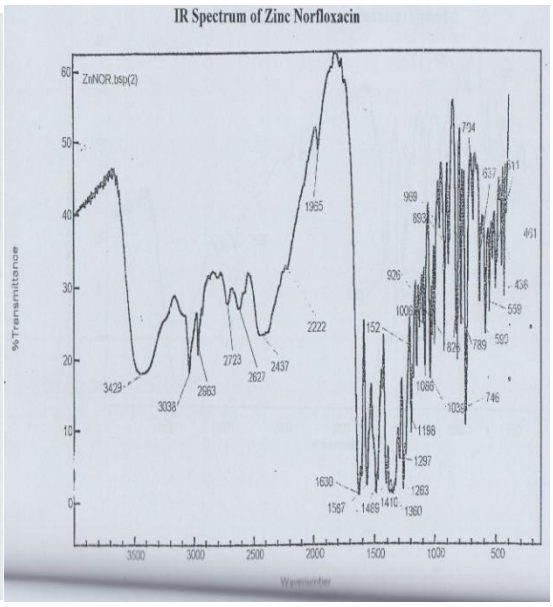
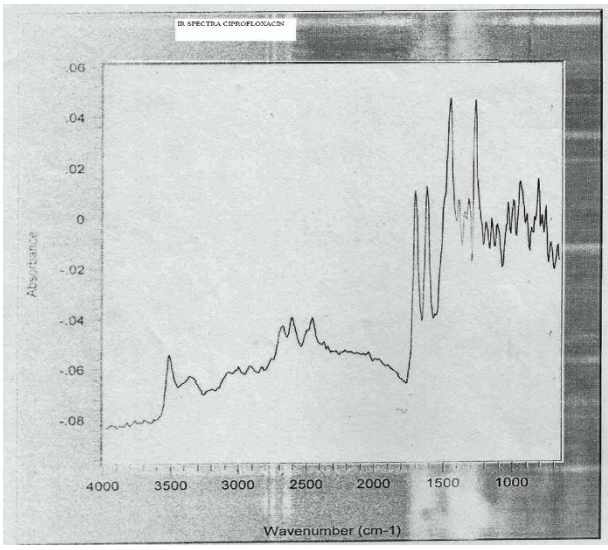


*Figure 3 (**IR spectra of Cr- norfloxacin)*

*Figure 4**(IR spectra of Zn- norfloxacin)***



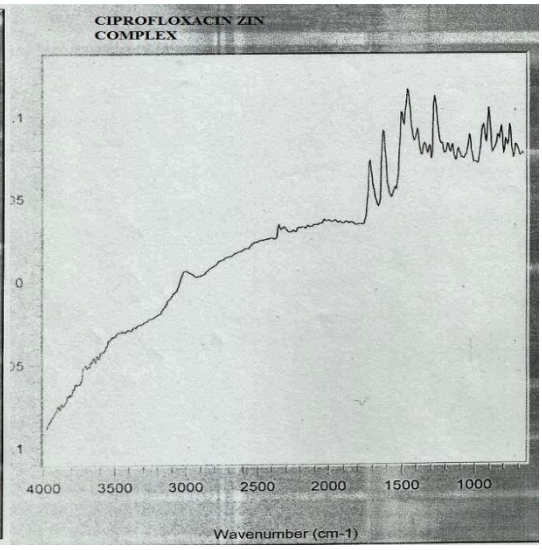


*Figure 5 (**IR spectra of Ciprofloxacin))***

*Figure 6 (**IR spectra of Zn-Ciprofloxacin)***

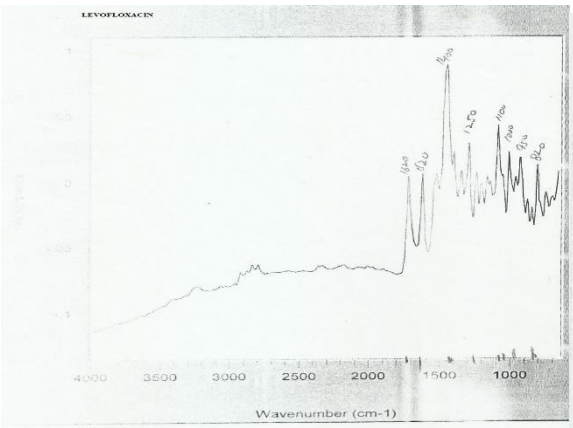


*Figure 7(**IR spectra of Levofloxacin)***

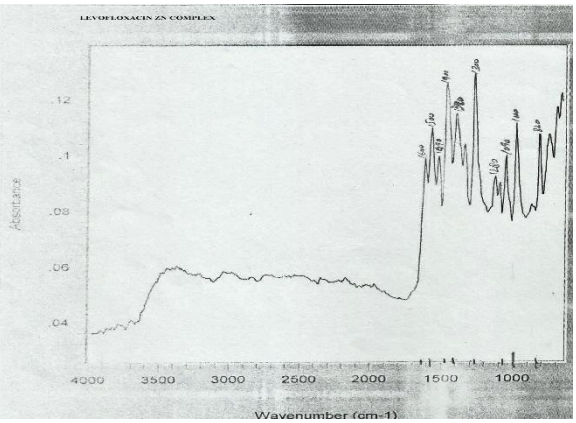


*Figure 8(**IR spectra of Zn- Levofloxacin)***

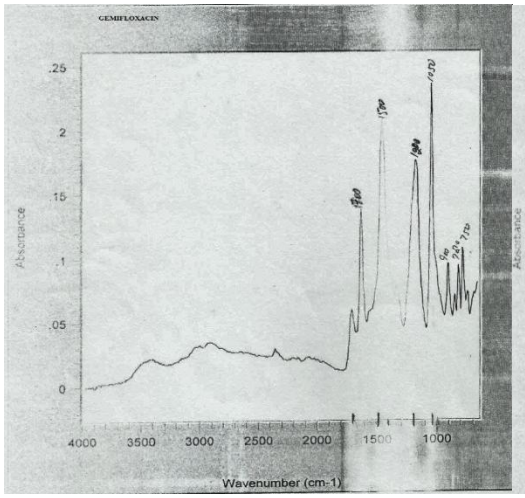


*Figure 9(**IR spectra of Levofloxacin)***

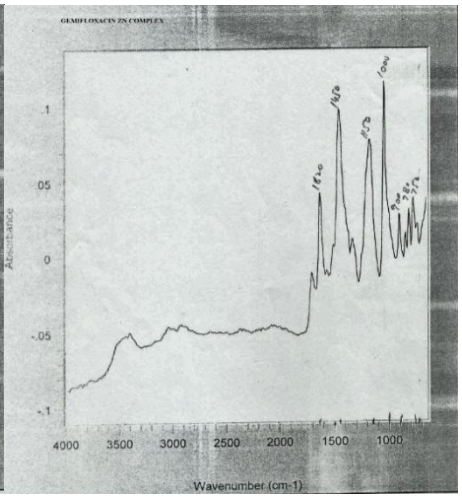


*Figure 10 **(IR spectra of Zn-Levofloxacin)***

(UV spectra data for Quinolone and their metal complexes.)

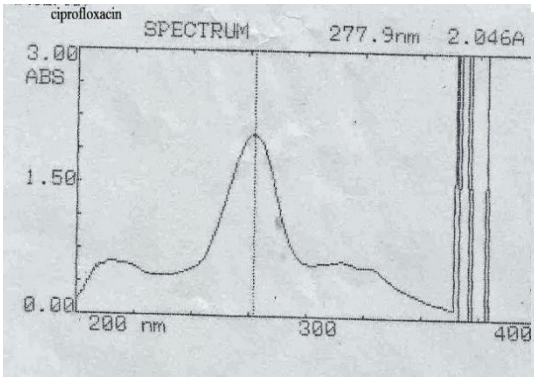


Figure 11UV spectra of Ciprofloxacin)

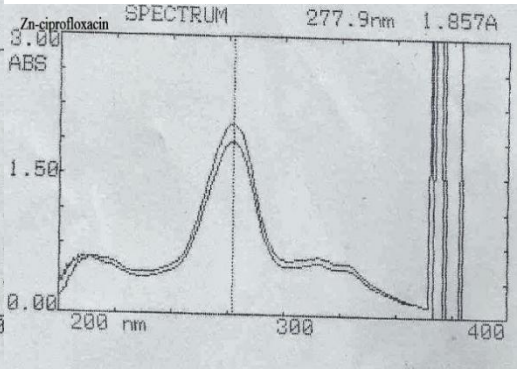


Figure 12(UV spectra of Zn-Ciprofloxacin)

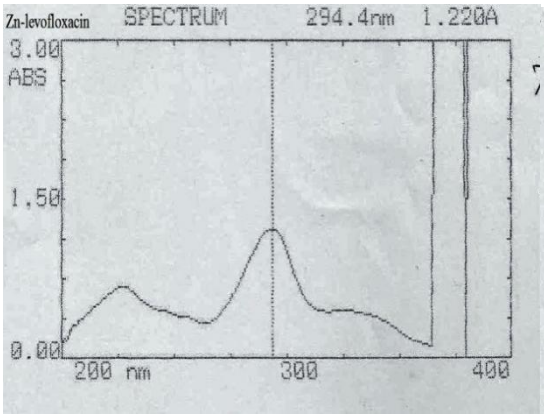


Figure 13(UV spectra of Zn- levofloxacin)

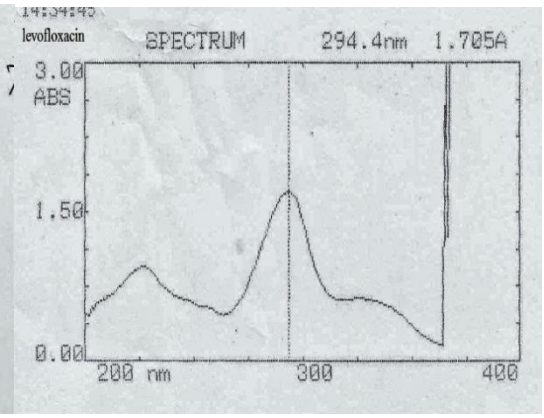


Figure 14(UV spectra of levofloxacin)

Table 2: Zone of inhibition measured in millimeters (Disc with 1 mg in water / disc)

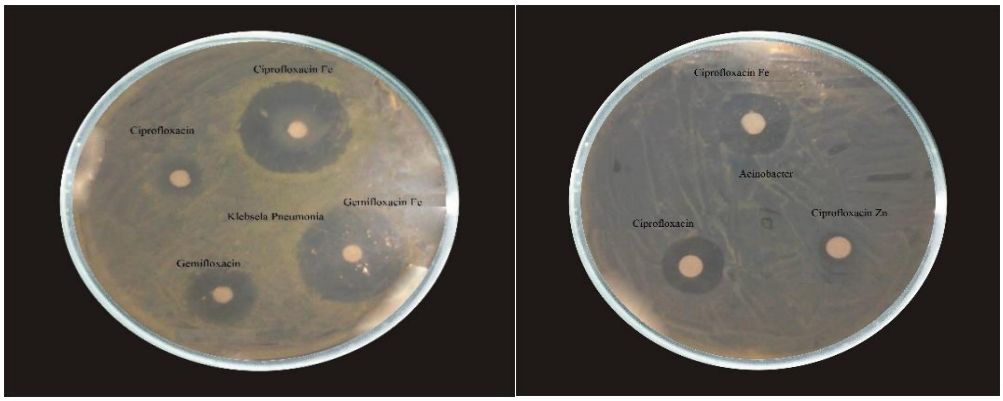
Compounds	*Klebsella Pneumonia*	*Staphylococcus Strains*	*E.coli*	*Acinetobacter*
Ciprofloxacin	13.4	10.6	20.2	14.6
CiprofloxacinZn	12.5	11.8	12.5	10.8
CiprofloxacinFe.	18.81	12.39	25.12	19.5
Gemifloxacin	11.8	20.8	25.11	22.35
GemifloxacinZn	24	21.5	16.45	19.50
Levofloxacin Zn	22.9	20.7	12.1	16.4
Levofloxacin Fe	19.15	21.29	27.15	19.15
Levofloxacin	22.9	20.9	24.5	18.5
Norfloxacin	17	21	22	18
Norfloxacin Zn	14	15	16	16
Norfloxacin Fe	16	19	18	18

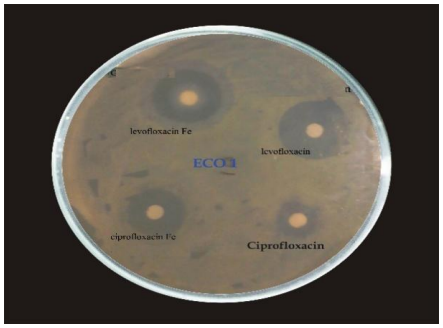
Table 2

Atomic absorption Analyses

Compounds	Molecular weight Gmlmol	Atomic weight of Metal	Theoretical percentage of metal in complex	Experimental results in ppm 0.4mg/ml conc	Experimental %age of metal(20mg/ 50 ml)
$Zn(Ciprofloxacin)_2$	728.2	65.45	9.1	37.15	9.3
$Fe(Ciprofloxacin)_2$	718.65	55.95	7.8	28.25	7.09
$Fe(Gemifloxacin)_2$	834.50	55.90	6.75	26.22	6.65
$Zn(Gemifloxacin)_2$	844.25	65.45	7.8	30.75	7,75
$Fe\ (levofloxacin)_2$	778.6	55.95	7.25	29.1	7.3
$Zn\ (levofloxacin)_2$	788.2	65.65	8.35	32	7.85
Fe ($(Norfloxacin)_2$	694.14	55.95	8.15	35.6	8.9 %
$Zn\ (Norfloxacin)_2$	702.75	65.45	10.3	37.90	9.45%

Table 3 (Elemental studies of Quinolones complexes using AAS for zinc and iron)





(Antibacterial activity of Quinolone and metal complexes.)

Table 3: Values of the quantity that causes half of the rats to die, or LD50

Compound name	**Normal dose MG/KG**	**Lethal dose GM/KG**
Norfloxacin	**50**	**5**
Norfloxacin **Zn**	**50**	**9**
Ciprofloxacin	**50**	**5**
Ciprofloxacin **Zn**	**50**	**7**
Levofloxacin	**50**	**5**
Levofloxacin **Zn**	**50**	**6**

(Toxic study of Quinolone and metal complexes)

CONCLUSION

As Quinolone is highly recommended by physicians today, it is concluded that Klebsella pneumoniae exhibits greater sensitivity against the novel Iron-ciprofloxacin and Zinc-Gemifloxacin. It also demonstrated that metal complexes are less toxic than their parent compounds. Zinc and iron are essential trace elements in the body. FTIR and AAS prove that Quinolone chelates these essential trace elements in a ratio of 2:1. UV spectra indicate that complex molecule is heavier than ligand itself.

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