

# Synthesis, Characterization and Antimicrobial studies of Transition metal complexes of Co(II) and Ni(II) derived from Cefadroxil

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## Abstract

*Cefodroxil (CEFDX) is a broad spectrum cephalosporin belonging to the first generation antibiotic agents. In this study, attention has been paid to the synthesis, characterization and biological evaluation of new Co<sup>II</sup> and Ni<sup>II</sup> complexes of CEFDX. The stoichiometrics and the mode of bonding of the complexes were deduced from their elemental and electrical conductivity measurements. For the characterization of the metal complexes various techniques like FTIR, UV-Vis Spectral study and TG-DSC were used. The composition of the complexes was identified as 1:1 ratio. Based on the study of infrared spectra, coordination through amide group and carboxylate group is proposed. Octahedral structures were proposed for these complexes depending upon the electronic spectral data. The thermal analysis data shows that water molecules have coordinate bonds with transition metal ion. Antimicrobial activity of the complexes was determined using Gram-positive strains of (*Staphylococcus aureus*) and Gram-negative strains of (*Escherichia coli*) bacteria by disc diffusion method. The antibacterial study of ligand and metal complexes were found to be better than the parent antibiotic.*

**Keywords:** Synthesis, characterization, transition metals, antibacterial.

## Introduction

The most important class of drugs against infectious disease caused by bacteria is  $\beta$ -lactamic antibiotics. Cefadroxil (CEFDX) belongs to the first generation of cephalosporin antibiotics<sup>1</sup>. It is effective in the case of sensitive gram +ve and gram -ve organisms and is used similarly in the treatment of mild to moderate susceptible infections and bitter taste. Chemically it is designated as (6S, 7S)-7-[[amino (4hydroxyphenyl) acetyl] amino] -3- methyl- 8 -oxo- 5 -thia-1 azabicyclo [4.2.0] oct-2-ene-2-carboxylic acid<sup>2,3</sup>. Based on literature, it is observed that, the metal complexes of CEFDX may have better therapeutic activity in comparison to uncoordinated by metals antibiotic<sup>4,5</sup>. The aim of the present work is to investigate the behavior of CEFDX upon complexation with metal ions. In this aspect the Co<sup>II</sup> and Ni<sup>II</sup> metal ions have been chosen because of their existence in human body at times. These metal complexes have been found to possess biological activity. Antibacterial activity has also been reported for the Ni<sup>II</sup> complex of drugcefadroxil. The structure is given below in figure 1.

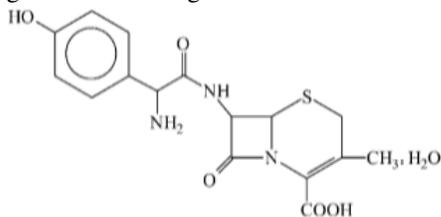


Figure-1

Structure formula of the Cefadroxil (CEFDX) ligand (L)

## Material and Methods

All the chemicals and solvents were used of analytical grade and were procured from Sigma Aldrich in a condition of high purity. Cefadroxil (CEFDX) was obtained as a gift sample from lupin. Elemental analysis (C, H, N) were carried out on elemental and Vario analyzer. The FTIR spectras of the ligand and the complexes were recorded using KBr disc on Bruker FT-IR spectrometer. UV spectras were obtained from Perkin Elmer UV Win Lab spectrophotometer and a simultaneous TG/DSC was recorded on Mettler Toledo model. The antibacterial activity was determined by the disc diffusion method.

**Synthesis of complexes:** For the synthesis of the complexes, 0.02 mol ligand solution was prepared in 80 % Ethanol–water solvent and thereafter the required metal salt (0.01mol) was added. The pH of the solution was adjusted in the range of 8 to 8.5 by adding sodium hydroxide. The resulting solution was refluxed for 4–5 h. The refluxed solutions were kept for some days whereby solid crystalline compounds appeared in the solution, which were filtered, washed with 80 % ethanol–water mixture, dried and weighed.

**Antibacterial Activity:** For antibacterial study of ligand and complex, the disc diffusion method was adopted. For this 200ml of Nutrient Agar Media was prepared. 1 ml of prepared inoculum was poured in sterile Petri dish and then 15 ml of Nutrient Agar Media was also poured into it. The solution was allowed to solidify. After solidification the filter paper disc were placed at the center of the Petri dish of different doses with the

investigation organisms. The plates were incubated for 24 hrs at 37 °C. The inhibition zone was evaluated after 24 hrs.

## Results and Discussion

Complexes of Co<sup>II</sup> and Ni<sup>II</sup> with ligand were found in a stable state at room temperature. They are insoluble in water, but soluble in dimethyl sulphoxide (DMSO). All the complexes were characterized by various spectral and analytical methods. Based on the data of elemental analysis the composition was assigned to the complexes and presented in table 1. The results suggest the non-electrolytic nature of complexes in the solvent.

**IR spectra:** The IR spectra of the complexes have been compared with those of the free ligand in order to determine the coordination sites that may involve in chelation. The same has been presented in figure 2 and its assignments have been presented in table 2. The spectra of Co(II) and Ni(II) complexes are very similar to each other. The IR spectrum of CEFDX shows sharp band at 3507.34 cm<sup>-1</sup> is due to stretching vibrations of OH group of hydroxyl phenyl from CEFDX. This band disappeared in spectra of metal complexes that may point to ionization of the hydroxyl group<sup>6,7</sup>. In addition, the ligand exhibits bands in the wave number regions 3202.90–3024.35 and 3024.35–2838.54 cm<sup>-1</sup> due to the ν(NH) and ν(CONH) groups. These bands remain unchanged on complex formation. It is also pertinent to mention that, the amide group is not affected with all the complexes and thus it remains unchanged in various cases, which strongly indicates non-involvement in chelate ring formation. The band observed at 1685.84 cm<sup>-1</sup> is coming from stretching vibrations of amide carbonyl group.

This band shifted at 1606.09 and 1602.24, cm<sup>-1</sup> in Co(II) and Ni(II) metal complexes. In spectra of Co(II) and Ni(II) metal complexes this ν<sub>as</sub>COO and ν<sub>s</sub>COO band is shifted towards lower wave number. This information suggests interaction between metal ions and carboxylate group of CEFDX. The band observed at approximately 837.74–807.95 cm<sup>-1</sup> and the same was assigned to coordinated water and OH groups. The presence of bands at 638.67–611.80 cm<sup>-1</sup> (M–N) confirms the bonding of nitrogen and oxygen atoms of ligand groups to the metal cation. Thus, the IR spectral results provide strong evidences for the complexation of drugs with metal ions.

**Electronic spectra:** The magnetic moment of the Co<sup>II</sup> complex is 4.03 B.M. is consistent with a high spin octahedral structure. The electronic spectra of Co<sup>II</sup> complex shows two bands of medium intensity at 21,008 and 16,339 cm<sup>-1</sup>, which may be due to partial reduction of Co<sup>II</sup> in its complexes. These bands are assigned to the transitions <sup>4</sup>T<sub>1g</sub>(F) → <sup>4</sup>T<sub>1g</sub>(P) and <sup>4</sup>T<sub>1g</sub>(F) → <sup>4</sup>A<sub>2g</sub>(F)<sup>6</sup>. This indicates a certain distortion from a true octahedral geometry due to the presence of a CEFDX and H<sub>2</sub>O in the moiety of the complex. The magnetic moment of the Ni<sup>II</sup> complex has been found to be 3.34 B.M. which is within the range of values corresponding to distorted octahedral geometry. The absorbance spectra of Ni<sup>II</sup> complex are consistent with this proposal. The appearance of three bands at 13,227-18,870 cm<sup>-1</sup>, <sup>3</sup>A<sub>2g</sub>(F) → <sup>3</sup>T<sub>1g</sub>(F) and 23,825-33,470 cm<sup>-1</sup>, <sup>3</sup>A<sub>2g</sub>(F) → <sup>3</sup>T<sub>1g</sub>(P) were found supportive and consistent with this proposal. The (U.V–Vis) spectra for Co<sup>II</sup> complex is shown in figure 3 and the absorption data for the complexes are given in table 3.

**Table-1**  
Elemental analysis data and some physical properties of cefadroxil and its metal complexes

Empirical formula of Ligand/Complex	Molecular Weight (g/mol)	Colour	M.P. (°C)	Elemental analysis % found (calculated)			
				C	H	N	Metal
[(L)]	363.389	Off white	197.64	42.28	4.32	8.15	-
				41.58	4.35	8.47	-
[Co(L).(H <sub>2</sub> O) <sub>2</sub> ]	511.56	Dark purple	330.35	40.39	4.10	8.35	11.32
				40.02	4.01	8.29	12.20
[Ni(L).(H <sub>2</sub> O) <sub>2</sub> ]	512.08	Light green	340.42	41.40	4.57	9.09	12.92
				41.32	4.39	9.25	12.60

**Table-2**  
Infrared stretching frequencies (cm<sup>-1</sup>) of the various functional groups of ligand and its metal complexes

Ligand /complexes	ν(OH)	ν(N-H)	ν(C=N) β-lactum	ν(C=O) β-lactum	ν <sub>asym</sub> (COO)	ν <sub>sym</sub> (COO)	ν(M-O)	ν (M-N)
[(L)]	3507s	3202b	1352m	1757s	1562b	1396s	-	-
[Co(L).(H <sub>2</sub> O) <sub>2</sub> ]	3367b	-	-	-	1509m	1382m	837m	638m
[Ni(L).(H <sub>2</sub> O) <sub>2</sub> ]	3387b	-	-	-	1512m	1385m	838s	644b

ν<sub>as</sub> asymmetric stretching; ν<sub>s</sub> symmetric stretching; s strong; m medium; w weak; b broad.

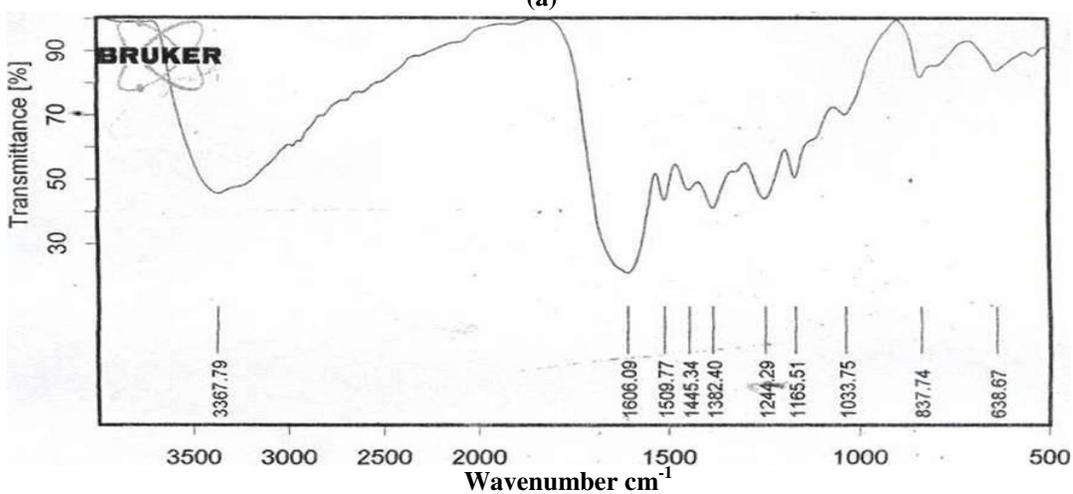
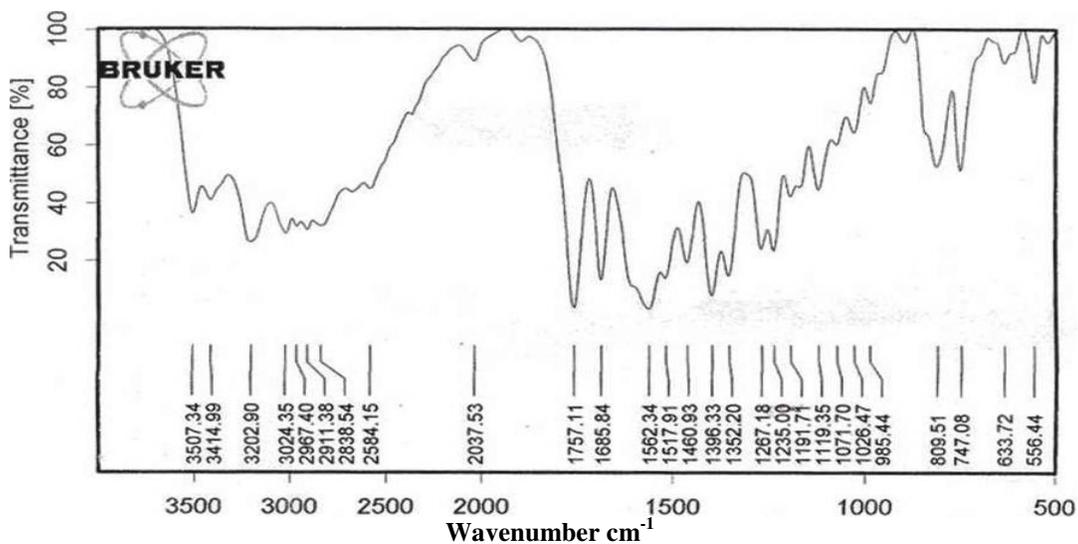


Figure-2  
The infrared spectra of (a) CEFDX and (b) CEFDX-Co(II) complex

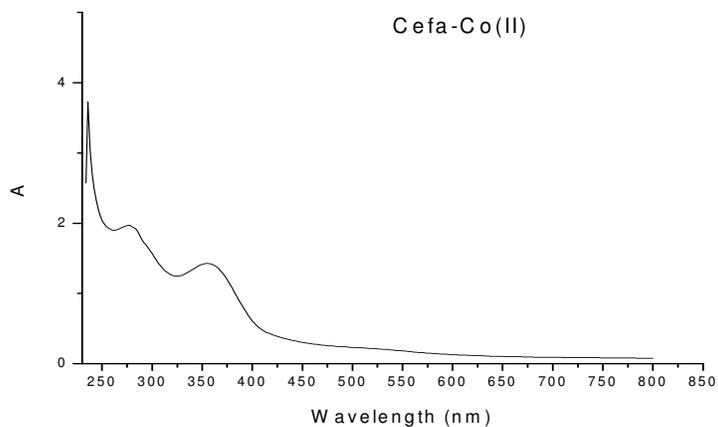


Figure-3  
CEFDX-Co<sup>II</sup> complex

**Thermogravimetric analysis:** Thermal analyses of drug CEFDX and its complexes were carried out by the TG-DSC technique in the temperature range 50-800°C with a sample heating rate 10°C/min in nitrogen atmosphere. The experimental results revealed that the degradation occurred in multiple stages, followed by a complex mechanism. The simultaneous TG-DSC thermogram of the drug CEFDX is shown in figure 3(a). The TG curve follows the decrease in sample mass with increasing temperature. In the simultaneous TG/DSC curve, CEFDX show a sharp exothermic peak at 209 °C that corresponds to the thermal decomposition.

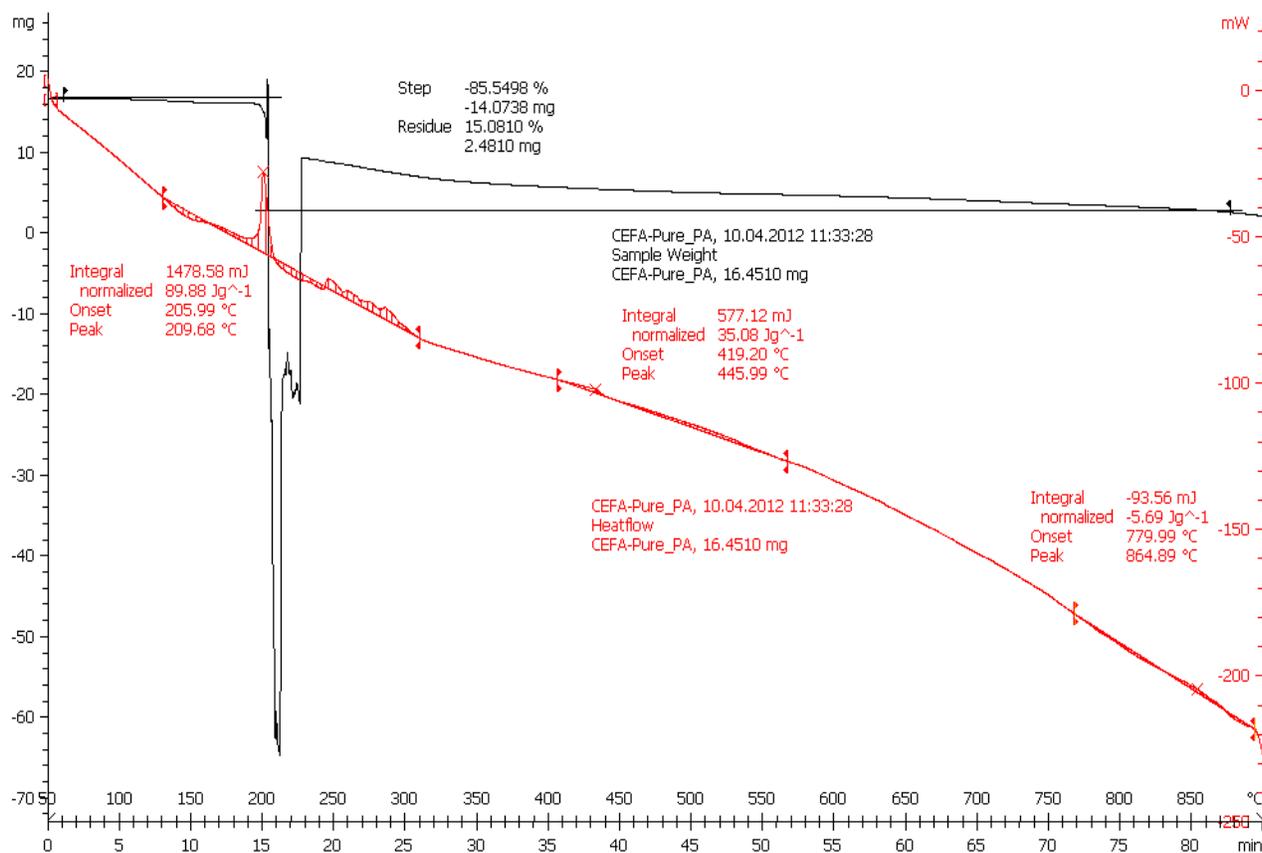
In the thermal decompositions of the Co(II) and Ni(II) complexes (figure 3(b) and (c)) the weight-loss step between

100-300°C may correspond the elimination of coordinated water molecules. The weight-loss step between 350-500 °C may be attributed to the loss of organic moiety of the complex molecule. The final decomposition continues till 800°C and on further increasing temperature. No weight loss was observed during this period, which may be attributed to formation of stable metal oxide<sup>4,8</sup>.

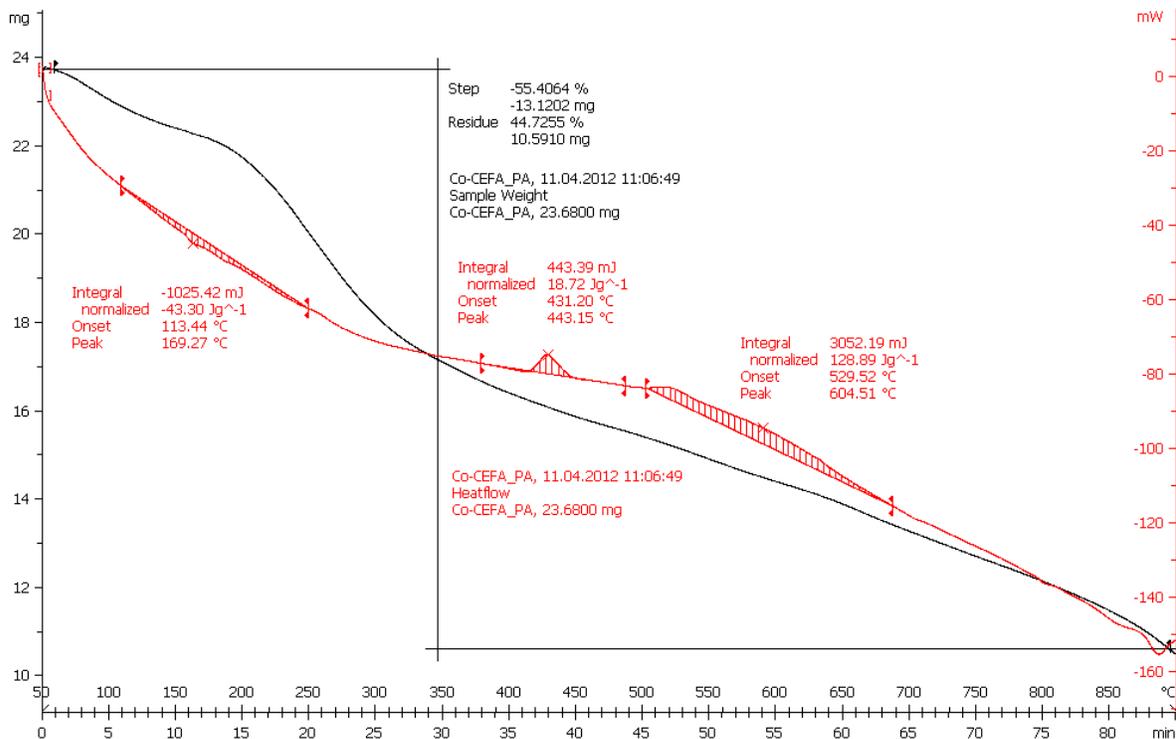
The TG-DSC results of both drugs and its metal complexes reveal that all the complexes followed the same pattern of thermal decomposition. The disappearance and shifting of endothermic or exothermic peak of both drugs with respective loss of mass with different temperature range proves that a complex was formed between the two substances.

**Table-3**  
**Electronic spectral data and magnetic moments values of the ligand and its complexes**

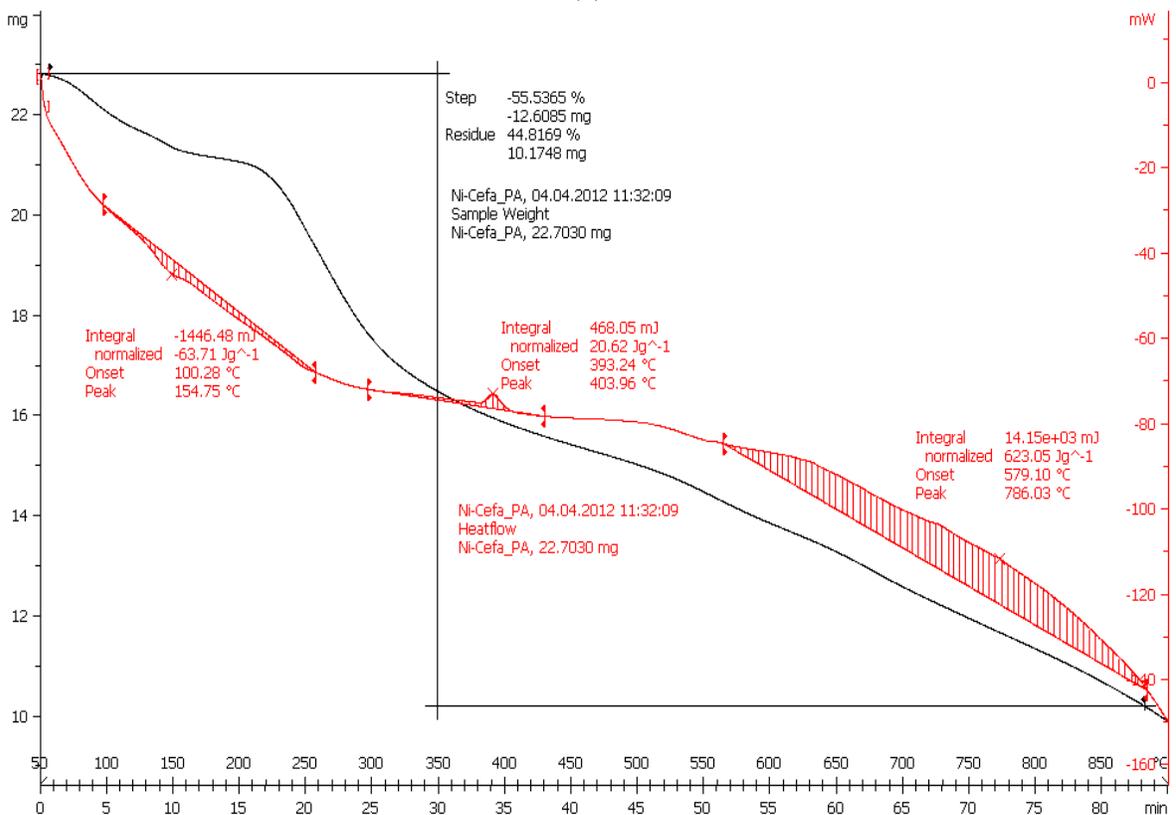
S. No.	Complex	Magnetic Moment $\mu_{\text{eff}}$ (B.M.)	Band Position (cm <sup>-1</sup> )	Possible Assignments
1	[Co(L).(H <sub>2</sub> O) <sub>2</sub> ]	4.03	16,339. 21,008	<sup>4</sup> T <sub>1g</sub> (F) → <sup>4</sup> A <sub>2g</sub> (F) <sup>4</sup> T <sub>1g</sub> (F) → <sup>4</sup> T <sub>1g</sub> (P)
2	[Ni(L).(H <sub>2</sub> O) <sub>2</sub> ]	3.34	13,227 -18,870 23,825-33,470	<sup>3</sup> A <sub>2g</sub> (F) → <sup>3</sup> T <sub>1g</sub> (F) <sup>3</sup> A <sub>2g</sub> (F) → <sup>3</sup> T <sub>1g</sub> (P)



(a)



(b)



(c)

Figure-4

TG/DSC thermogram of (a) CEFDX, (b) Co-CEFDX and (c) Ni-CEFDX metal complexes.

Based on the above studies, following structure may be assigned to the Co<sup>II</sup> and Ni<sup>II</sup> complexes of CEFDX.

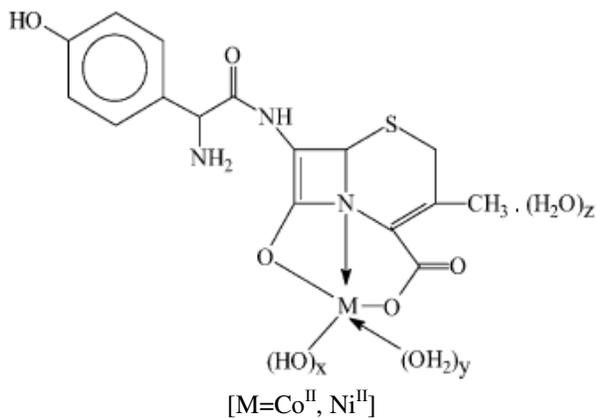


Figure-5

The proposed structure of the complexes: M=Co(II), x=0, y=1, z=0 and Ni(II), x=1, y=0, z=1

**Antibacterial activity:** Antibacterial activities of the ligands and the complexes were evaluated against the *Staphylococcus aureus* and *Escherichia coli*. The inhibition effects of the synthesized complex on the growth of the both microorganisms are shown in table 4.

Table-4  
Biological activity of compound

S N	Ligand/Complex	Microbial species (Zone of inhibition in mm)	
		<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>
1.	CEFDX	16.54	14.86
2.	[Ni(CEFDX) <sub>2</sub> (H <sub>2</sub> O) <sub>2</sub> ]	29.45	28.36

In general the results confirm that, the Ni<sup>II</sup> complex has been found showing good activity against *E. coli* and *S. aureus*. It has been established that the metal complex shows enhanced antibacterial activities as compared to the free ligand<sup>6</sup>. This may be explained by chelation behavior. This chelation increases the lipophilic nature of the central atom, which favour the permeation of the complexes through the lipid layer of the cell membrane and results in enhancement of activity.

## Conclusion

The physio analytical data showed that all the complexes are formed from the reactions of the ligands and the metal salts.

Elemental analysis suggests the metal complexes at the ratio of 1:1 (ML). The complex is probably having octahedral geometry, based on analytical, IR and electrical data. The results obtained by different characterization techniques clearly indicate that the complexation of CEFDX with Co(II) and Ni(II) ions will lead to a better therapeutic efficacy as compared to the parent drug. Antibacterial activity data suggest that the complex is biologically active and showed enhanced antimicrobial activities compared to the free ligand.

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