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Synthesis, spectroscopic characterization and biological applications of Cu(II) and Ni(II) complexes with 2-butyl-4-chloro-5-formylimidazole thiosemicarbazone

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ABSTRACT

Cu(II) and Ni(II) complexes of 2-butyl-4-chloro-5-formylimidazole thiosemicarbazone (L) are synthesized and characterized by using spectroscopic techniques like elemental analysis, FT-IR, mass spectrometry, electronic and EPR spectra. The complexes are found to have characteristic electronic spectra and the geometry of the complexes are identified as octahedron. Both the complexes are found to exhibit similar anti-microbial activity against the gram –ve and gram +ve bacteria. Anti-cancer activity against the cancer cell lines (MDA-MB 231 cell lines) among the compounds studied for % of viability, the inhibition concentration 50 values were shown by Cu(II)-L complex at 80 µg/ml and by Ni(II)-L complex at 100 µg/ml.

INTRODUCTION

Thiosemicarbazones have often been used as chelating ligands in the field of coordination chemistry and their metal complexes have been of great interest to researchers for many years. Thiosemicarbazones and their metal complexes represent an interesting class of compounds with a wide range of analytical and pharmacological applications (Chandra and Anil Kumar, 2007; Sanjay *et al*., 2014; Gonzalez *et al*., 2009). Both the thiosemicarbazones and their metal complexes have been known to possess potent anti-tumor (Jagadeesh *et al*., 2014; Offiong and Martelli, 1997), anti-oxidant (Subba Rao *et al*., 2010; Choudhary *et al*., 2011) and anti-bacterial (zhu Y.K *et al*., 2011) properties. The core structures are found in compounds used clinically, such as the important chemotherapeutic anti-cancer agent, 3-aminopyridine-2-carboxaldehyde-thiosemicarbazone (Triapine) (Yu *et al*., 2006). Particularly the thiosemicarbazones can be used as reagents for Co(II), Ni(II), Cu(II) and Pd(II) and diverse biological activities(Ana *et al*., 2001; Matesanz and Souza, 2007; Mendes *et al*., 2006). Thiosemicarbazones have also been used as analytical reagents for the analysis of metal ions (Prathima *et al*., 2011) and as devices for optical storage and optical information processing (Mostapha *et al*., 2001). Thiosemicarbazones and their metal complexes derived from 2-butyl-4-chloro-5-formylimidazole have been subjected to extensive investigation (Sreenath *et al*., 2014) recently. However, the structural and biological studies of Cu(II) and Ni(II) complexes have not been thoroughly examined.

In Continuation of our research, we report synthesis, IR spectra, UV-vis, EPR spectra and biological properties like anti-bacterial, anti-oxidant and anti-tumor properties of copper(II) and nickel(II) complexes with 2-butyl-4-chloro-5-formylimidazole thiosemicarbazone in this paper.

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EXPERIMENTAL

Chemicals

All the chemicals used in the present work were of analytical grade. The organic solvents were obtained from the commercial sources and used without further purification. 2-Butyl-4-chloro-5-formylimidazole (BCFI) was purchased from Sigma Aldrich. Thiosemicarbazide, copper(II) chloride and nickel(II) chloride were purchased from Sd-Fine chemicals.

Instrumentation

A Shimadzu 2450 UV-visible spectrophotometer equipped with a 1.0 quartz cell was used for the absorbance studies. Elemental analysis (CHN) were performed using an SEM attached Inca Penta FETX3 Oxford instruments. Infrared spectra of the compounds were recorded on a Bruker Alpha−Eco ATR−FTIR (Attenuated total reflection−Fourier transform infrared) interferometer with single reflection sampling module equipped with ZnSe crystal. Mass spectra of Cu(II)-L and Ni(II)-L complexes were recorded in ESI mode using a Bruker HRMS stationed at University of Hyderabad. EPR spectra were recorded on a poly crystalline sample at 298 ºK and a Bruker-ERO 73 instrument equipped with an EMX micro X Source for X band measurement using Xenon 1.15.60 Software provided by the manufacturer.

Synthesis of $Cu(C_9H_{14}N_5SCl)_2$ complex

To an ethanolic solution (10 ml) of 2-butyl-4-chloro-5-formylimidazole thiosemicarbazone (L) (0.001 moles; 0.259 gm), 5 ml of $CuCl_2.2H_2O$ (0.0005 moles; 0.067 gm) dissolved in aqueous ethanol is added under stirring and the resultant solution is refluxed for 5 h in a R B flask. Green coloured solid formed is collected after filtration and washed with hot ethanol. The residue is then dried in a desiccator. The colour of the precipitate: green, yield of the product is 65%, elemental analysis (%) for $[Cu(C_9H_{13}N_5SCl)_2]$: calc. C, 37.08; H, 4.84; N, 24.02: found. C, 37.15; H, 4.76; N, 24.12: HRMS (m/z): 582.06 $[Cu(C_9H_{13}N_5SCl)_2]^+$ ion. IR (cm^{-1}): 3154 br, (ν_{as} NH_2 and ν_s NH_2); 1600 s, $\delta(NH_2)+\nu$(C=N); 1519 w, $\nu_{imidazole}$(C=N); 1237 m, 801 m, ν(C=S); 481 m, ν(Cu-N).

Synthesis of $Ni(C_9H_{14}N_5SCl)_2$ complex

To an ethanolic solution (10 ml) of L (0.001 moles; 0.259 gm), 5 ml of $NiCl_2.4H_2O$ (0.0005 moles; 0.118gm) dissolved in aqueous ethanol is added under stirring and the resultant solution is refluxed for 5 h in a R B flask.

The blueish green coloured solid is collected after filtration and washed with hot ethanol. The residue is then dried in a desiccator. The colour of the precipitate: bluish green, yield: 64%, elemental analysis (%) for $[Ni(C_9H_{13}N_5SCl)_2]$: calc. C, 37.39; H, 4.88; N, 24.22: found. C, 37.56; H, 4.76; N, 23.96: HRMS (m/z): 577.06 $[Ni(C_9H_{13}N_5SCl)_2]^+$ ion. IR (cm^{-1}): 3346 br, 3246 s, (ν_{as} NH_2 and ν NH_2); 1611 w, $\delta(NH_2)+\nu$(C=N); 1201 s, 777 w, ν(C=S); 447 m, ν(Ni-N).

Anti-microbial activity

The synthesized complexes were subjected to in vitro anti-microbial assay against two gram negative anti-biotic resistant bacteria Escherichia coli strains (Mutant and Recipient) and two gram-positive bacteria Bacillus megaterium and Staphylococcus aureus in the present study by the agar disc diffusion method (Asiri and Khan, 2010). The pathogens were subcultured in nutrient agar medium by incubating at 37 ^{0}C for 24 hrs. A bacterial suspension of about 10^{-5} CFU/mL was mixed and poured on to the agar medium in the agar plate maintained at room temperature in a laminar flow cabinet. The minimum inhibitory concentrations of the synthesized compound was predicted by preparing two different concentrations (30 mcg and 60 mcg) of test samples that were previously dissolved in 0.1 percent DMSO. Filter paper discs of about 6.0 mm in diameter were soaked in the samples of varying concentrations and fixed on to the nutrient agar medium. Amoxiclav (30 mcg) was used as a positive control and filter discs wetted with 0.1 percent DMSO were used as negative controls. The results obtained from anti-microbial activity are assessed after incubating the sample for about 24 hrs at 37 ºC. Each experiment is performed in duplicate.

DPPH anti-oxidant assay

The free radical scavenging activity was determined by using 2,2-diphenyl-1-picryl hydrazide (DPPH) scavenging method as described by Brutis and Bucar (Brutis *et al.*, 2011). 10 mg of each synthesized compound was dissolved in 10 mL of 1% DMSO which serves as a stock. Different concentrations of the compound (25-100 µg/ml) prepared were added to 1 ml of 2 mM DPPH dissolved in methanol and incubated for 30 min in dark. The absorbances were taken against blank at 517 nm. The colour change was measured by taking the absorbance values at 517 nm against BHT. Inhibition of DPPH radical by the compound in terms of percent of scavenging activity was calculated by using the following equation.

$$1\ \% = A_{control} - A_{sample} / A_{control} \times 1000$$

Where, $A_{control}$ is the absorbance of the control (containing all reagent except the test compound) and A_{sample} is the absorbance of the test compound.

Anti-cancer activity

Standard MTT assay method was employed to assess the anti-cancer activity against the cancer cell lines (MDA-MB231 cell lines). The MDA-MB231 cells were seeded (1×10^4) in 100 and 200 ml of DMEM (dulbecos modified eagle's medium) in a 96 well plate and incubated at 37 ºC in 5% CO_2 atmosphere. Different concentrations of the synthesized compounds (20-100 µg/ml) in 0.1% DMSO were incubated at 37 ºC for 24 h. After incubation, 0.02 ml of MTT was added to each well and the incubation was extended to another 3h period. The Formazan crystals were dissolved in DMSO (0.15 ml/well) and the plate was read in a micro plate reader at 570 nm and the absorbance value was correlated with the viable cell number (untreated).

Table 1: IR values with assignments for the complexes.

Compounds	ν_{as} $(NH_2)+\nu_s(NH_2)$	ν (NH_2)	$\delta(NH_2)+\nu(C=N)$	$\nu_{imidazole}$ (C=N)	$\nu_{imidazole}$ (C-N)	N (C=S)	N (N-N)	$\nu(C=S)+\rho(NH_2)$	ν (M-N)
Cu(II)-L complex	3154br		1600s	1519w	1327	1237m	1074	801m	481
Ni(II)-L complex	3346br 3246m	3146	1611w	1558m	1307m	1201s	1080s	777w	483

RESULTS AND DISCUSSIONS

Infrared spectral analysis

The infrared spectral study is one of the evidences to determine the mode of coordination. The functional group vibrational band shifts to either lower and higher energies or intensity changes give information about complexation. IR data of the complexes are presented in Table 1.

The absence of ν(S-H) band at 2570 cm^{-1} shows that the ligand is in the thione form in these complexes **(**Yu-Peng *et al.*, 2002). Variation in the stretching frequency of (C=N) band in complexes with the ligand indicates the involvement of azomethane nitrogen in complexation. The two bands appearing in the ranges of 1200-1360 cm^{-1} and 750-900 cm^{-1} (thioamide IV) in the spectrum of the ligand shifted about 15-30 cm^{-1} after complexation, is indicating the coordination of thione sulphur **(**Jhon *et al.*, 2002). Stretching frequency of imidazole (C=N) band deviation about 20-40 cm^{-1} in the complexes specify that it is also involved in the complexation. As azomethane nitrogen, thione sulphur and imidazole nitrogen are involved in complexation, the ligand appeared to have three possible coordination modes of NNS type.

The stretching frequency of (C=N) function is found with the strong and sharp stretching vibrational band at 1609 cm^{-1} coupled with the N-H bond bending vibrations of the free ligand. After complexation, the bands shift to lower energy in Cu(II) (1600 cm^{-1}) but shift to higher energy in Ni(II) complex (1611 cm^{-1}). The ν(C=N) band in the imidazole ring is characterized by a sharp peak at around 1557 cm^{-1} in the case of the free ligand (Leovac *et al.*, 2007) but after complexation it shows 1519 cm^{-1} in Cu(II) complex and 1558 cm^{-1} in Ni(II) complex. The thione (C=S) function of the ligand shows a sharp intense peak at 1231 cm^{-1} but after complexation it shows some characteristic shifts towards 1237 and 1201 cm^{-1} in Cu(II) and Ni(II) complexes, respectively.

The small amount of shift after coordination may be because of the neutral form of the thione group (Krishnan *et al.*, 2010). The three donor atoms involved in bonding with the metal ion resulted frequency changes in the bond order between ν(C=N) and ν(C=S) bands which stands as a characteristic sign for the formation of the complex. Strong band found at 1068 cm^{-1} in the ligand is assigned to ν(N-N).

The increase in the frequency of this band in the spectra of complexes is due to increase in bond strength, again confirming the coordination via azomethane nitrogen [Joseph *et al.*, 2004). In complexes, the presence of new bands at 481 cm^{-1} and 447 cm^{-1} are assigned to ν(Cu-N) and ν(Ni-N), respectively.

Fig. 1 and **Fig. 2** show the FT-IR spectra of Cu(II)-L and Ni(II)-L complexes, respectively. **Fig. 3** shows FT-IR spectrum of ν(M-N) band in the complexes.

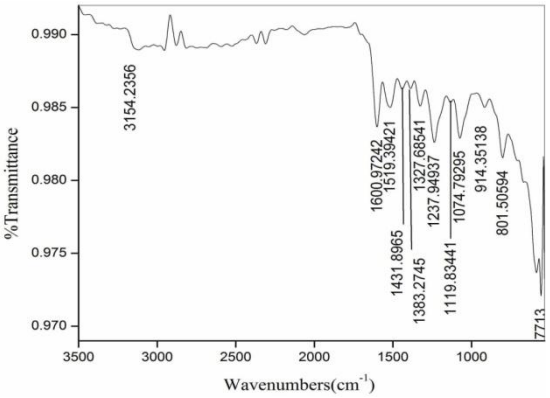

Fig. 1: FT-IR spectrum of the Cu(II)-L complex.

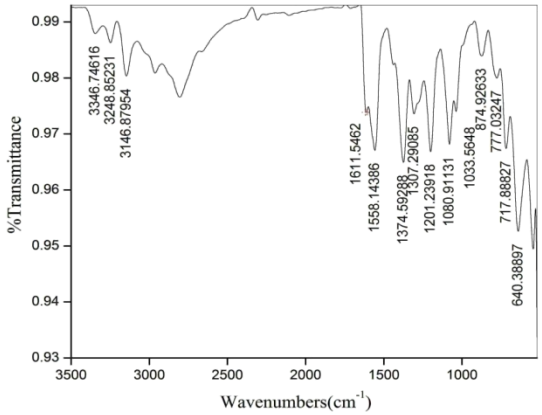

Fig. 2: FT-IR spectrum of the Ni(II)-L complex.

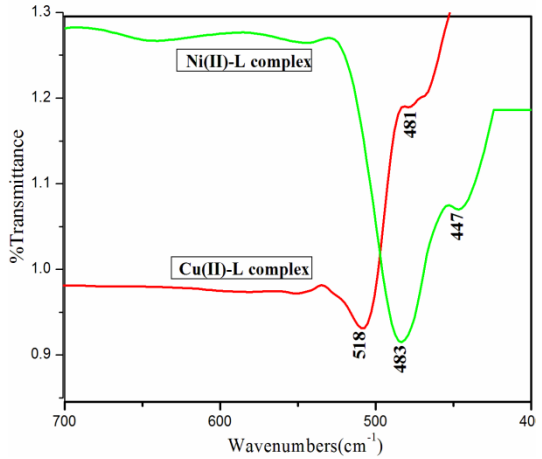

Fig. 3: FT-IR spectra of ν(M-N) band in the complexes.

Electronic spectra

The electronic absorption spectra are often very helpful in the evaluation of results furnished by other methods of structural investigation. The electronic spectra of Cu(II)-L and Ni(II)-L complexes in DMSO are recorded from 400 nm to 650 nm, respectively. The tentative assignments of the significant electronic spectral bands are presented in **Table. 2**.

Table 2: LMCT and n→π* values of complexes

Compounds	LMCT	n→π*
Cu(II)-L complex	23980	26315
Ni(II)-L complex	22935	26666

The complexes have shown typical electronic spectral bands for the metal ions in an octahedral environment. The charge transfer bands are observed around 25000 cm^{-1} and their broadness can be explained due to the combination of S → M, N → M and LMCT transitions (Kala *et al*., 2007).

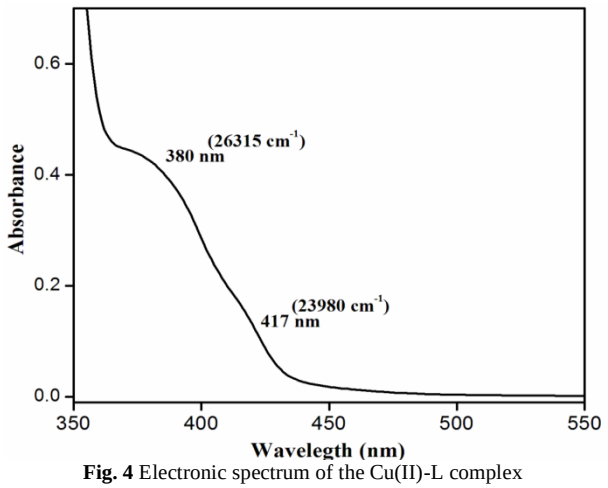

Fig. 4 Electronic spectrum of the Cu(II)-L complex

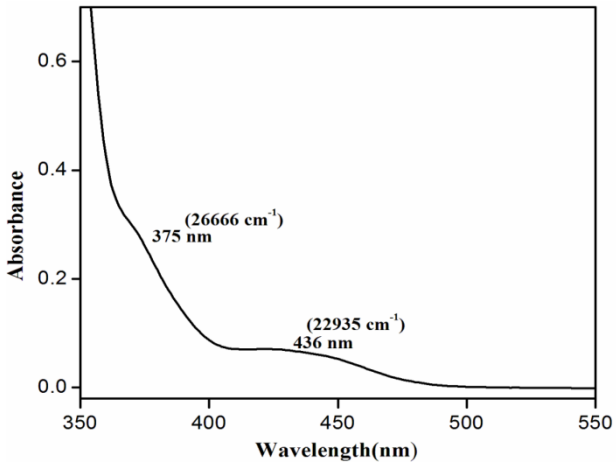

Fig. 5 Electronic spectrum of the Ni(II)-L complex

For the Cu(II)-L complex there are three spin allowed transitions, B1g → A1g, B1g → B2g and B1g → Eg, but it is very difficult to resolve them into separate bands due to very low energy difference among these bands. A weak shoulder at 23980 cm^{-1} is assigned to charge transfer transition. Similarly in Ni(II)-L complex, a shoulder appearing at about 22935 cm^{-1} is probably due to CT band (Leovac *et al*., 2007). The electronic spectra of Cu(II)-L and Ni(II)-L complexes are shown in **Fig. 4 and Fig. 5**, respectively.

EPR spectra

The EPR spectra of the complexes are recorded as polycrystalline sample in Bruker-ERO 73 instrument equipped with an EMX micro X source for X-band measurement spectrometer by using DPPH as the standard. A single non-resolved broad spectrum obtained for the complex at room temperature is attributed for the restricted rotations of the molecule in solid state and due to the negligible levels of zero field splitting (Krishnan *et al*., 2010). The EPR spectrum of Cu(II)-L1 complex exhibits two resonance signals which indicates a tetragonal distorted octahedral geometry. The 'g' values are calculated as $g_{\parallel}$=2.385 and $g_{\perp}$ = 2.067. Cu-L1 complex exhibits $g_{\parallel} > g_{\perp}$ indicating the elongated tetragonal distorted in the octahedral geometry, the $g_{\parallel}$ value more than 2.3 also indicated significant ionic nature in bonding in both the cases and no hyperfine splitting is observed in polycrystalline sample which can be accounted for magnetically non-dilute system and also confirmed the oxidation state of Cu(II) ion. Ni(II)-L1 complex does not show the EPR spectrum at room temperature. For an axially symmetric Cu(II)-L complex, the 'g' values are related by the expression G = $(g_{\parallel}-2)/(g_{\perp}-2)$, which is useful in measuring the exchange interaction between Cu(II) centers in the polycrystalline solid sample. The G value (5.751) greater than 4, indicated that the interaction is appreciably less between the Cu (II) centers. The EPR spectrum of Cu(II)-L is shown in **Fig. 6**.

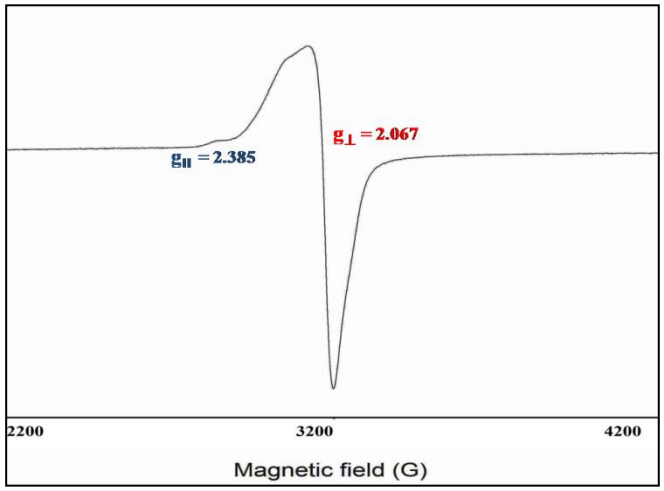

Fig. 6 EPR spectrum of the Cu(II)-L complex

Anti-microbial activity

The synthesized compounds are subjected to anti-microbial activity assay against some human pathogenic microorganisms like *Escherichia coli* strains (Mutant and Recipient), *Bacillus megaterium* and *Staphylococcus aureus* by

using agar disc diffusion method. The complexes have shown almost similar behaviour with the gram +ve and gram –ve bacteria. **Table 3** shows the inhibition zones formed on the agar plates after incubation at 37 ºC for 24 hours.

Table 3: Antibacterial screening data of the complexes.

compounds	Conc. Of compound per disc (mcg)	Gram-negative bacteria		Gram-positive bacteria	
		E. coli (mutant)	E. coli (recipient)	Bacillus megaterium	Staphylococcus aureus
		Zone of inhibition in mm (mean of two replicates)			
Cu(II)-L complex	30	9	9	8	10
	60	17	18	19	21
Ni(II)-L complex	30	8	9	10	11
	60	16	17	19	20
Amoxiclav	30	12	13	12	13

All the complexes show good activity against *Staphylococcus aureus*. The Cu(II)-L complex shows moderate activity against gram +ve bacteria.

Determination of minimum inhibitory concentration (MIC)

The minimum inhibitory concentration (MIC) is the lowest concentration of visible growth after overnight incubation. Minimum inhibitory concentrations are important in diagnostic laboratories to confirm the resistance of microorganisms to anti-microbial agents and also to monitor the activity of the new microbial agents. MIC measurement is performed using a modified agar well diffusion method. Minimum inhibition concentration values are tabulated in **Table 4**.

Table 4: Minimum inhibition zone values of complexes.

Compounds	Gram-negative bacteria		Gram-positive bacteria	
	E. coli (mutant)	E. coli (recipient)	Bacillus megaterium	Staphylococcus aureus
	Zone of inhibition in mm			
Cu(II)-L complex	**6**	**9**	**10**	**6**
Ni(II)-L complex	**5**	**8**	**9**	**7**

Anti-oxidant activity

The anti-oxidant activity of an inhibitor mainly depends on the way it participates in neutralizing the radical centers generated in the biological systems by donating an electron or hydrogen. As reported previously (Patel *et al*., 2005), the structure and properties of inhibitor play a prominent role in showing the anti-oxidant activity. The synthesized complexes, when subjected to anti-oxidant activity assay using DPPH, the following results are mentioned in **Table 5**. The percentage of scavenging activity is found to be increasing with increase in the concentration. DPPH anti-oxidant assay is based on the ability of the compounds to decolourize the pink colour of DPPH solution after minimum period of incubation. The percentage of scavenging activity is measured quantitatively by reading the absorbance of the sample solutions using a spectrophotometer. In the present method, Cu(II)-L and Ni(II)-L complexes are found to be moderate when compared to ascorbic acid.

Table 5: The 50% scavenging activity values of complexes.

Cu(II)-L complex	50
Ni(II)-L complex	50
Ascorbic acid	25

Anti-cancer activity

The synthesized Cu(II)-L and Ni(II)-L complexes are tested for the anti-cancer activity against the cancer cell lines (MDA-MB 231 cell lines). The anti-cancer assay is carried out using the MTT assay method as reported previously (Shibata *et al*., 2002). The percentage of cell viability with respect to each compound is given in **Fig. 7**. Among the compounds studied for % of viability, the inhibition concentration 50 values were shown by Cu(II)-L complex at 80 µg/ml and by Ni(II)-L complex at 100 µg/ml.

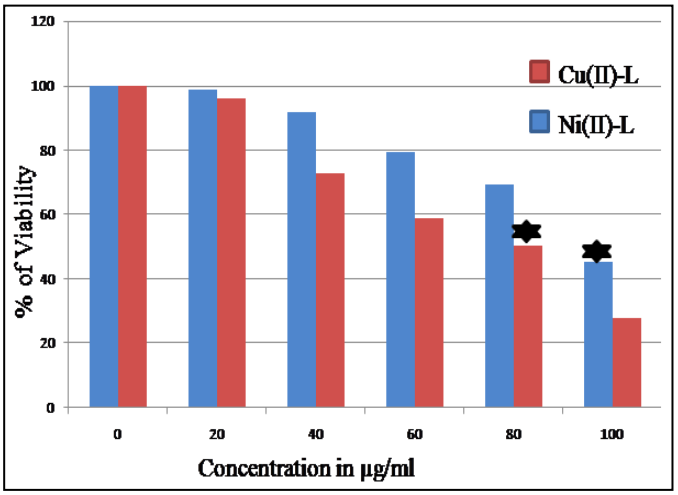

Fig. 7: The percentage of cell viability of Cu(II)-L and Ni(II)-L complexes

CONCLUSION

A strong coordination is found between the ligand and complexes from the IR spectral data. The ligand acted as uninegative species in basic medium to satisfy the primary and secondary valances of the metal ion. A distorted octahedral geometry is assigned for the complexes from the electronic spectra and EPR calculations. Finally, both the complexes were found to show only moderate anti-microbial activity against the human pathogens when compared to the standard amoxiclav. Anti-cancer activity against the cancer cell lines (MDA-MB 231 cell lines) the inhibition concentration 50 values were shown by Cu(II)-L complex is better than Ni(II)-L complex.

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