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Synthesis, characterization and biological studies of sulfadiazine drug based transition metal complexes

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ABSTRACT

The metal complexes of sulfadiazine drug have gained considerable importance due to their pronounced biological *activity. A series of transition metal complexes of the above drug have been prepared and characterized by elemental analysis, molar conductance, electronic spectra, FT-IR, thermogravimetric analysis, proton NMR and cyclic voltammetry techniques. The electronic spectra of the ligand and complexes revealed the octahedral geometry for Ni(II) and Co(II)complexes and distorted octahedral geometry for Cu(II)complex. The corresponding infrared spectra suggest that the ligand behaves bidentate and confirm the presence of water molecules in the coordination sphere. The NMR spectral studies established changes in chemical shift of sulfa-imino proton and free –NH_2group of ligand indicating complexation involving these groups. The thermal stability of the complexes has been studied by thermogravimetric and differential scanning calorimetry, which support the presence of water ligand and metal. The complexes exhibit an octahedral geometry around the metal Centre. The cyclicvoltammetric studies of the metal complexes showed that all but the cobalt complex exhibit an irreversible electron transfer redox processes. The cobalt complex, however, revealed a quasi-reversible behavior. The antimicrobial studies of synthesized metal complexes and ligand were screened for antibacterial activity against bacteria such as Escherchia coli, Staphylococcus aureus, Pseudomonousaureginosa and antifungal activity against P. Aeruginosa and Candida albicans species. Metal complexes of sulfadiazine drug exert a greater effect on the antimicrobial activities than the ligand drug*

Keywords: Sulfadiazine; cyclicvoltammetry; antimicrobial activity; metal complexes

INTRODUCTION

Sulpha drugs are chemotherapeutic agents whose molecular structures contain a 4- amino benzene sulfonamide moiety. Sulfonamide was introduced in therapy about half a century ago for prevention and cure of bacterial infections in humans[1]. Due to low cost, low toxicity, and excellent activity against bacterial diseases, sulfonamides are among the most widely used as antibacterial agents. Sulfadiazine is a sulphanilamide derivative that is used as an antibacterial as well as an antimalarial drug. However, it is mostly used now in combination therapy with pyrimethamine to treat chloroquine-resistant malaria parasite[2-7].

Studies related to new developments in metal based drugs are both promising and of great interest in the development of therapeutic agents[8,9].In thesearch for novel drugs against chloroquine-resistantmalaria parasites, the modification of existing drug by coordination to a metal centre has attracted considerable attentionrecently[10,11].The efficacy of the sulpha drugs can be enhanced upon coordination with a suitable metal ion[12]. The metal complexes of sulfadiazine drug have gained considerable importance due to their pronounced biological activity. The sulfonamides were the first effective chemotherapeutic agents to be employed systematically

for the prevention and cure of bacterial infection in human beings. Compounds containing the sulfonamide group have long been used as drugs for diseases. It has now been observed that some of these drugs show increased biological activity when administered in the form of metal complexes[13]. Thus, the search for metal-based drug with low level of toxicity and high biological activityagainst parasites responsible for malaria has gained prominence[14-15]. However complexes containing sulfa drugs are limited. A few metal complexes of sulfa drugs containing silver,[16-17] cadmium,[18] and mercury[19] complexes of sulfadiazine and cadmium[20-21] complexes of sulfamethazinehavehave been reported. Many sulfonamide derivatives possess antibacterial activity including sulfamerazinewhich has strong antibacterial properties[22]. This consideration prompted us to synthesize a new series of sulfadiazine metal complexes to investigate their antimicrobial activities. The antimicrobial activity of these drugs is believed from the structural resemblance between sulfanilamide group and p-amino benzoic acid where the sulpha drug mimics this metabolite and block folic acid synthesis in bacteria, thereby causing cell death. Many sulfa drugs like sulfadiazine, sulphamethoxazole, sulphamerazine possess SO2NH moiety as an important toxophoricfunction[23]. It has been reported that the biological activity has been increased when administered as metal complexes than as free ligands.The typical application of metal complexes of sulphadiazine has recently revived the usefulness of these compounds in medicine[24]. Indeed metal sulphadiazine complexes are now widely used to prevent bacterial infection during burn treatments. The interest in metal based sulfonamides was stimulated by the successful introduction and preparation of Ag (I) and Zn (II) sulphadiazine complexes to prevent various bacterial infections[25].

This paper deals with the synthesis, characterization, and Biological studies of Sulfadiazine Drug Based Transition Metal Complexes Derived from N, O Bidentate Ligands. Such complexes attract much attention due to their interesting properties.

EXPERIMENTAL SECTION

The drugs (Sulfadiazine [4-amino-N-pyrimidin- 2-yl-benzenesulfonamide]), chemical and solvents (Methanol, Dimethylsulfoxide (DMSO), 10% Potassium hydroxide (KOH) solution and Diethyl ether) used in this study were of analytical grade and used as obtained from Aldrich without further purification. The antibacterial activities of the drug/complexes were assessed by using nutrient agar medium and antifungal activity by using potato dextrose agar medium. The *invitro* antibacterial and antifungal assays were performed by Agar Well Diffusion and disc diffusion method using bacteria such as *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonasaeruginosa*as well as fungi that include Candida albicans and Aspergilustyped cultures as obtained from the American Type Culture Collection. The inoculated organisms in nutrient broth media together with the prepared liquid Mueller-Hinton agar were poured into plates and allowed to solidify. Wells were bored into the solidified agar medium using a sterile 7 mm corkborer[26,27]. The wells were then filled up with the solution of prepared metal complexes and ligand(10ppm) ensuring that each solution does not spill to the surface of the medium. The plates were allowed to stand for 1-2 hours and for the proper inflow of the complex solution into the medium before incubating at 37^{o}C. The plates were observed for the zones of inhibition after 24 hours. The diameter of inhibition zones was measured using a ruler with an accuracy of 0.5mm. A control using only inoculation by DMSO solvent was also carried out.

The elemental analysis (C, H, and N) of the sample was determined at SAIF, Cochin University, Cochin, and Kerala. The metal contents were estimated by standard methods[28].IR spectra were recorded on FT-IRJASCO 460 PLUS spectrophotometer using KBr pellets. AShimadzu UV-3101PC spectrophotometer was used to record UV-Vis spectra using cuvettes of 1 cm path length. Conductivity measurements were carried out in DMSO solutions of complexes with an Elico conductivity bridge type CM 82 using a dip-type cell with a cell constant of 1.0. Cyclic voltammeter measurements were made on Princeton EG and G-PARC model potentiostat. The thermal analyses were performed with a Perkin Elmer Diamond instrument at a heating rate of 5 °C/min under a dynamic air atmosphere (150 ml/min). All complexes were investigated in the temperature range 20-800 °C.

Synthesis of complexes containing Sulfadiazine Drug as ligands:

Synthesis of Mn Complex with Sulfadiazine[$MnC_{20}H_{20}N_{10}S_2O_{11}$] :

To a solution of Sulfadiazine (4-amino-N-(2-pyrimidinyl) benzenesulfonamide), (0.590 g, 2mmol) in 23 ml of methanol was treated with a methanolic solution of Manganese (II) nitrate (0.245 g,1mmol). The reaction mixture was stirred on a magnetic stirrer. The light brown crystalline product formed after 7-8 hrswere collected by filtration. The solid was washed several times with methanol (50 mL), then with diethyl ether (30 mL) and finally dried in a vacuum. Mol. Formula **(**Complex **1)**, Mn $C_{20}H_{20}N_{10}S_2O_{11}$: Mol. Wt. 700.93, M.P. 276◦ C, Yield: 0.192g.Colour: Pale brown.

Synthesis of Co, Ni, Cu and Zn complexes with Sulfadiazine: (2-5):

The metal complexes **(2-5)** were synthesized from the respective precursor Sulfadiazine (SD) by adopting a similar procedure used (with slight modifications) for the synthesis of the above mentioned complexes. Mol. Formula **(**Complex **2)**, $CoC_{20}H_{20}N_{10}S_2O_{11}$: Mol.Wt.704.93,Yield: 0.287 g,Colour-pink; Mol. Formula **(**Complex **3)**, Ni $C_{20}H_{20}N_{10}S_2O_{11}$: Mol. Wt. 704.69, Yield: 0.276 g, Colour -pale green; Mol. Formula **(**Complex **4)**, Cu $C_{20}H_{20}N_{10}S_2O_{11}$: Mol. Wt. 709.55, Yield: 0.215 g, Colour-brown; Mol. Formula (Complex **5)**, Zn $C_{20}H_{20}N_{10}S_2O_{11}$: Mol. Wt. 711.38, Yield: 0.223 g,Colour -dull white.

The formations of the structure of complexes are shown in **Fig.1**

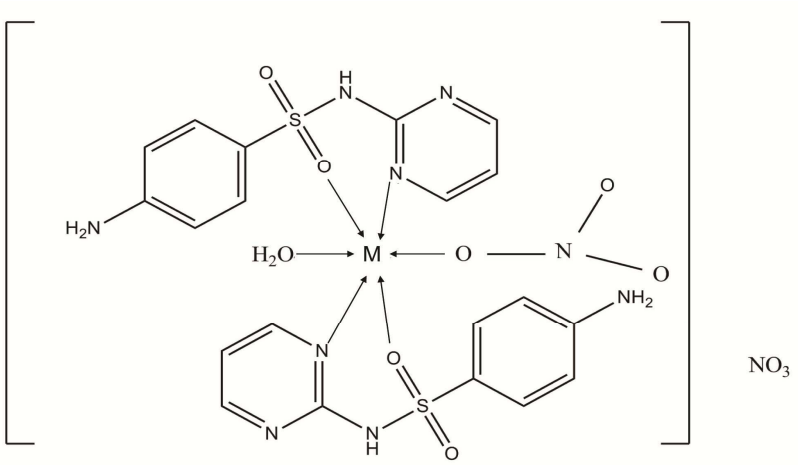

Fig.1
M=Mn, Co, Ni, Cu, Zn

RESULTS AND DISCUSSION

Melting point and conductance

The mononuclear complexes **1-5** were in powdery form. These complexes obtained from nitrates were soluble in organic solvents such as DMSO and DMF. The analytical data (melting point and conductance) obtained are presented in **Table 1**. The analytical data of these complexes showed that the solids are stable and can be stored for months without any significant change in their formulae. The melting points of the synthesized complexes showed higher values (above 265^0C) than the parent ligand (SD). This probably indicates the formation of complexes. The order of melting point of complexes **1-5** is, **1**<**2**<**3**<**4**<**5** which is also the order of increasing atomic number.It may be due to the increasing ionization potential of the central metal ions that enhances the lattice energy as we move from **1** to **5.** The molar conductivity values showed that the complexes are non electrolytes in the solvent DMSO and establishes the stability of the complexes.

Table 1: Analytical data of Sulfadiazine and their Metal complexes

Drug/Complexes	Melting Point	Conductivity
Sulfadiazine	253	0.88
(**1**) $[Mn(SD)_2(H_2O)(NO_3)]$ NO_3	276	0.56
(**2**)$[Co(SD)_2(H_2O)(NO_3)]$ NO_3	290	0.56
(**3**)$[Ni(SD)_2(H_2O)(NO_3)]$ NO_3	281	0.39
(**4**)$[Cu(SD)_2(H_2O)(NO_3)]$ NO_3	310	0.78
(**5**)$[Zn(SD)_2(H_2O)(NO_3)]$ NO_3	347	0.32

Elemental analysis

The purity of the complexes were derived from C, H, N analysis, and the results were found to be in good agreement with the calculated values given as follows: Complex **1** Found: C, 34.04%; H, 2.44%; N, 18.96%; S, 9.05%; O, 24.88%; Mn,7.84%; Mn $C_{20}H_{20}N_{10}S_2O_{11}$calcd: C, 34.24%; H, 2.85%; N, 19.97%; S, 9.13%; O, 25.11%; Mn,8.70% Complex **2** Found: C, 34.95%; H, 2.39%; N, 18.44%; S, 10.1%; O, 23.15%; Co,9.04%; Co $C_{20}H_{20}N_{10}S_2O_{11}$calcd: C, 34.04%; H, 2.83%; N, 19.86%; S, 9.08%; O, 24.97%; Co,9.84%; Complex **3** Found: C, 34.33%; H, 2.39%; N, 19.06% S, 10.1%; O, 24.15%; Ni,8.78%;Ni $C_{20}H_{20}N_{10}S_2O_{11}$calcd: C, 34.06%; H, 2.83%; N, 19.86%; S, 9.08%; O, 24.98%; Ni,9.2% ; Complex **4** Found: C, 32.73%; H, 2.45%; N, 19.00%; S, 9.1%; O, 23.73%; Cu, 9.03% Cu $C_{20}H_{20}N_{10}S_2O_{11}$calcd: C, 33.82%; H, 2.81%; N, 19.73%; S, 9.01%; O, 24.80%; Cu,9.80% Complex **5** Found: C,

32.13%; H, 2.31%; N, 18.18%; S, 7.98%; O, 24.09%; Zn, 10.14% ;Zn $C_{20}H_{20}N_{10}S_2O_{11}$calcd: C, 33.74%; H, 2.80%; N, 19.68%; S, 8.99%; O, 24.74%; Zn, 10.05%.

Electronic absorption

The absorption of electromagnetic radiation in the visible and ultraviolet regions of the spectrum results in changes in the electronic structure of ions and molecules. When a molecule is irradiated with visible or ultraviolet light, it may undergo an electronic transmission during which the molecule absorbs a quantum of energy and an electron is excited from the ground state to a higher energy state. The amount of energy involved in the excitation is proportional to the wavelength of light to cause the transition[28,29]. The electronic spectra of simple ligand and the complexes were recorded in10^{-3} M DMSO solution in the range 200–800 nm.

The ligand exhibits a band at around 275 nm which is due to the intra ligand π -π*transition. The peak at320 nm is assigned ton-π*transition of imine group and the transitions occurring in the range of 275–300nm are due to n -π* transitions of carbonyl group.[30] High spin Mn (II) complexes are weakly coloured due to spin forbidden d-d transition. The d-d bands of Complex **1**are not well defined and submerged in the tail of the strong inter ligand transitions or charge transfer bands. The octahedral cobalt Complex**2** showed two bands in the visible region. The absorption band at 552 nm may be assigned to$4T_{1g}$-$4A_{2g}$transition and a band at 571nm is attributed to$4T_{1g}$ - $4T_{2g}$.The Complex **4** showed a broad band at 760nm attributable to $2E_g$ -$2T_{2g}$assuming the distorted octahedral geometry. The electronic spectrum of Complex **3** displaysthree bands in the visible region. The band at 422 nm is assigned to $3A_{2g}$ -$3T_{1g}$(P),a second band at 455nm is assigned to $3A_{2g}$ -$3T_{1g}$ and a third band, centered at about 542 nm, is attributed to $3A_{2g}$ -$3T_{2g}$.These assignments are in accordance with octahedral geometry of Complex**3.**

FT-IR Spectra

Infrared spectroscopy is used for identifying functional groups in pure organic and inorganic Compounds. The absorption of infrared light brings about the vibration of the molecules[31-36].An infrared spectrum originates from the different modes of vibration and rotation of a molecule. The infrared spectrum of a compound tells about the functional groups that are present in compounds/Complexes. When the ligand forms a complex with a metal ion, there is a shift in the frequency of the region or disappearance of the region indicated that the ligand is involved in the complexation[37].The infrared spectroscopy has been used to study the mode of coordination of Drugs/Ligands and their metal complexes.

The IR spectra of the free ligand and its metal complexes were measured in the region of 4000-400 $cm^{-1}$and proposed assignments for the spectral bands are shown in **Table 2**.Tentative band assignments (cm^{-1})of some characteristic bands of sulfadiazine and their related systems were reported.The IR spectra of all complexes show a broad band at around 3440 cm-1 and a strong band between1610-1655 cm^{-1}.These may be assigned to asymmetric O-H stretching, which indicates the presence of water molecule in the complexes[38].

Table 2: Important infrared frequencies (cm^{-1}) of pure drug and their metal complexes

Assignment	Sulfadiazine cm^{-1}	Complex (1) cm^{-1}	Complex (2)cm^{-1}	Complex (3)cm^{-1}	Complex (4)cm^{-1}	Complex (5)cm^{-1}
νN-H (as) ofNH_2	3425(vs)	3420	3410	3331	3419	3429
νN-H (sy)	3360(vs)	3355	3357	3355	3268	3362
ν(SO_2)asyνa(SO_2-N)moiety	1325(vs)	1342	1411	1370	1408	1350
ν s(SO_2-N)moiety	1155	1126	1133sh	1120	1103	1128
ν(S-N)	945(s)	973,941	1018	979	980	977
ν(C=N)	1652(vs)	1680	1610 sh	1627	1611	1640
	1580(s)	1560				
ν(M-N)	-	682	658	603	602	684
		613				650
ν(C-S)	-	973	-	979	902	977

In the IR spectrum of pure sulfadiazine, intense bands appear at 3423 cm^{-1} and 3360 cm-1, which were assigned to the $\nu_{(NH2as)}$ and $\nu_{(NHsym)}$vibrations[38].The symmetrical 3360 cm^{-1} and asymmetrical 3425 cm^{-1}modes of νa(N-H)and νas(NH2) vibration undergo only slight changes in the spectra of the present Complexes **1-5** indicating that NH2group of free ligand is not affected by coordination to the metal ions. However, the $\nu_{(C=N)}$stretching vibration bands that occur at 1652 and 1580 cm^{-1}in the free sulfadiazine get shifted in all complexes and thus confirm the complexation of the metal ions through thepyrimidinyl nitrogen atom of sulfadiazine. Similarly, in the metal complexes (**Figures.2, 3**)the $\nu_{(S-N)}$ band shifted to higher wave number by about 27-45 cm^{-1}. This observation confirmed the coordination of metal ions to sulfadiazine through sulphonamido N atom. The sharp and intense bands at 1325 and 1155cm^{-1} are assigned to the asymmetric and symmetric $\nu_{(SO2)}$ modes respectively.These bands are shifted to lower values with respect to those of the ligand,suggesting no interaction with the metal ion.As SO_2 group

is not involved in metal bonding, this shift may be due to hydrogen bonding effects. The bands in the 600-680cm^{-1}region for complexes maybe assigned to the ν (M-N) stretching vibration of the coordinated N atom of the ligand.Further, IR spectra of all complexes exhibit new bands at 480-570, 420-460 cm^{-1}which may be assigned to M-O, M-N stretching modes respectively [39-41].Complexes showed an adsorption band at 1494cm^{-1}, where the free nitrate is known to absorb [42, 43]. All complexes **(1-5)** exhibit a band around 1350 cm^{-1}corresponding to monodentate nitrate groups. From the IR spectra of the complexes and free ligand, it is concluded that the ligand behaves bidentate and is coordinated to the metal ions via pyrimidinyl and sulfonamido N atom.

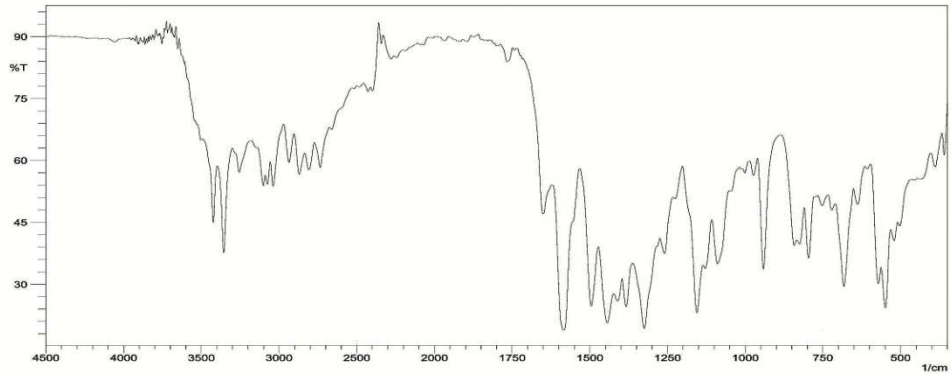

Fig 2 FT-IR Spectrum of Complex (1)

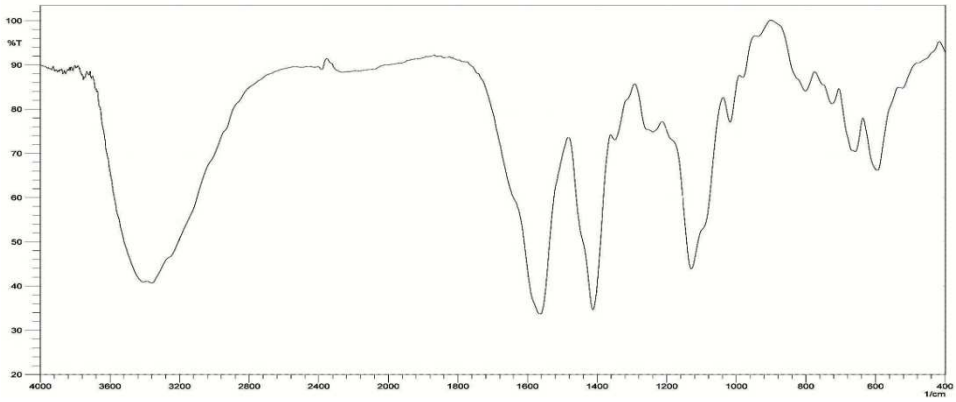

Fig. 3 FT-IR Spectrum of complex (4)

Nuclear magnetic,resonance (NMR) spectroscopy

Nuclear magnetic resonance is concerned with the magnetic properties ofcertain atomic nuclei. It shows the differences in the magnetic properties of thevarious nuclei present and deduced in large measure what the position of thesenuclei are within the molecule. The NMR studies will also reveal the change in the chemical shift of the complexes and the ligands as a result of complexation [44, 45]. The H^1NMR spectra of sulfadiazine and its complexes were recorded in DMSO-d6 solution using TMS as internal standard. The protons in the ligand shifted downfield due to the metal ions [46-49]. Thespectra of the ligand show broad signals at 7.74-6.56 ppm and 4.1 ppm due to aromatic and N-H proton of free NH_2respectively. The signals at 5.5-4.2ppm indicate the O-H proton of water molecule. NMR spectral studies of Complex **1**(**Fig.4**) revealed changes in the chemical shift and intensity of bands in relation to that of the free ligand. This may indicate the formation of complexes. Upon complexation, the sulfa-H imino proton signal disappeared suggesting the covalent binding of sulfonamido nitrogen to metal atom.

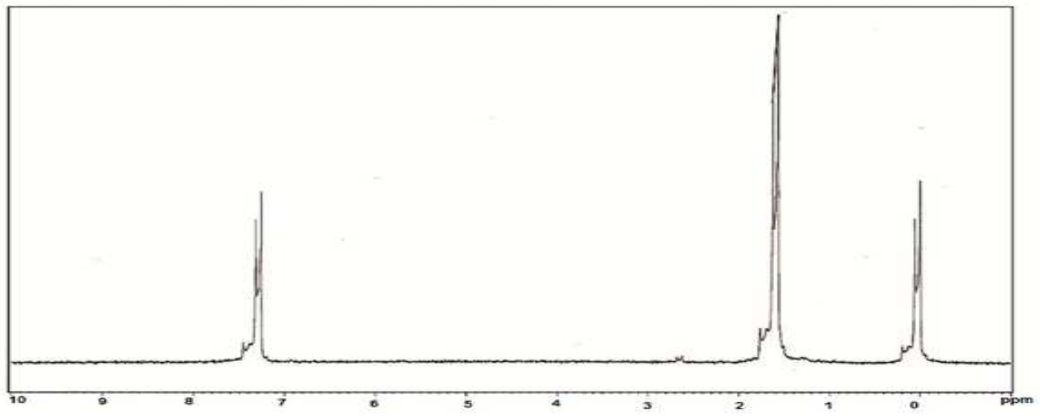

Fig.4 H^1NMR Spectrum of Complex (1)

Chemical shift

TGA, DSC and DTA studies

Thermal gravimetric analysis (TGA) is a method of thermal analysis in which changes in physical and chemical properties of complexes and drugs are measured as a function of increasing temperature from 0^oC to 800 ^oC (with constant heating rate). Thermal stability, oxidation, and combustion, all of which are possible interpretations of TGA traces, will also be discussed. From thermal studies, complexation should occur between drugs and metal.

The thermal studies of sulfadiazine and its complexes were carried out and their thermo gramsare given in (**Fig.5**and**6**). In the TGA of pure ligand, There is no change up to250 ^oCwhich indicates water molecule is absentin the ligand. Thermal studies show that complexes **1-5** decompose mainly in three steps. The first step in the temperature range 70^oC -270 ^oC shows an endothermic peak. The mass loss in these ranges120 ^oC -145 ^oCcorresponds to elimination of coordinated water molecule and nitrate ion. The second step in the temperature range of150 ^oC -200 ^oC reveals an endothermic peak at 190^oC caused by the loss of the uncoordinated nitrate ion. The third step in the temperature range 240 ^oC -280^oC caused by the loss of organic ligand. From the residue metal oxide, the metal content was calculated. A plateau was obtained after heating above 600^oC which corresponds to the formation of the stable metal oxide.

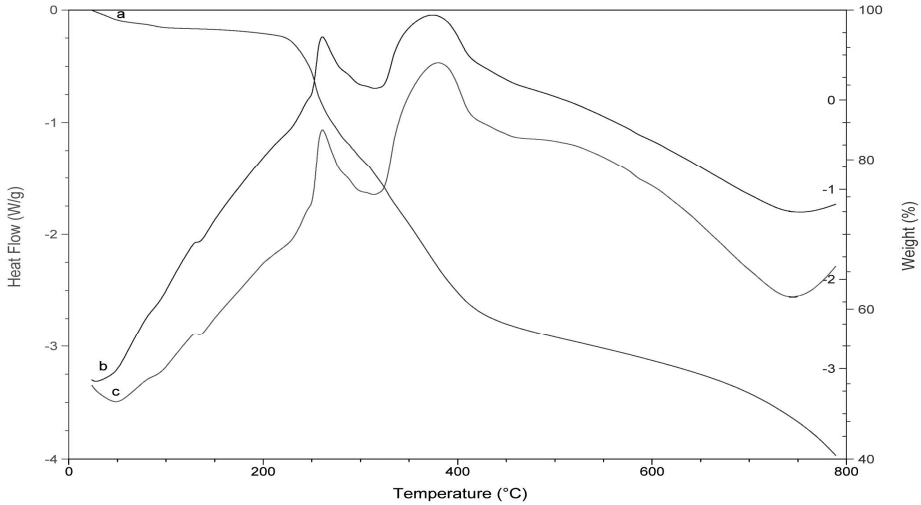

Fig.5. Superimposedthermogravimetric ((a)TG), differential thermo gravimetric ((b)DTG) and differential scanning calorimetric ((c)DSC) curves for complex (2)under N_2 atmosphere; heating rate:10^0C/min

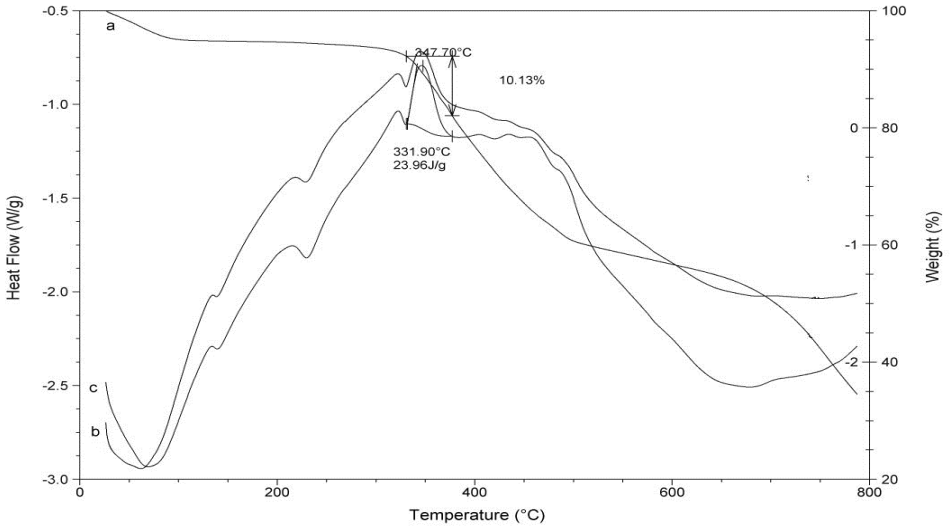

Fig. 6.Superimposedthermogravimetric ((a)TG), differential thermogravimetric ((b)DTG) and differential scanning calorimetric ((c)DSC) curves for complex (5)under N_2 atmosphere; heating rate:10^0C/min

Cyclic Voltammetry

Cyclic voltammetry (CV) has become an important and widely used electro analytical technique in many areas of chemistry. It is widely used to study a variety of redox processes, for obtaining stability of reaction products, the presence of intermediates in oxidation-reduction reactions, reaction and electron transfer kinetics and the reversibility of a reaction [50-53]. Cyclicvoltammetric behaviors of complexes were recorded in the range from +2 to -2V. From cyclic voltammetry data, we can analyze the redox property of metal in synthesized complex. Cyclicvoltammetricbehaviour of Complexes**1-5** were recorded in the range from+2Vto -2V at a scan rate of 50mVs^{-1}.With the increasing scan rates, ΔEp value also increases and there is a negative shift of the cathodic peak potential with increasing sweep rate giving further evidence for the quasi-reversible Co (II)/Co (I) couple(**Fig.7**). Complexes (**1, 3**-**5**) showed reduction at the potential range of-0.1V to- 0.5 V and the reduction process is found to be irreversible in nature (**Fig. 8**).

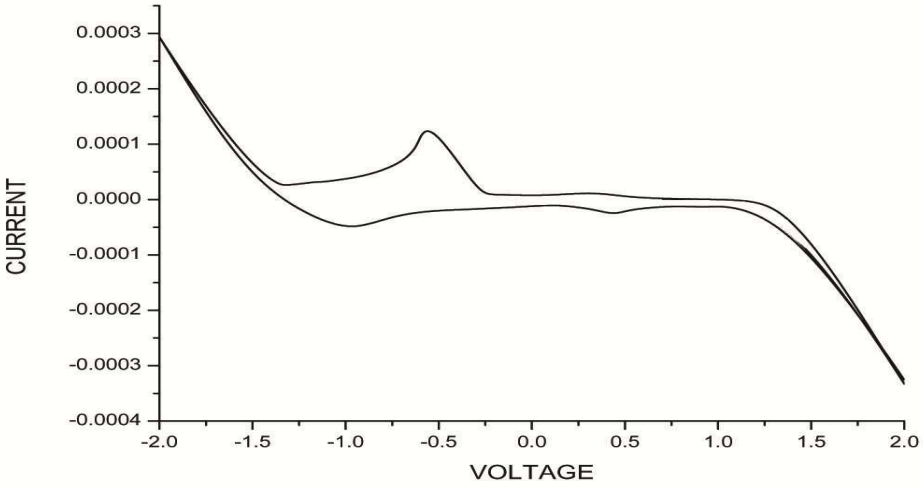

Fig.7.Cyclicvoltammogram of complex (5) in DMSO with 0.5 M NBu_4ClO_4assupporting electrolyte and scan rate of 50mVs^{-1}

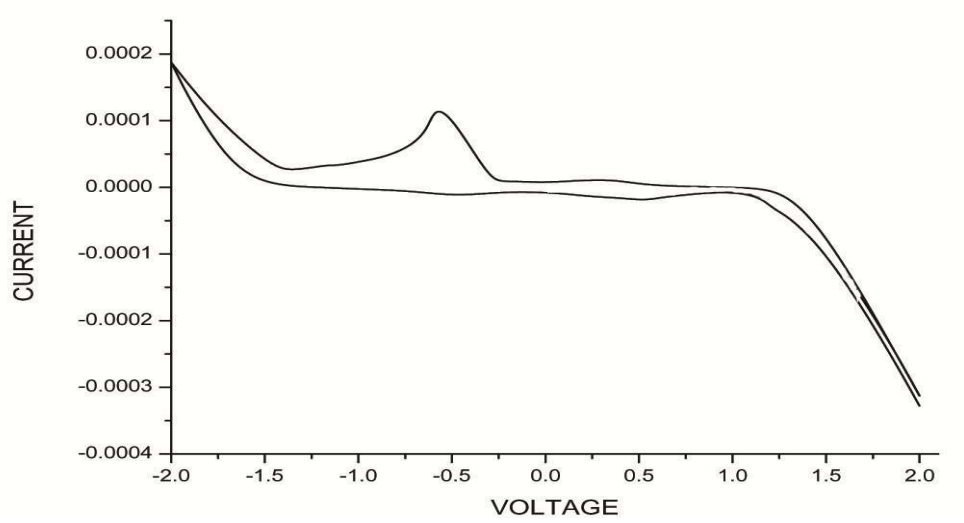

Fig.8Cyclicvoltammogramof complex(2) in DMSO with 0.5 M NBu_4ClO_4assupporting electrolyte and scan rate of 50mVs^{-1}

Antimicrobial studies

The *invitro* antimicrobial activity of sulfadiazine and its metal Complexes **1-5** was evaluated against gram positive, gram negative bacteria and fungi. The antimicrobial activities of all complexes were measured by measuring inhibition zone observed around the tested material. All metal complexes show increased zone of inhibition when compared with the ligand sulfadiazine against bacteria and fungi under study. Complexes **3, 4**and **5** were active against both gram positive (staphylococci) and gram negative (E.coli and pseudomonousauerginosa) bacteria, whereas Complexes**1** and **2** show lesser activity (**Fig. 9(a)**). Except Complex **3**, Complexes **1, 2,4and 5**exhibit lethal antifungal activity towards CandidaAlbicans, whereas Complexes **3,4**and **5** were found to be active against aspergillusflavus in **Fig. 9(b)**. On comparing the antibacterial and antifungal activities of the metal complexes, it is observed that at the concentration level of 10ppm, Complexes **3**and **4** gave promising results. It could be observed that the metal complexes have shown promising results compared to the ligand sulfadiazine drug. The increased inhibition activity of the metal complexes can be explained on the basis of Tweedy's Chelation theory[54].

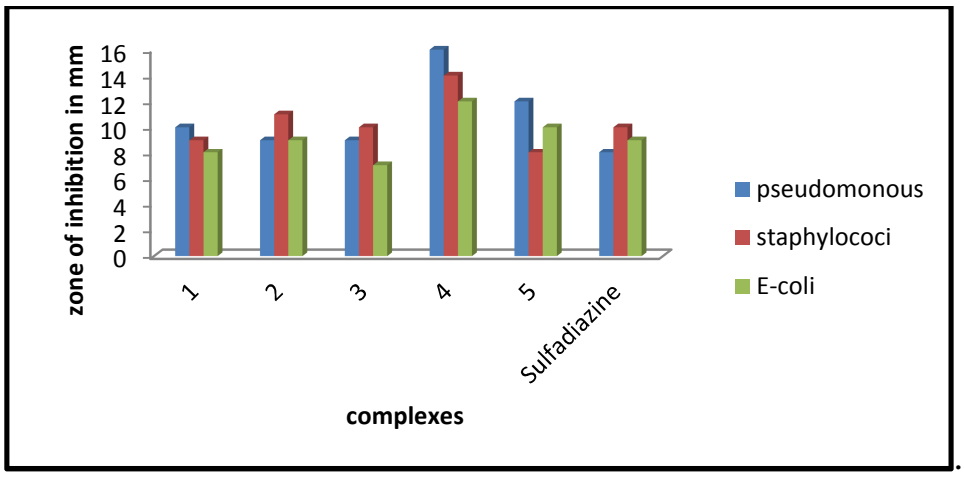

Fig. 9 (a): Antibacterial activity of Drug/complexes

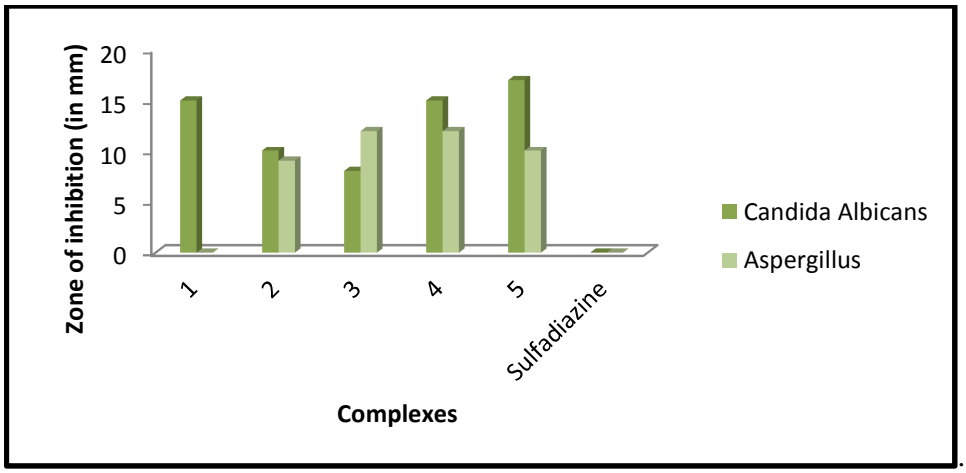

Fig. 9 (b): Antifungal activity of Drug/complexes

CONCLUSION

The present work focuses on the synthesis, characterization and biological studies of transition metal complexes (**1-5**) containing sulfadiazine drug as ligands. The structural information obtained from these complexes is in agreement with the data reported in this paper based on the elemental and thermal analyses, NMRstudies. The IR and thermal studies confirmed the presence of water molecule and nitrate ion in the coordination sphere of [M (SD) $_2$(H_2O) (NO_3)].NO_3. All the complexes have octahedral coordination in which the metal ions are coordinated to sulfadiazine molecule as bidentateligand, water molecule and nitrate ion as monodentateligands. The probable structure of metal complexes were shown below in chart-1. Cyclic voltammetry studies of the metal complexes (**1, 3-5**) and complex **2** revealed the irreversible and quasi-reversible one electron transfer redox processes respectively. Antimicrobial study reveals that metal complexes have more bioligical activity than the free ligand. The antimicrobial activity of sulfadiazine drug enhanced upon complexation with metal ions particularly for Copper(II) and Zinc(II) ion.

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