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Thermo gravimetric and Biological study of cadmium and mercury complexes of sulfadiazine

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ABSTRACT:

Cadmium (I) and mercury (II) complexes of 4-Amino-N-(2-pyrimidinyl)benzenesulfonamide (sdz) have been synthesized and characterized by UV spectroscopy.Electrical conductivity measurement indicate that no anion is present outside the coordination sphere in both the complexes (I) and (II).The results of UVspectral data and thermal analysis for both the complexes(I) and (II) suggest that the binding of cadmium and mercury atom to the sulfonamidic nitrogen are in good agreement.Along with this, the antimicrobial activities of cadmium (I) and mercury (II) complexes of sulfadiazine are studied by the dilution method against *Staphylococcus aureus* and *Escherichia coli* strains. Both the complexes (I) and (II) exhibit higher antibacterial activity than free sulfadiazine ligand against gram negative bacteria.

KEYWORDS: Cd and Hg complexes; Sulfadiazine; Thermogravimetric analysis; Spectroscopic analysis; Antimicrobial activity

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1. INTRODUCTION:

Sulfa drugs are widely used for the treatment of various infectious diseases. Sulfonamides and their different derivatives are extensively used in medicine due to their pharmacological properties such as antibacterial activity. The clinical application of sulfadiazine complexes with silver(I) and zinc(II) in burn therapy aroused interest in metal complexes of sulfa drugs [1–3]. Metal complexes of sulfonamides have received great interest in the field of bioinorganic chemistry [4–8] as sulfonamides composed a vital class of the antimicrobial agents in the world owing to their low cost, and their ability to slow down the bacterial growth in the wounds or infected organs without appreciable toxicity to normal tissues. Sulfadiazine(sdz) compound is widely used for their bactericidial action and X-ray structures of many of them have been solved [9,10].Sulfadiazine, a well-known antibiotic sulfonamide, contains several groups with donor atoms that are able to interact with metal ions: Ar–NH_2, NH sulfonamide, SO_2–R and N heterocyclic atoms. Chemical structure of Sulfadiazine is shown in Figure 1 and which can act as a monodentate or a bidentate ligand. The metal complexes of sulfadiazine have gained a significant role in coordination chemistry. The structure of polymeric zinc complex [$Zn(sdz)_2$] was determined by Yuan et al. [11]. Additionally, the single crystal X-ray structure of [$Cu(sdz)_2(NH_3)_2$] and [$Hg(sdz)_2(DMSO)_2$] are also reported by Brown et al. [12] and Garcia-Raso et al. [13], respectively. Along with this, Menabue et al. [14] reported the cadmium complex of sulfadiazine [$Cd(sdz)_2$].$2H_20$ having distorted tetrahedral geometry.

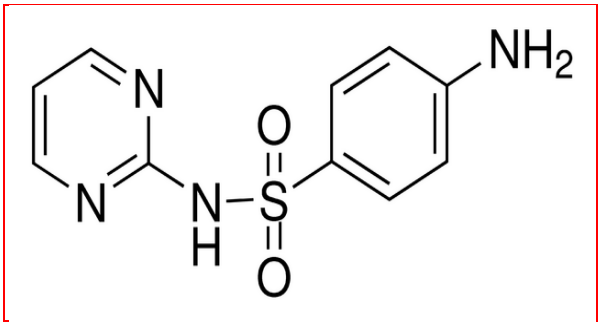

Figure 1: Chemical structure of sulfadiazine

The present work brings a complete study on synthesis, spectroscopic, Thermogravimetric analysis and antibacterial assays over gram positive and gram negative pathogenic bacterial strains of Cd(II) and Hg(II) complexes with sulfadiazine.

2. EXPERIMENTAL:

2.1. Chemicals

Sodium sulfadiazine (Sigma, >99%), cadmium acetate (Loba Chemie, 99%), mercury acetate (Loba Chemie, 99%) and all other reagents are of the highest grade commercially available and used without further purification.

2.2. Instruments

UV spectra (200-400 nm) are recorded on a Shimadzu UV-160 spectrometer in DMSO. Electrical conductivity is measured using EQ-660A conductivity meter. Thermogravimetric analysis are carried out at heating rate of 5°C min^{-1} in the temperature range of 25–998°C under nitrogen flow of 100 mL min^{-1} by a simultaneous TGA/DTA analyzer using Seiko SII-EXSTAR TG/DTA-7200.

2.3. Synthesis of the complexes

2.3.1 Synthesis of the cadmium sulfadiazine complex [Cd-sdz] (I)

Sodium salt of sulfadiazine (0.545 g, 2 mmol) was dissolved in hot methanol and to this, an aqueous solution of cadmium acetate (0.230 g, 1 mmol) was added with constant stirring and the mixture was refluxed for 3 hours. A white precipitate was formed, filtered and washed with hot distilled water and methanol successively and dried in a desiccator over anhydrous $CaCl_2$. The yield at the end of reaction for the complex was around 40%.

2.3.2 Synthesis of the mercury sulfadiazine complex [Hg-sdz] (II)

Sodium salt of sulfadiazine (0.545 g, 2 mmol) was dissolved in hot methanol and to this, an aqueous solution of mercury acetate (0.310 g, 1 mmol) was added with constant stirring and the mixture was refluxed for 2 hours. A white precipitate was formed, filtered and washed with hot distilled water and methanol successively and dried in a desiccator over anhydrous $CaCl_2$. The yield at the end of reaction for the complex was around 45%.

2.4. Microbiological assays

Micro broth dilution method is used to determine the minimal inhibitory concentration (MIC) of the antimicrobial agent against gram negative (*Escherichia coli*) and gram positive (*Staphylococcus aureus*). The steps for performing the Micro broth dilution method are based on recommendations from the National Committee for Clinical Laboratory Standards [15].

The standard strains used are *Escherichia coli* MTCC 422 and *Staphylococcus aureus* MTCC 96. Mueller Hinton Broth is used as Nutrient medium at 37˚C to grow and dilute the drug suspension for the test bacteria. The solvent DMSO is used as diluent to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions are prepared in primary and secondary screening. Each synthesized compound and standard drugs are diluted obtaining 2000 µg/mL concentration, as a stock solution. In primary screening 1000, 500, and 250 µg/mL concentrations of the synthesized drugs are taken. The active synthesized compounds found in this primary screening are further diluted to obtain 200, 125, 100, 62.5, 50, 25, 12.5, and 6.250 µg/mL concentrations for secondary screening. Inoculum's size for test strain is adjusted to 10^8 CFU.ml^{-1} by comparing the turbidity. MIC is the lowest concentration of a compound in DMSO that exhibited no visual growth of the organisms in the culture tubes. Each of the above experiments is repeated thrice along with a control set using DMSO. The mean value obtained for three individual replicates is then used to calculate the growth inhibition zone of each sample.

3. RESULTS AND DISCUSSION:

3.1. UV spectra

The UV spectra of free sulfadiazine and its cadmium and mercury complexes are recorded in DMSO solution shown in Figure 2. The electronic spectrum of sulfadiazine gave absorption band at 275 nm which is assigned to $\pi \rightarrow \pi^*$. The cadmium ion has completely vacant 5d orbital consequently ligand to metal (L→M) binding can take place by the acceptance of one pair of electron from the donor nitrogen atom of the ligand. According to literature [16], no d-d transition is expected for cadmium complex. Similarly, the mercury complex show only the charge transfer transitions which can be assigned to charge transfer from the ligand to the metal and vice versa, no d-d transition are expected for d^{10} Hg(II)

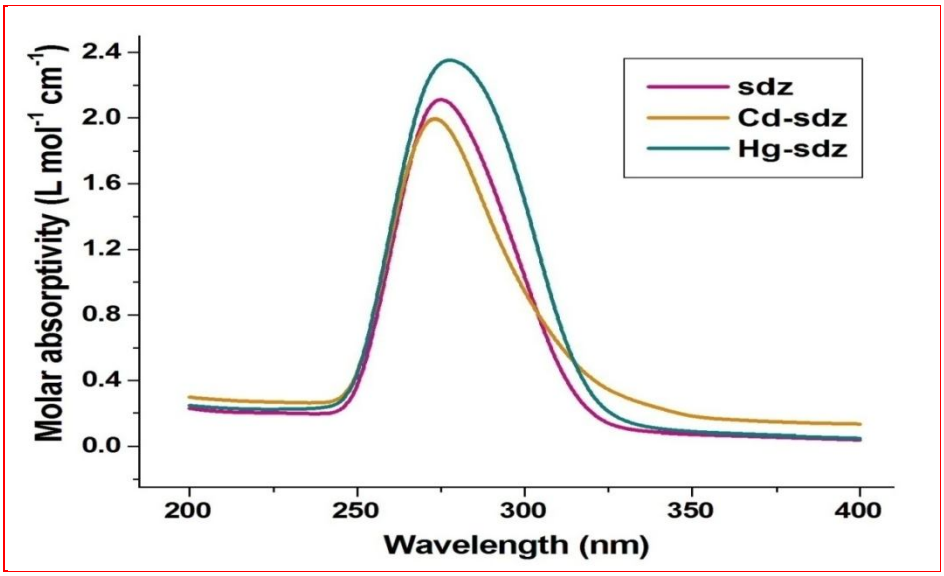

Figure 2: UV spectra of sulfadiazine (sdz), Cd-sdz and Hg-sdz

complexes [17]. In both the cadmium and mercury complexes of sulfadiazine, the ligand to metal charge transfer transition takes place that is π→π* of ligand to metal, which is responsible for the change in the value of λ_{max} of the complexes compared to sulfadiazine, moreover the difference in the ionic radii of the metal ions attribute to the change in the value of absorbance, the same transition is observed with ^{1}S spectroscopic term. The absorbance value of sulfadiazine (sdz) and its cadmium and mercury complexes are shown in Table 1.

Table 1: Molar absorptivity, wavelength and assignment of sulfadiazine along with its cadmium and mercury complexes

Ligand/ Complex	Wavelength (nm)	Energy (cm^{-1})	Assignment	Molar absorptivity (L mol^{-1} cm^{-1})
sdz	275	36363	π → π* /n→π*overlap	2.1119
Cd-sdz	272	36764	π → π* (LMCT)	1.9960
Hg-sdz	278	35971	π → π* (LMCT)	2.3526

3.2. Electrical conductivity

The electrical conductivity of sulfadiazine along with its cadmium and mercury complexes in 10^{-3} M pyridine solution are measured at room temperature. The molar conductance (Λ_m) values of sulfadiazine is 6.02 ohm^{-1} cm^2 mol^{-1}, while its cadmium and mercury complexes are 3.82 and 6.25 ohm^{-1} cm^2 mol^{-1}, respectively showing their non-electrolytic [18] nature. The results indicate that no anion is present outside the coordination sphere in both the complexes (I) and (II). The very low molar conductivity value of cadmium and mercury complexes with sulfadiazine reveals that both the complexes remain neutral in solution.

3.3. Thermo gravimetric analysis

The cadmium and mercury complexes of sulfadiazine (sdz) and free sdz are studied by thermogravimetric analysis from ambient temperature to 998°C in nitrogen atmosphere. The TGA curves are shown as % mass loss versus temperature, the DTG curves are as the rate of loss of mass versus temperature. The thermal decomposition of cadmium complex of sulfadiazine (I) occurs with DTG curve maxima showing endothermic peak at 113.33°C (ΔH = 29.6825 $kJmol^{-1}$) and 379.33°C (ΔH = 177.8638 $kJmol^{-1}$) and mercury complex of sulfadiazine (II) occurs with DTG curve maxima showing endothermic peak at 287.64°C (ΔH = 116.89 $kJmol^{-1}$) while in free sulfadiazine endothermic peaks are observed at 275.80°C (ΔH = 144.287 $kJmol^{-1}$) and 339.80°C (ΔH = 23.333 $kJmol^{-1}$). The final residual mass left at 998°C correspond to 27.93% for complex (I) and 15.34% for complex (II) while in free sdz correspond to 25.60%. The thermogravimetric (TG) and differential thermogravimetric (DTG) curves for free sulfadiazine (sdz) and its cadmium and mercury complexes are shown in Figure 3 and 4.

Thermodynamic parameters of both the synthesized complexes (I) and (II) of sulfadiazine and ligand (sdz) itself have been evaluated by Broido's graphical method [19] for straight line decomposition portion of the thermodynamic analytical curve. Activation Energy (E_a) are calculated by the slope of ln(ln1/y) versus 1/T, where y is the fraction of the number of initial molecules not yet decomposed. The thermodynamic parameters like change in enthalpy (ΔH), entropy (ΔS), Gibb's free energy (ΔG) and Arrhenius constant (A) are calculated using the standard equations [20,21] and data presented in Table 2.

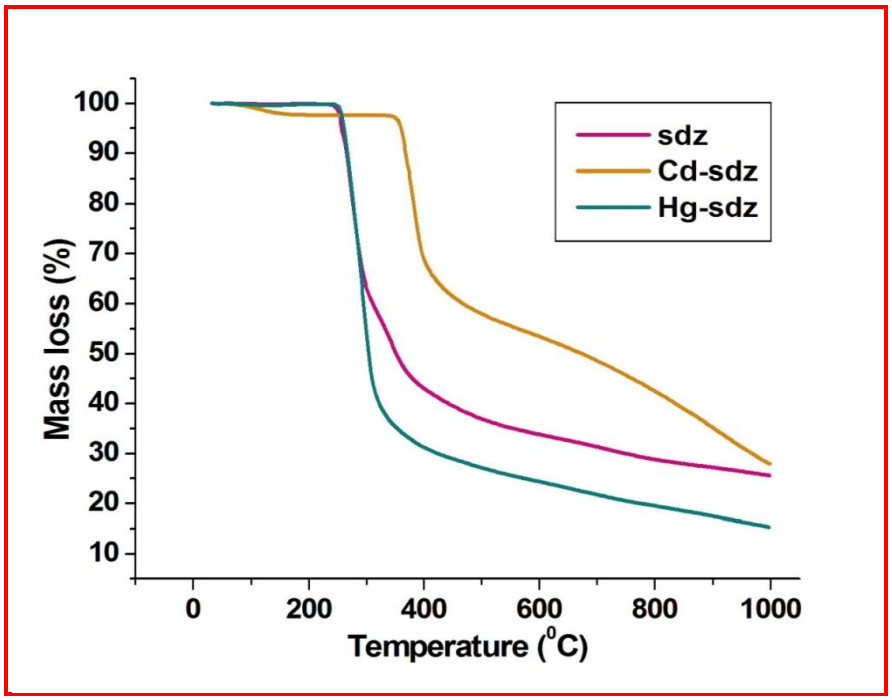

Figure 3: TGA curves of sulfadiazine (sdz), Cd-sdz and Hg-sdz

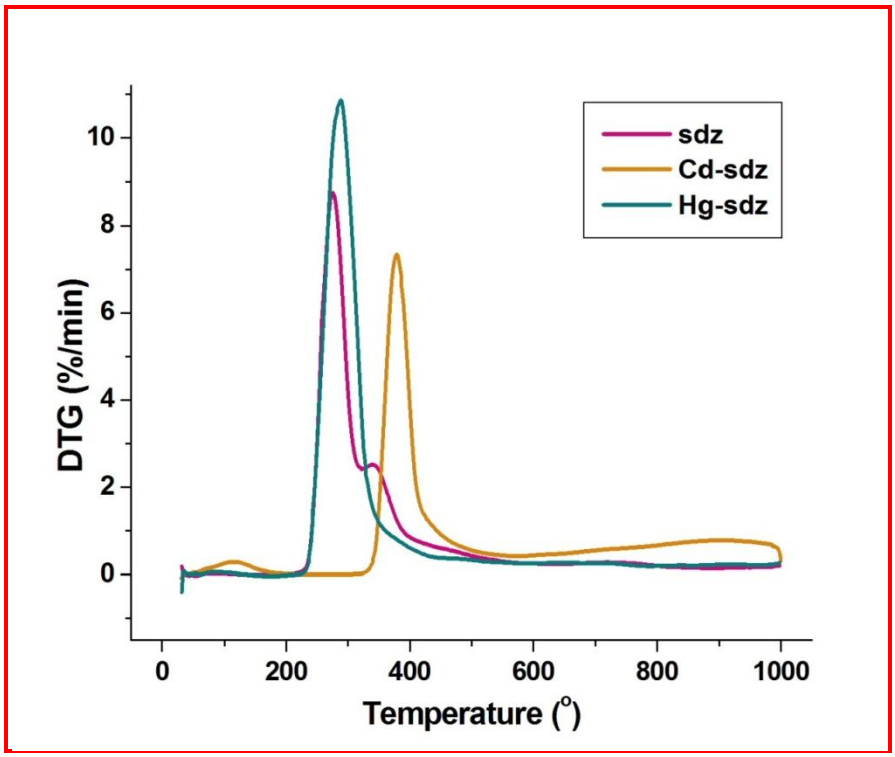

Figure 4: DTG curves of sulfadiazine (sdz), Cd-sdz and Hg-sdz

Table 2: Thermodynamic parameters of sulfadiazine along with its cadmium and mercury complexes

Ligand/ Complex	Decomposition Temperature range (K)	Activation Energy (kJ mol^{-1})	Arrhenius constant	ΔH (kJ mol^{-1})	ΔS (J K^{-1} mol^{-1})	ΔG (kJ mol^{-1})
sdz	528.80-568.80	148.85	31.27	144.28	-221.38	265.78
	592.80-632.80	28.42	5.58	23.33	-236.63	168.34
Cd-sdz	366.33-406.33	32.89	6.04	29.68	-232.12	119.36
	632.33-672.33	183.28	32.42	177.86	-222.51	323.02
Hg-sdz	540.64-580.64	121.55	25.80	116.89	-223.16	242.00

3.4. Microbiological assays

The minimum inhibitory concentration (MIC) values of sulfadiazine along with its cadmium (I) and mercury (II) complexes exhibited varying inhibitory effect against *Staphylococcus aureus* and *Escherichia coli* strains are tabulated in Table 3. The MIC values of metal salts, ligand sulfadiazine and pyridine should be tested separately which shows that the solvent pyridine gives negative results against *Escherichia coli* and *Staphylococcus aureus* strain tabulated in Table 3. The complex (I) is found to impart activity toward both gram positive bacteria (*Staphylococcus aureus*) and gram negative bacteria (*Escherichia coli*) while the complex (II) is found potent against gram negative bacteria (*Escherichia coli*). The complex has ability to kill the investigated bacteria with large inhibition zone diameters comparing with that of free ligand, but at higher concentration than the sodium salt. Sulfonamides penetrate bacterial cells in the neutral form, and once inside a cell, their bacterial action is from the ionized form [22]. In the present study, the MIC value of cadmium sulfadiazine complex is 200 µg/ml for *Escherichia coli* strain while 62.5 µg/ml for *Staphylococcus aureus* strain. The results show that the biological activity screening of Cd-sdz for both *Escherichia coli* and *Staphylococcus aureus* strain are more compared to free sulfadiazine and cadmium acetate. According to literature [23], the reported MIC values of mercury sulfanilamide and mercury sulfathiazole towards gram negative bacteria (*Escherichia coli*) are 64 and 16 µg/ml. In the present work, the MIC value of mercury complex of sulfadiazine is 62.5µg/ml for *Escherichia coli* strain while 125 µg/ml for *Staphylococcus aureus* strain. The results indicate that the *Escherichia coli* strain is more sensible for mercury complex compared to *Staphylococcus aureus* strain. Moreover, a standard drug Ampicillin was used a positive control for the study. The inhibitory potency of the complexes against the bacterial species as compared to the standard drug molecule was found to be comparable as well as complex containing cadmium metal ion exhibited

better activity against gram positive bacteria while complex comprising mercury as central atom demonstrated better potency against gram negative species as compared to standard reference drug Ampicillin. The above study indicates that the complexes synthesized from metal salts and ligands were found to be more potent against the bacterial species as compared to the ligand molecules, which favors the increase in the potency of ligands after complexation [24, 25]. The results indicate that the gram negative bacteria *Escherichia coli* strain is more venerable to mercury complex compared to gram positive *Staphylococcus aureus* strain [26].

Table 3: MIC value (µg/ml) of sulfadiazine along with its cadmium and mercury complexes

Sulfa drug	**MIC for *Escherichia coli* MTCC 442**	**MIC for *Staphylococcus aureus* MTCC 96**
sdz	250	100
Cd-sdz	200	62.5
Hg-sdz	62.5	125
Ampicillin	100	100
DMSO (control)	Nil	Nil
Cadmium acetate	350	450
Mercury acetate	350	300

Our observations reveal that the MIC for cadmium and mercury complexes changes according to the target bacteria. It is known that gram positive bacteria (*Staphylococcus aureus*) and gram negative bacteria (*Escherichia coli*) have different cell wall constitution. *Escherichia coli* have an outer lipidic membrane layer while *Staphylococcus aureus* does not have one.

4. CONCLUSION:

Cadmium and mercury complexes of sulfadiazine (I) and (II) are synthesized, characterized and tested as antimicrobial agents. The spectroscopic data are in agreement with the synthesized complexes. Both the complexes (I) and (II) exhibit higher antibacterial activity than free sulfadiazine ligand against gram negative bacteria.

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