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Synthesis, Characterization and Antimicrobial Activities of Meta l Complexes of Cu (II) and Zn (II) with Prednisolone in Water–Isopropy Alcohol Medium

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Abstract: *Synthesis of Cu (II) and Zn (II) Prednisolone complexes in water- isopropyl alcohol at different ratio concentrations were carried out. The results of metal complexes obtained were characterized on the basis of differences in their physical properties in terms of % yield, colour, and melting point, solubility tests on the transparent solvents and sulphur contents which were determined by gravimetric method. Spectroscopic studies of the metal complexes were also carried out on UV-Visible Spectroscopy ranging between 200 – 800 nm and FT-IR spectroscopy also ranging from 400 – 800 cm^{-1}.Anti-microbial studies of the metal complexes and prednisolone ligand as well as the standard (control) were screened against the following bacteria: Xanthomonas axonopodis, Streptococcus faecadis, Pseudo cmonas aeruginosa, Chromo bacterium, Erwinnia carotovoraand fungi include Collectotrchum falcutrum, Phythophytora palmivora, Ceratocystis paradoxa, Pericularia oryzal, Helminthosporium toxicum. The % yields of the metal complexes were reasonably high. The melting points were sharp and solubility tests proved that metal complexes were non- polar. The UV- visible results also confirmed d – d transition and coordination of metals to the ligand were found to be through C=O and -OH as shown by the FT-IR spectroscopy. The results of antimicrobial studies have revealed that metal complexes were more toxic than the ligand. The thermogravimetric analyses have revealed that thermal decomposition of the metal complexes involved three stages 0^oC – 100^oC uncoordinated water, 100^OC - 200^oC (coordinated water), 200^oC – 400^OC (organic ligand) and 400 ^OC – 800^OC (metallic oxides).*

Keywords: *Prednisolone, Transition metal complexes, gravimetric method, antimicrobial activities, thermogravimetric analyses.*

1. INTRODUCTION

Coordination complexes are so pervasive that the structures and reactions are derived in many ways [1].Many biologically active compounds possess modified pharmacological and toxicological potentials when administered in form of metal based compounds. Various metal ions potentially and commonly used are Co, Cu, Ni and Zn because of forming low molecular weight complexes and therefore, prove to be more beneficial against several diseases [2].

Research has shown significant progress in utilization of transition metal complexes as drugs to treat several human diseases. Transition metals exhibit different oxidation states and can interact with a number of negatively charges molecules. The activity of transition metal based drugs have promising application and may offer unique therapeutic opportunities [3]. The advances in inorganic chemistry provide better opportunities to use metal complexes as therapeutic agents as mode of action of metal complexes on living organism is different from non - metals [4].Medicinal inorganic chemistry can exploit the unique properties of metal ions for the design of new drugs. This leads to the clinical applications of chemotherapeutic agents

Prednisolone is a man- made corticosteroid, used to treat variety of acute and chronic inflammatory diseases such as rheumatoid arthritis, systematic lupus and reduce other inflammatory diseases like swelling and pains in joints and other organs anti-immune disorder and cancer as well as other

conditions including adrenocortical insufficiency, high blood calcium, dermatitis, eye inflammation, asthma and multiple sclerosis [5]. Prednisolone and corticosteroid have strong anti- inflammatory effects and can reduce the swelling and pain in joint and other organs. They do not cure diseases and they should not be confused with male and female steroid hormone, which are known for their misuse among athletics. Prednisolone and other corticosteroids should be taken with non-steroidal and anti-inflammatory drugs as the risk of side effects such as stomach ulcer is increased. Moat common possible side effect of prednisolone include weight loss, osteoporosis (thinning of the bones), skin becomes thin, slow to heal, diabetes (causes a ruse in blood sugar) rise in blood pressure, rise in blood cholesterol, psychological effects such as change in irritability, agitation or depression [19]. Prednisolone is used for allergic reactions, for seasonal allergies to drug and immunosuppressive drugs for organ transplanting [19].

Many biologically active compounds used as drugs possess modified pharmacological and toxicological potentials when administered in form of metal based compounds. Various metal ions potentially and commonly used are Co, Cu, Ni and Zn because of forming low molecular weight complexes and therefore, prove to be more beneficial against several diseases [6, 18]. The efficacy of the various organic therapeutic agents can often be enhanced upon coordination with a suitable metalions [7]. The newly prepared compounds should be more effective and possibly act as though a distinct mechanism from those of well – known classes of anti-microbial agents to which many clinically relevant pathogens are now resistant. Therefore, the aim of this research work is to synthesis, characterize and evaluate both the thermal studies and biological activities of Prednisolone and Urea mixed ligand complexes with Copper (II) and Zinc (II) at different concentrations in water-isopropyl alcohol medium.

2. MATERIALS AND METHODS

Reagents used for this study were purchased from commercial source and were found to be great analytical grades and were used without further purification. The reagents include copper (II) sulphate, zinc(II)sulphate, barium sulphate, sodium hydroxide, hydrogen peroxide, hydrogen chloride and Prednisolone obtained from Aldrich Limited.

2.1. Experimental

Copper(II) Prednisolone complexes in ratio 1:1 and 1:2 concentrations were prepared as follows: Equimolar concentrations of the metal and ligand was carefully weighed by dissolving 0.50g (0.1M) copper(II) sulphate pentahydrate in 10ml distilled water followed by 10ml isopropyl alcohol and a light blue solution obtained. 0.72g of prednisolone (ligand) (0.1M) was also dissolved in in a mixture of 10ml water and 10ml isopropyl alcohol in a separate conical flask and a colourless solution was obtained.

The two solutions were mixed together and a blue solution was formed immediately. The resulting solution was stirred on a magnetic stirrer with hot plate for 3 hours along the line, a brownish solution was formed. The resulting mixture was filtered through a sintered glass porosity No 4, the residue was washed with a mixture of distilled water and alcohol and the residue dried in a desiccator containing silica gel for 4 days until a constant weight obtained. The ratio 1.2 copper (II) prednisolone was also obtained as the above but the concentration of the prednisolone (ligand) was increased (double) to 1.40g (0.2M). The processes of filtration, washing, drying and weighing was the same as the above.

Zn (II) prednisolone complexes in water – isopropyl alcohol in ratio 1:1 and 1:2 were prepared by weighing carefully an equimolar concentrations of 058g (0.1M)of Zinc (II) sulphate heptahydrate (metallic salt) and 0.72g (0.1M) prednisolone (ligand) and dissolvingin a ratio mixture of water and isopropy alcohol 10/10 by volume in a separate conical flask and both gave the colour white. The two solutions were mixed together and stirred for 5minutes, followed by the addition of 0.1M NaOH solution, it gave the solution white and the stirring continued for 3 hours. The resulting mixture was filtered through the sintered glass porosity. The white residue obtained was washed, dried in a dessicator containing silica gel for 5 days and weighed. Furthermore, Zn (II) prednisolone complex in ratio 1:2 was prepared by doubling the concentration of prednisolone (ligand). The processes above were repeated and finally, a white residue was also treated as in the 1:1 Zn (II) prednisolone.

2.2. Physical Measurement

The physical measurements of the solid metal complexes which included the melting points of the solid complexes were determined in open capillary tubes using an electrothermal melting point apparatus. The solubility tests were determined in both polar and non-polar solvents. Sulphur contents were determined using barium chloride solution and quantitatively by Mohrs precipitation method [5]. The metal analyses were carried out by complexometric titration method. The electronic absorption spectra of the ligand and the complexes in DMF were recorded at room temperature within the wavelength range 200 – 800nm by the aid of UV – visible spectrophotometer (Shimadzu UV – 160 IPC). The FT- IR spectra (4000 – 400cm^{-1}) of the compounds or complexes were recorded using FTIR (Nicolet is 10) spectrophotometer. The basic theory involved is that the stretching modes if the ligands changes upon complexation. Complexation due to weakening, strengthening of the bonds involved in the bond formation resulting in subsequent change in the position of the bands appearing in the IR spectrum. The changes in the structural features of the ligands are observed as changes in bands observed, mainly in the fingerprint region, that is, in the 1500 –750 cm^{-1} [8,9]. The bands due to the metal ligand bands are mainly observe in the far IR regions 400 – 600cm^{-1}. The thermal studies of all synthesized complexes were carried out in temperature range of 50 – 1000^{o}C under inner temperature (oven drying method). The biological activities of the synthesized complexes or compounds were studied for antimicrobial activity using disc agar diffusion method. The in vitro antimicrobial properties of the complexes were performed in the Plant Pathology Department of Crops, Pests and Management, Federal University of Technology, Akure, Ondo State, Nigeria.

3. RESULTS

Table1. *Results of Physical Properties Of Metal Complexes*

COMPLEXES	RATIO	COLOUR	% YIELD	MELTING POINT^{o}C	% SULPHUR	% METALS
$CuL(H_20)SO_4H_2O$	1 : 1	BROWN	46.70	212 – 214	15.10	12.65
$CuL_2(H_20)SO_4H_2O$	1 : 2	BLUE	60.50	188 – 200	21.71	12.43
$ZnL(H_20)SO_4H_2O$	1: 1	WHITE	50.20	200 – 202	19.80	
$ZnL_2(H_20)SO_4H_2O$	1: 2	WHITE	65.20	203 – 205	15.10	
LIGAND		WHITE		?		

Table2. *Results of Solubility Tests Of Metal Complexes*

SOLVENTS	Cu $L(H_20)SO_4H_2O$	$CuL_2(H_20)SO_4H_2O$	Zn $L(H_20)SO_4H_2O$	$ZnL_2(H_20)SO_4H_2O$
Formalldehyde	Soluble	Soluble	Insoluble	Insoluble
Chloroform	Insoluble	Insoluble	Soluble	Soluble
n- Hexane	Soluble	Soluble	Soluble	Soluble
Toluene	Insoluble	Insoluble	Insoluble	Insoluble
Methanol	Insoluble	Insoluble	Insoluble	Insoluble
Butanol	Insoluble	Insoluble	Insoluble	Insoluble
Distilled water	Insoluble	Insoluble	Insoluble	Insoluble

Table3. *The FTIR of Theprominient Regions of Metal Complexes*

COMPLEXES	M - L	M – O	C = O	-OH Non Bounded H_2O	C -C	C = C Aromatic	H_2O (Bounded H_2O)
Cu $L(H_20)SO_4H_2O$	504,640	412,480	1709	3390	2853	1612	721,772
Cu $L(H_20)SO_4H_2O$	571,599	419,484	1709	3415	2853	1612	772
Cu $L(H_20)SO_4H_2O$	503,680	434,470	1700	3405	2853	1612	745,773
Cu $L(H_20)SO_4H_2O$	543,570	421,454	1707	3414,3508	2853	1612	741,770
$C_{12}H_{28}O_5$(Ligand)	----	----	1697,1711	3360	2852 2853	1443613	====

Table4. *Thermogravimetric Studies of Cu(II)Prednisolone Complex 1: 1*

TEMP. ^{o}C	0	100	200	300	400	500	600	700	800
Mass of residue	0.20	0.13	0.09	0.06	0.03	0.03	0.03	0.03	0.03
Mass loss	0.00	0.07	0.11	0.14	0.17	0.17	0.17	0.17	0.17
% Mass	0.00	35.00	55.00	70.00	85.00	85.00	85.00	85.00	85.00
% Residue loss	0.00	65.00	45.00	30.00	15.00	15.00.	15.00	15.00	15.00

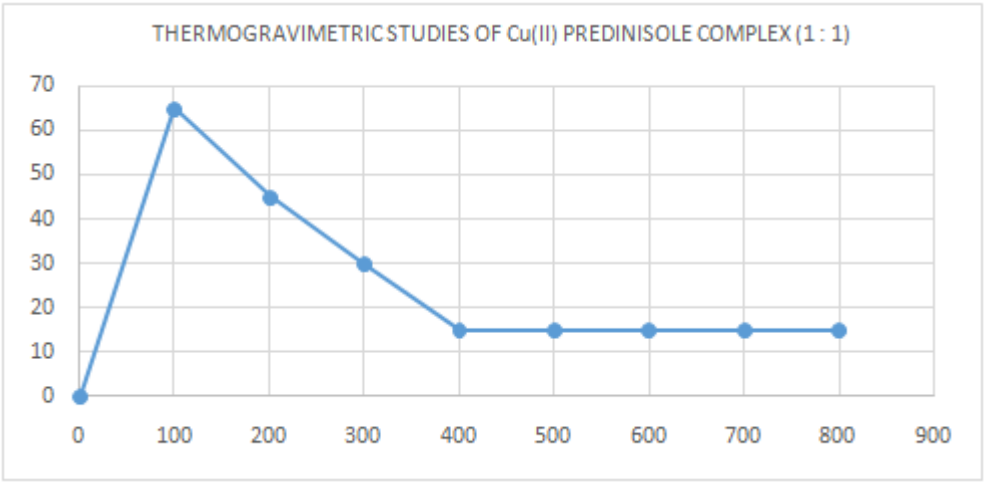

Table5. *Thermogravimetric Studies of Cu(II) Prednisolone Complex I: 2*

TEMP. °C	0	100	200	300	400	500	600	700	800
Mass of residue	0.20	0.17	0.13	0.10	0.06	0.05	0.05	0.05	0.05
Mass loss	0.00	0.03	0.07	0.10	0.14	0.15	0.15	0.15	0.15
% Mass	0.00	15.00	35.00	50.00	75.00	80.00	80.00	80.20	80.00
% Residue loss	0.00	85.00	65.00	50.00	25.00	20.00	20.00	20.00	20.00

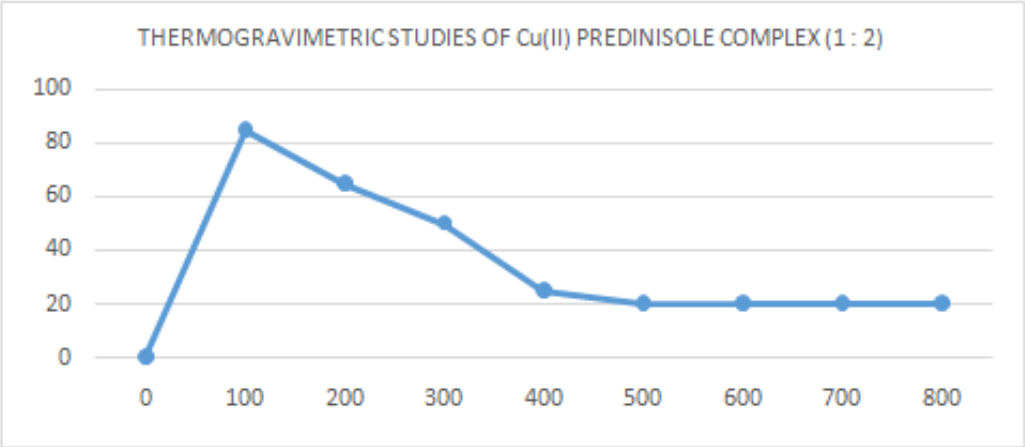

Table6. *Thermogravimetric Studies Of Zn (II) Prednisolone Complex 1 : 1*

TEMP. °C	0	100	200	300	400	500	600	700	800
Mass of residue(g)	0.20	0.13	0.13	0.11	0.07	0.04	0.04	0.04	0.04
Mass loss(g)	0.00	0.07	0.07	0.09	0.13	0.16	0.16	0.16	0.16
% Mass	0.00	35.00	35.00	45.00	65.00	80.00	80.00	80.00	80.00
% Residue loss	0.00	65.00	65.00	55.00	35.00	20.00	20.00	20.00	20.00

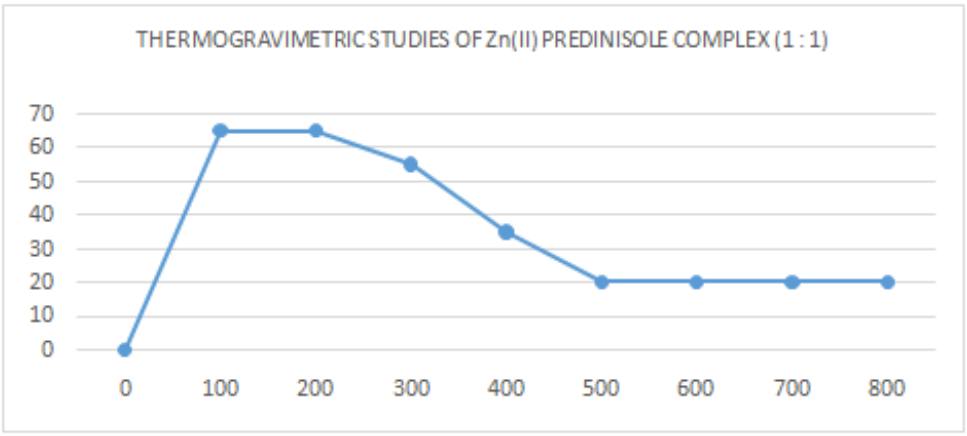

Table7. *Thermogravimetric Studies of Zn (II) Prednisolone Complex 1: 2*

TEMP. °C	0	100	200	300	400	500	600	700	800
Mass of residue(g)	0.20	0.16	0.13	0.11	0.08	0.07	0.07	0.07	0.07
Mass loss(g)	0.00	0.04	0.07	0.09	0.12	0.13	0.13	0.13	0.13
% Mass	0.00	20.00	34.00	45.00	60.00	65.00	65.00	65.00	65.00
% Residue loss	0.00	80.00	65.00	55.00	40.00	35.00	35.00	35.00	34.00

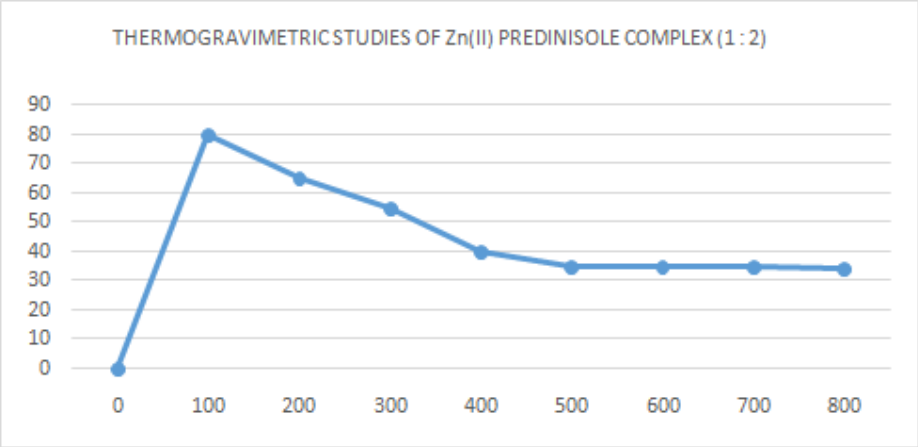

Table8. *Antibacterial Screening of Metal Complexes.*

Complexes	RATIO	A	B	C	D	E
$CuL(H_2O)SO_4H_20$	1 : 1	17.00	18.00	17: 00	5.00	4.00
$CuL(H_2O)SO_4H_20$	1: 2	20.00	12.00	8.00	4.00	17.00
$ZnL(H_2O)SO_4H_20$	1: 1	14.00	10.00	6.00	5.00	4.00
$ZnL_2(H_2O)SO_4H_20$	1 : 2	16.00	14.00	5.00	5.00	3.00
LIGAND		5.00	5.20	4.60	5.00	4.00
S T(CONTROL)		27.00	31.00	31.00	33.00	22.00

Key: *A Xanthomonas avonopodis B Streptococus faecadis C Pseudomonas aeruginosa D Chromobacterium EErwinia carotovora LIGAND Prednisolone S T Streptomycine sulphate (Control)*

Table9. *Antifungal Screening Of Metal Complexes*

Complexes	RATIO	A	B	C	D	E
$CuL(H_2O)SO_4H_20$	1 : 1	49.35	14.00	6.00	12.50	25.00
$CuL(H_2O)SO_4H_20$	1: 2	56.66	16.00	10.00	25.00	30.00
$ZnL(H_2O)SO_4H_20$	1: 1	23.33	8.00	20.00	35.00	13.00
$ZnL_2(H_2O)SO_4H_20$	1 : 2	26.66	16.00	17.00	40.00	25.00
LIGAND		8.00	8.00	8.60	10.00	8.00
Mancozeb (CONTROL)		60.66	62.00	66.67	68.00	70.00

Key: A *Collectotrichum falctrm B Phythophthora palmivora C Ceratocystis paradoxa D Helminthosporium toxicum E Pericularia oryzal LIGAND Prednisolone CONTROL(Mancozeb)*

4. DISCUSSION

Prednisolone formed stable complexes with both copper and zinc at different ratio 1:1 and 1:2 respectively. The suggested molecular formulae, colour, percentage yield, melting point or decomposition temperatures percentage of sulphur contents in the complexes and metal analyses for the metal complexes of Cu(ll) and Zn(ll) as given in Table l. The copper complexes gave brown and blue colours. This in an implication of dominant effect of the ligand on the copper (II) ion while, zinc complexes gave white colours which have shown that ligand has no effect on the metal. The percentage yield was reasonably high. The sharp melting points for the metal complexes suggested pure metal complexes. The elemental analyses results obtained experimentally were in good agreement with the theoretical values.

Table 2 also explained solubility of the metal complexes in different solvents. They were found to be soluble in most organic solvents but insoluble in water, implying that they were non polar in nature.

The antimicrobial screenings of the metal complexes, ligand (prednisolone), and the control were carried out on both the fungi and bacteria of plant pathogens. The selected fungi species were Collectotrchum falcutrum, Phythophytora palmivora, Ceratocystis paradoxa, Pericularia oryzal, Helminthosporium toxicum and the bacteria species included Xanthomonas axonopodis, Streptococcus faecadis, Pseudomonas aeruginosa, Chromobacterium, Erwinnia carotovora. The results obtained for both the antifungi and antibacteria activities have indicated that metal complexes were more proactive than the parent ligand and this is enhanced by the reactions of metals with the ligand. It also envisaged that the activity increases on complexation as the concentration of the ligand increases [10]. The pharmacological activity of metal complexes is highly dependent on the nature of the metal ions and the donor sequence of the ligands because different ligands exhibit different biological properties [11]. The anti- fungi activity of metal complexes was found to be in order Cu(ll) > Zn (lI) with an increase in concentrations [4]. Table 8 indicates that the parent and ligand do not inhibit the proliferation of the tested microbes and that zinc conjugation synergistically enhances the antimicrobial activity of their parent ligand. Such enhancement may be due to an increase in cell permeability of the lipophilic zinc conjugate which allows for the intracellular chelate accumulation [12].

Different stages of thermal decompositions were recognized from 10-100^{o}C. This represents the boiling point of water present outside the coordination sphere of metal complexes 35% of water of crystallization calculated which corresponded to about two molecules of H_2O and which could be found as unbounded water molecule while 55% of the complex in ratio 1:1 of Cu(ll) prednisolone. This could be ascribed to the amount of water molecule present in the inner sphere of the metal complex at the temperature of 100-200^{o}C. This is corresponding to the three or 3 molecules of water present as coordinated water. However, a fall in temperature between 200-400^{o}C represented the organic compound and the residue could be confirmed to fall between 400-800^{o}C as CuO [13].Thermal decomposition or dehydration of the complex in ratio 1:2 occurred in two stages, the first stage which is a loss of a water molecule in the outer sphere of the coordination which occurred between 0-100^{o}C followed by a fall in temperature between 100-200^{o}C, representing two water molecules in the inner sphere of metal complex leaving behind non hydrated molecule [14]or complex which took place between 200-400^{o}C which is corresponded to the decomposition of prednisolone ligands and end product was CuS which later oxidized to CuO. Zn(ll) prednisolone complexes in ratio 1:1 and ratio 1:2 thermal decomposition result have demonstrated four stages. The first stage was the removal of two outer uncoordinated water molecules from the coordination sphere of the metal complexes at the temperature between 0-100^{o}C. Another curve observed around 100-200^{o}C could be ascribed to the removal of inner coordinated water molecule. Thermal decomposition found between the temperature 200-400^{o}C, leading to sloppy gradient could be attributed to prednisolone ligand while a steady decline and constant percentage weight loss recorded at temperature 400-800^{o}C. This could be ascribed to metallic sulphide (ZnS) which later oxidized to metallic oxide of ZnO[15].The proposed structure would be $ZnLSO_4(H_2O)_3(H_2O)_2$.However, Zinc(II) prednisolone complex in ratio 1:2 has displayed a similar curve with high % of inner coordinated water to ligand. The % residual weight loss obtained at temperature between 0-100^{o}C, equivalent to the removal of outer uncoordinated water molecules, also decomposition temperature around 100-200^{o}C equivalent to the coordinated water molecule. The % weight loss at the temperature between 200-400^{o}Crepresented the ligand while the temperature found around 400-800^{o}C with steady % weight loss could be equivalent to the end product ZnS which later oxidized to the metallic oxide ZnO.

The FTIR spectra of the complexes were compared with that of the ligand to determine the change that might take place during complexation. The ligand (prednisolone) showed a broad band at 3360cm^{-1} which could be assigned due to OH group. The intense band found in the 1697-1711cm^{-1} region could be attributed to the presence of carbonyl (C=O) stretch before the complexation. This was also observed by Chandraleka and Chandramohan in 2014 [13]. The IR spectra of the copper(II) prednisolone ratio 1:1 and 1:2 have shown a broad band at 3390cm^{-1} and 3415 and 3508cm^{-1} respectively with deviations from the ligand with band at 3360cm^{-1}. The FT IR spectra of the copper(II) prednisolone complexes in ratio 1: 1 and 1:2 have shown broad bands at 3390 cm-1 and 3415 and 3508 cm^{-1} respectively with deviations from the ligand band which occurred at 3360cm^{-1}. This is an indication of complexation and the presence of water molecules in form of –OH in the

outer coordination sphere of the metal complexes. However, an intense bands found around 1697-1711 cm^{-1} in the ligand but with a lower shift to 1709–1707 cm^{-1} respectively in the metal complexes, indicating the involvement of the C=O in the coordination of metal to the ligand. Furthermore, the strong peaks found around 777 and 722 cm^{-1} regions in the metal complexes but conspicuously absent in the ligand could be attributed to the coordinated water molecules as confirmed or shown by the presence of water molecules in the inner sphere of the metal complexes [16]. On the other hand, some prominent bands were around 604 and 605cm^{-1} in the metal complexes but not found in the ligand, also, the band in the regions 412 and 410cm^{-1}respectively but not foundin the spectrum of the ligand are the evident of M–L and M–O coordination posited earlier by Siddiq and coworkers in 2006[17]. Zn(II) prednisolone complexes in ratio 1:1 and 1:2 spectra have displayed prominent regions or bands around 3414 , 3508 and 3505 and 3565cm^{-1} which might be responsible for phenolic (-OH) group bonded to O– prednisolone (ligand).Also, the strong bands at 1707 and 1707 cm^{-1} in the metal complexes are attributed to C=O of prednisolone ligand but with reduced bands when compared with the ligand which absorbed at 1697 – 1711cm^{-1}, suggesting the coordination of metal through the ketonic group of prednisolone. However, the observable bands at 773 and 770 cm^{-1} could be ascribed to the coordinated or bounded water molecules to the inner sphere of metal complexes but these regions are obviously absent in the IR spectrum of the ligand, while, M–L and M–O absorbance are equivalent to the bands or peaks at 603 and 606cm^{-1} and 470 - 485 cm^{-1}respectively, which were not originally present in the ligand [16]. Furthermore, the prominent strong bands or peaks between 1080 – 1130cm^{-1} in the copper (II) and zinc (II) prednisolone complexes which are not found in the ligand could be attributed to the presence of sulphate ions (SO_4^{2-}), which was confirmed in the gravimetric analysis of sulphur in form of sulphate by bariun chloride Mohrs method [4,5].

5. CONCLUSION

Prednisolone complexes with cobalt (II) and Zn (II) were synthesized and characterized. The results obtained have indicated that metal complexes were non – polar in nature, sharp melting points and stable at room temperature. Metals coordinated to the prednisolone (ligand) through the C-O (ketonic group) and –OH (phenonic group) bidentately. The thermogravimetric studies on metal complexes have shown that metal decomposition proceeded in three stages. The anti-microbial results have also revealed that prednisolone ligand has a poor anti-microbial properties while the metal complexes are better and can be recommended for the tested organisms under studied for their proactive properties.

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