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Liquid - Assisted Solid State Synthesis and Antibacterial Activity of Fe (II) and Mn (II) Complexes of Amoxicillin

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Abstract: ***Amoxicillin (amox) interacts with transition metal ions to give $[M(amox)_2Cl_2]$ in 1:2 mole ratios, where M= Fe(II) and Mn(II). The complexes were characterized by physicochemical and spectroscopic methods. The IR spectra of the complexes suggest that the amoxicillin acted as bidentate ligand which coordinated to the metal ion through υ(COO) and υ(C=O). Antibacterial activities of the amoxicillin and the complexes were tested and compared.***

Keywords: Liquid-assisted grinding, synthesis, antibiotic, Transition metal, complex.

I. INTRODUCTION

Mechanochemistry (solid state) is a branch of chemistry concerned with the chemical and physicochemical transformations of substances in all state of aggregation induced by mechanical energy [1]. Solid state has been successfully developing in recent years and has appeared as efficient methods for the synthesis of single-and multi-component crystalline solids (co-cryatals and salts). A mechanical technique has been employed in the synthesis of active pharmaceutical ingredients (APIs) using both liquid assisted and net grinding. Using this principle, Braga and co-workers used mechanical grinding to prepare derivatives of the neuroleptic drug gabapentin with zinc and copper (II) chlorides [2]. Inorganic synthesis in manual (ball mills) or non-manual (mortar and pestle) methods has been applied in a number of cases to ligand and hosts. Recently, a number of researchers have shown that, as reported by [3] the complex salts of the form $[H_2bipy][MCl_4]$ and $[H_2im]_2[MCl_4]$ (bipy=4,4^1-bipyridine; Him=imidazole; M=Zn, Cu, Fe and Pt) can be transformed into their corresponding coordination compounds $[MCl_2(bipy)]$ and $[MCl_2(Him)_2]$. [4] reported solid state synthesis by simple grinding using agate mortar and pestle of the prepared $[H_2pymo][ZnCl_4]$ by reacting $[H_2pymo]Cl$ and $[ZnCl_4]$.
The term grinding is generally describing the mechanical action by hand surfaces on a material, normally to break up the material and reduce its particle size. It may therefore refer to manual method (ball milling) or non-manual methods (mortar and pestle). Also, other techniques are associated with grinding solids in the presence of liquids. Few nominal amount of liquid can accelerate, and even enable, mechanochemical reactions between solids. Such reactions are called minimal solvent rather than entirely solvent free. The original term to describe them is “solvent drop grinding” (SDG) which has been superseded by “liquid assisted grinding “(LAG) [1]. LAG is also effective in screening for pharmaceutical salts. In particular, [5] compared LAG and net grinding in screening for salts of APIs trimethoprim and pyrimethamine. LAG was more efficient in forming salts or salts polymorphs. Recently, LAG was used by [6] to screen for new solvate and salt forms of the anti-biotic 4-aminosalicyclic acid. The aimed of this research is to synthesize and characterize Fe(II) and Mn(II) chlorides via liquid assisted grinding (solid state) methods. To also determine the activity of the complexes in order to establish how metal-drug binding influence the activity of the drug.

II. MATERIALS AND METHOD

All the reagents were of analytical grade and used without any further purification. The active pharmaceutical ingredient, amoxicillin was obtained from Sigma Aldrich. Metal salts used include metal (II) chlorides of Fe, and Mn. All weighing was done using weighing balance model B154 METTLER TOLEDO. Molar conductance measurement was done using Jenwey conductivity meter model 4010 in dimethyl sulfoxide (DMSO). Jenwey 6305 UV-Visible Spectrophotometer was used for UV-absorbance measurement. Decomposition/ melting temperature were recorded using Stuart melting point apparatus (SMP 10). Magnetic susceptibility measurement of the complexes was recorded using Magnetic Susceptibility balance of Sherwood Scientific Cambridge UK. The bacterium isolates; *Escherichia Coli, Staphylococcus Aureus* and *Salmonella typhi* were obtained and identified at Department of Microbiology, Bayero University Kano. Metal to Ligand ratio was determined using Job’s method of continuous variation and Infrared spectra of ligands and complexes was recorded using Fourier Transform Infrared Spectrophotometer by Agilent Technologies.

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A. Synthesis of $[Fe(amox)_2Cl_2]$ and $[Mn(amox)_2Cl_2]$ complexes

The method reported by [7] was adopted and modified for the preparation of complexes. Metal salts (1 mmol, 0.03654 g of $FeCl_2.4H_2O$ and 0.198 g of $MnCl_2.4H_2O$ were grinded with 0.7308 g (2 mmol) of amoxicillin in 1:2 stoichiometric molar ratios in the presence of one drop of methanol for about 10-15mins to obtain brown and yellow cream powder as a product. The product then dried in desiccator.

$$2Amox + Mcl_2.4H_2O \xrightarrow[10\text{-}15\ min]{LAG(CH_3OH)} [M(amox)_2Cl_2] \qquad \text{where M= Fe \& Mn}$$

Scheme 1: Synthetic reactions of $[Fe(amox)_2Cl_2]$ and $[Mn(amox)_2Cl_2]$ complexes

B. Physical Measurements

Melting points and decomposition temperature of the ligand and the complexes were determined on Sturt melting point apparatus (SMP 10). The results are presented in Table 1.

The solubilities of both the ligand and the complexes were determined in different solvents ranging from polar to non-polar such as methanol, ethanol, chloroform, ethyl acetate, hexane, CCl_4, DMF and DMSO. The results are presented in Table 2.

Molar conductivity for the complexes were recorded using Jenwey conductivity meter model 4010 at the Department of Pure and Industrial chemistry, Bayero University Kano, Nigeria. Concentration of 10^{-3} molar solution of the complexes were prepared in DMSO. The results are presented in Table 3.

C. Magnetic Susceptibility Measurement

Metal complexes prepared were introduced into a capillary tube up a given mark and the reading recorded using the magnetic susceptibility balance of sherwood scientific combridge UK. The formula below was used to calculate the magnetic susceptibilty (Xg).

That is,

$$Xg = \frac{CL\ (R - Ro)}{10^9\ M}$$

D. Infrared Spectra

Fourier transform infrared (FT-IR) spectra were recorded on Spectrophotometer by Agilent technologies model at Biochemistry Department, Bayero University Kano, Nigeria, in the range 4000-500cm^{-1} as KBR pellets. Spectra was recorded for both ligand and complexes. The data presented in Table 4.

E. Determination of Metal to Ligand Ratio

The number of ligand coordinated to the metal ion was determined using Job's method of continuous variation. 3.0mmol of Dimethyl sulfoxide (DMSO) solution of the ligands and the metal chlorides were prepared. The following ligand to metal salt ratio (in ml) 00:16, 01:15, 03:13, 05:11, 07:09, 09:07, 11:05, 13:03 were taken from the ligand solution and each of the metal chloride solution respectively. A total volume of 16ml was maintained (in that order) throughout the process and the mole fraction of the ligand was calculated in each mixture. The solution of the metal salts were scanned (as blank) to find the wavelength of maximum absorbance (λ_{max}) for that particular metal ion [8]. The machine was fixed at λ_{max} (in each case) before taken the absorbance values.

The absorbance values were extrapolated against mole fraction of the ligand and the number of coordinated ligand (coordination number) was determined using the relation below:

$$\frac{\overline{n}}{(1-x_i)} = x_i$$

Where $\overline{n}$ = number of coordinated ligand and X_i= mole fraction at maximum absorbance

F. Antibacterial Screening

Antibacterial properties of the antibiotic (ligand) and metal complexes were carried out using agar-well diffusion method against the following bacteria species of both (Gram-positive and Gram-negative); *Staphylococcus aureus, Salmonella typhi* and *Escherichia coli*. 0.02 g of antibiotic (ligand) and complexes were dissolved in 1 ml of Dimethyl Sulfoxide (DMSO) to give stock solutions of three different concentrations (5µg, 10µg and 20µg) which has been prepared by half serial doubling dilution method. Then, they

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were placed on the surface of the culture media and incubated at room temperature for 48hrs. Diameter of zone of inhibition produced by both the antibiotic (ligand) and the complexes was compared with the standard at 20µg [9].

III. RESULTS AND DISCUSSION

The complexes synthesized are colored brown and yellow cream. This is typically transition metal due to d-d transition, which is similar with the result reported by [10]. All the complexes have higher melting point than their parent drug probably due to complexation and also revealed the more stable nature of the complexes as shown in Table 1. The values are in agreement with similar metal(II) complexes reported by [11].

Table 1: The Physical Properties of the ligand and its Metal (II) Complexes

Compounds	Molecular Formula	Molar Mass	Colour	Melting point (^oC)	Decomposition temperature (^oC)
Amoxicillin	$C_{16}H_{19}N_3O_5S$	365.4 g/mol	White	189	
Amox -Fe(II)	$C_{16}H_{27}N_3O_9SCl_2Fe$	564.15 g/mol	Brown	-	217
Amox -Mn(II)	$C_{16}H_{27}N_3O_9SCl_2Mn$	563.24 g/mol	Yellow cream	-	245

All the complexes are soluble in hexane, CCl_4, and DMSO. They are insoluble in polar organic solvents. This is because polar compounds are expected to be soluble in polar solvent, while non-polar compounds are expected to be soluble in non-polar solvents (like dissolve like), which is in agreement with results reported by [9].

Table 2: Solubility of the ligand and its Metal (II) Complexes

Ligand/ Complexes	Methanol	Ethanol	Chloroform	Ethyl Acetate	Hexane	CCl_4	DMF	DMSO
Amoxicillin	S	S	IS	S	IS	IS	S	S
Amox -Fe(II)	IS	IS	IS	IS	S	S	IS	S
Amox -Mn(II)	SS	SS	IS	IS	S	S	SS	S

Key: S-soluble, SS-slightly soluble, IS-insoluble

Magnetic susceptibility studies show that, all the complexes are paramagnetic with the values of 4.0BM and 5.3 BM (Table 3), which all the values lie within the range that correspond to spin-only value magnetic moment for high spin octahedral geometry around Fe(II) and Mn(II) ions, which is in agreement with similar paramagnetic compounds reported in the literature by [12,13].

Table 3: Effective Magnetic Moment and Molar Conductance of the Complexes

Complex	Mass/ Magnetic Susceptibility (Xg) (g^{-1})	Molar Susceptibility (Xm) (mol^{-1})	Effective magnetic moment (BM)	Molar Conductivity ($\Omega^{-1}cm^2mol^{-1}$)
Amox -Fe(II)	$8.4x10^{-6}$	$7.2x10^{-3}$	4.0	8.42
Amox -Mn(II)	$1.7x10^{-5}$	$1.3x10^{-2}$	5.3	5.58

The molar conductivities values of the complexes obtained are 8.42 $\Omega^{-1}cm^2mol^{-1}$ and 5.58 $\Omega^{-1}cm^2mol^{-1}$ respectively, which shows the absence of ions or few ions present. The results indicated non-electrolytes of all the complexes due to the lower values. The results which are presented in Table 3 are in line with the report of [9, 12 & 14].

The infrared spectral data are presented in table 4. The bands at 1689.54 cm^{-1} and 1774.50 cm^{-1} in the spectrum of free amoxicillin are assigned to υ(C=O) of amide and carboxylic acid respectively, these shifted to the regions of 1584.78 cm^{-1} and 1778.92 cm^{-1}, 1737.91 cm^{-1} and 1778.93 cm^{-1} in the complexes, which suggested the coordination of carboxylic oxygen after deprotonation [11].

Table 4: The IR Spectra Data of the ligand and its Metal (II) complexes

Compounds	υ(C=O)cm^{-1} of amide	υ(C=O)cm^{-1} of carboxylic acid	υ(N-H)cm^{-1}	M-O
Amoxicillin	1689.54	1774.50	3454.83	-

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Amox-Fe(II)	1584.78	1778.92	3361.89	579.09
Amox-Mn(II)	1737.91	1778.93	3324.66	553.00

The bands at the range 579.09 cm^{-1} and 553.00 cm^{-1} in the spectrum of the complexes which could not be traced to the free ligand spectrum is tentatively assigned to M-O stretching frequencies. Similar complexes have been reported by other researchers [10,11,15] using solution based synthesis.

The octahedral geometry agrees with IR spectra and similar to the structures reported by [10,11,15].

Metal to ligand ratio was estimated using Job's method of continuous variation, in which shows mole fraction of the Ligand and absorbance for the respective metal ions (Fe^{2+} and Mn^{2+}) are presented in Table 5 as reported in the literature by [8].

Table 5: Mole Fraction of the Ligand and Absorbance of Fe^{2+} and Mn^{2+} with the Ligand

Mole fraction X(total volume=9ml	Fe:L_2' λmax=580nm	Mn:L_2' λmax=635nm
0.063	0.099	0.065
0.188	0.100	0.066
0.313	0.177	0.069
0.438	0.212	0.077
0.563	0.253	0.078
0.688	0.224	0.070
0.813	0.223	0.050
0.938	0.127	0.040
1.000	0.095	0.030

Plot of absorbance against mole fraction in each case gives a curve with maximum absorbance corresponding to the ligand mole fractions which were used in calculating the number of coordinated ligand, which suggest 1:2 Metal-Ligand ratio in all the prepared complexes as reported by [16].

Table 6: Anti-bacterial Activity Test of ligand and its Metal (II) complexes

		Inhibition Zones		
Compounds	Concentration (µg/agar-well)	S. aureus (mm)	E. coli (mm)	S. typhi (mm)
Amoxicillin	5	24	18	20
	10	28	28	33
	20	30	35	42
Amox-Fe(II)	5	-	-	17
	10	-	10	24
	20	-	15	37
Amox-Mn(II)	5	29	20	18
	10	37	25	21
	20	40	34	29
Standard (Gentamycin)	20	48	37	33

Key: S. aureus = Staphylococcus aureus E. coli = E scherichia coli S. typhi=Salmonella typhi

Antibacterial screening results shows that the complexes are active against all bacteria isolates in all concentration except Amox-Fe(II) which is inactive against Staphylococcus aureus and Escherichia coli at 5µ/ agar-well, as reported by [11].

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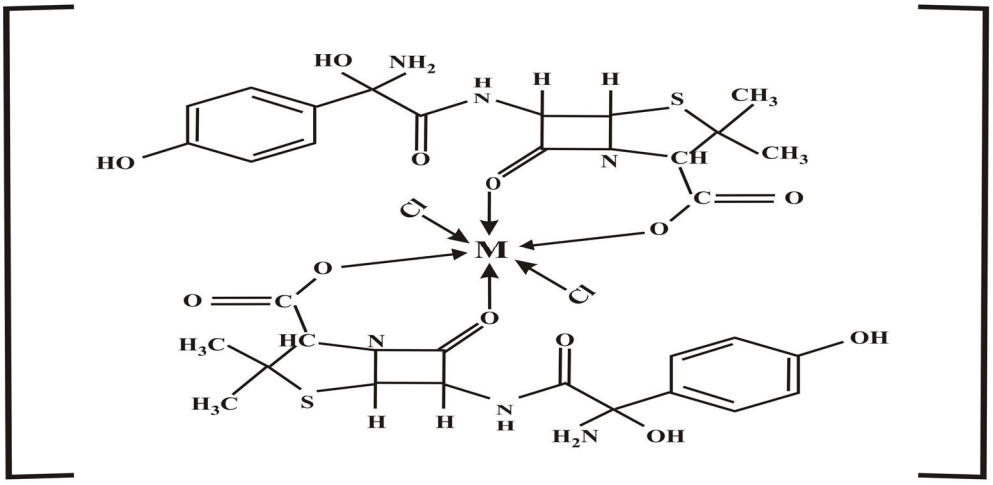

Fig 3: Proposed structure of the Complexes (M= Fe^{2+} and Mn^{+})

IV. CONCLUSION

This research work also demonstrated again, the use of solid state synthesis approach for the synthesis of active pharmaceutical ingredients (APIs). Also, it was proved that, the solvent free solid-solid state synthesis can be used to obtain the same product as that obtained from solution method.

From the data obtained; IR, molar conductivity and effective magnetic moment suggested geometry. The ligand is coordinated to the metal ions through υ(C=O) and υ(COO) given rise to octahedral geometry.

V. CONTRIBUTION OF AUTHORS

All the reported authors, Jibril S, performed the experimental work, Kurawa M. A supervised the research works. Sani S, assist in the interpretation of results while Shehu S. M and Mohammed K contributed in the literature search. All the authors agreed with the final manuscript.

VI. CONFLICT OF INTEREST

All authors declare and accepted that, no conflict of interest.

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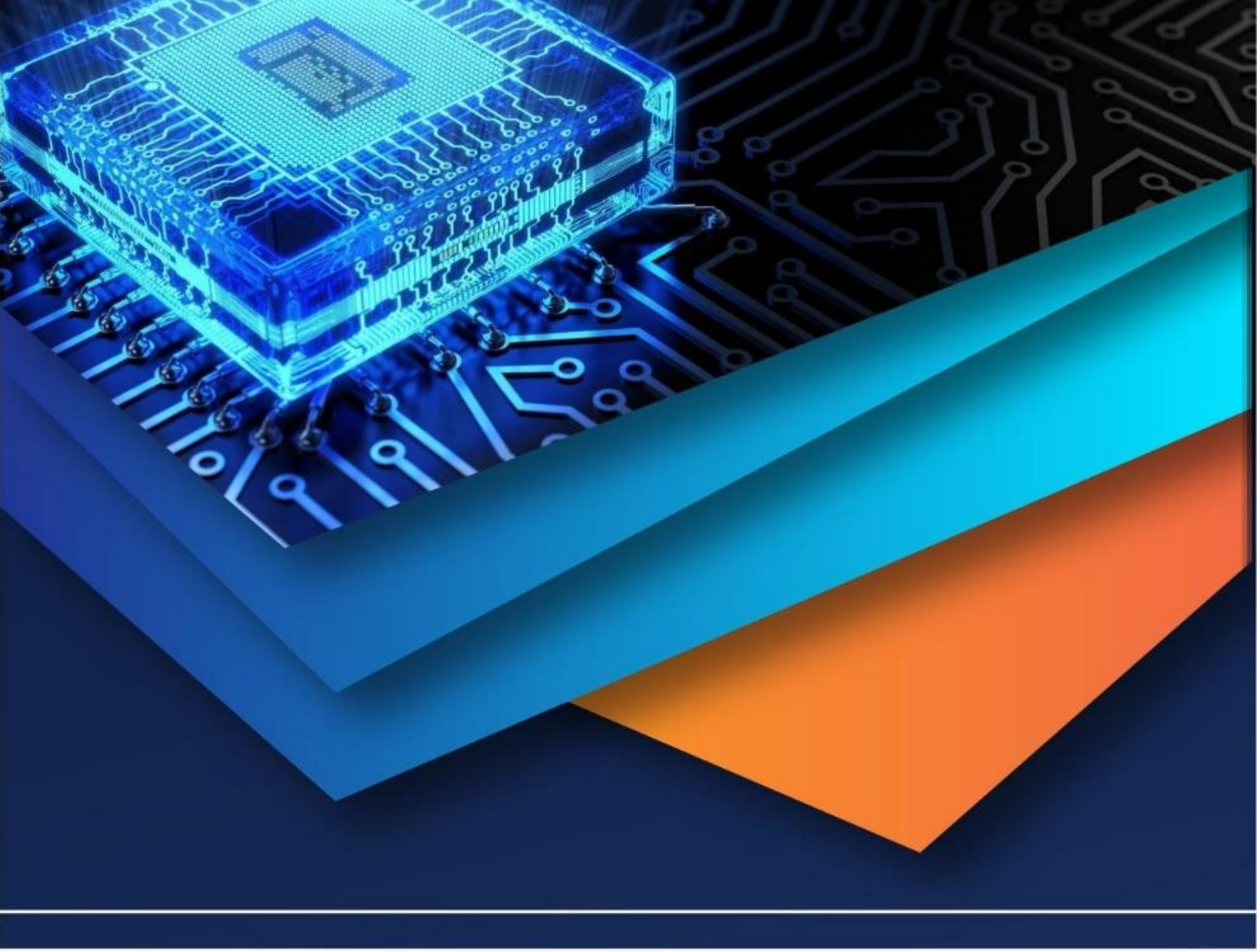

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