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Mechanochemical Preparation and Biological Activity of Mn (II) Complex from Ciprofloxacin

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Abstract: The mechanochemically prepared complex $[Mn(cip)_2Cl_2]$ was synthesized using simple neat grinding method and analyzed using spectral studies, elemental analysis and physicochemical properties. The complex shows increase in biological activity compared with both the free ligand of ciprofloxacin and the standard. The IR spectral analysis of the complex, the ligand ciprofloxacin acts as bidentate ligand that indicate a strong band in the spectra at 1707.92 cm^{-1} and 1628.81 cm^{-1} which was assigned to υ(C=O) cm^{-1} υ(COO) cm^{-1}. It shifted to a lower frequency's regions of 1707.92 cm^{-1} and 1625.40 cm^{-1} in the complex indicating the involvement of carbonyl groups of both amide and carboxylic acid in the coordination, the bands at 478.20 cm^{-1} and 750.39 cm^{-1} which is absent in the free ligand appeared in the complex was assigned to υ(M-O) and υ(M-Cl) band. The value obtained from molar conductivity at 10.7 $\Omega^{-1}cm^2mol^{-1}$ indicate that the complex is non-electrolyte in DMSO. Both the elemental and physicochemical analysis agreed with the proposed structure of the compound and also suggested one metal to two ligands ratio. Due to environmentally friendly, shortest reactions time, inexpensive, production of higher yields the authors recommend the use of mechanochemical methods over solution-based.

Keywords: Mechanochemically, Prepared, Complex, Ciprofloxacin

1. Introduction

As formalized by IUPAC, a mechanical-assisted reaction is "a reaction caused by the mechanical energy". In fact, mechanical actions, such as compression, stress, or friction, usually provides the energy to activate a process. The principal feature of mechanical-assisted process is the achievement of chemical changes by the only action of grinding (or milling), without needing to dissolve reagents (therefore without using any solvent) [1]. Grinding is a broad term that describes the effect of mechanical forces on a compound that allows a solid breaking into small parts. By grinding, the improved potential energy together with friction and shear contributions, generate surface and shape defects in the reactants.

This enabling technology is characterized by mechanical grinding of reactants and induces chemical reactivity by mechanical force (e. g. by compression, shear, or friction) [2]. In general, mechanochemical provides advantages such as prevent the use of excessive solvent, short reaction time, high efficiency, well as being more cost effective than traditional synthesis [3]. Nowadays, A firmly established application of modern mechanochemistry is generally in medicinal chemistry which termed as "medicinal mechanochemistry". Several researchers reported the mechanochemical synthesis of drugs, for example [4] reported the liquid-assisted mechanochemistry in the synthesis of pharmaceuticals. To date, mechanochemical approaches being applied to

transformations from across the chemical sciences have been reported, spanning from the synthesis of inorganic and organic compounds.

This research work aims to mechano-chemically prepared Mn (II) complex of ciprofloxacin and also to determine how metal-drug binding influence the activity of the drug.

2. Materials and Methods

2.1. Materials

The reagents used were of analytical grade and used without any further purification. The API of Ciprofloxacin was obtained from Bristol Scientific-Sigma Aldrich. Metal salt used is $MnCl_2 \cdot 4H_2O$. Glass wares used in the work were washed thoroughly, rinsed with distilled water and dried in an oven at 110°C. Weighing balance of model B154 Mettler Toledo was used during the experiment. Stuart melting point apparatus SMP0 was used to determine the melting point, Jenway conductivity meter model 4010 (10^{-3}g in 10ml DMSO) was used in determining molar conductance, while magnetic moment of the complexes was obtained using Magnetic susceptibility balance of Sherwood scientific Cambridge UK. Elemental analysis was carried out using Series II CHNS/O Analyzer 2400 and metal content of the complexes was determined in AA240FS, Fast Sequential Atomic Absorption Spectrometer. The FTIR spectra were recorded as KBr on FTIR-8400S in the range of 4000-400cm^{-1} while the electronic spectra of the complexes were recorded using ultraviolet spectrometer lambda 35 with the range of 200-700nm. The biological activity was determined using agar-well diffusion method.

2.2. Mechanochemical Preparation of the Complex

The method [5] was modified and adopted for the preparation of the complex by simple grinding of 2 mmol (0.66g) of ciprofloxacin with 1 mmol (0.166g) of $MnCl_2 \cdot 4H_2O$ in a mortar and pestle for about 10 minutes until a clear yellow powder was obtained as a product. The product obtained were dried in desiccator.

$$MnCl_2.4H_2O + 2\ cip \xrightarrow[10\ minutes]{Neat\ Grinding} [Mn(cip)_2Cl_2]$$

Figure 1. *Formation of $[Mn(cip)_2Cl_2]$.*

2.3. Antibacterial Screening

The [6] method was used in which 0.02 g of both metal (II) complex and the ligand were each dissolved in 1 ml of Dimethyl sulfoxide (DMSO) to gives a stock solution using half serial doubling dilution method of 20 µg/ml, 10 µg/ml and 5 µg/ml which were placed on the surface of the culture media and incubated at room temperature for 48hrs. Then in *vitro* antibacterial activity against *Escherichia coli, Salmonella Typhi* and *Staphylococcus aurous* were carried out by agar-well diffusion method. Standard was used to compare with the diameter of zone of inhibition produced by ligands and complexes.

3. Results and Discussion

The prepared complex was completed within shorter period of 10 minutes to yield a higher yield and yellow colour compound with a melting point of 300°C which is higher than the free ligand of ciprofloxacin due to coordination with the metal ion as presented in Table 1 [7].

Table 1. *The Physical Properties of Ciprofloxacin and its Metal (II) Complex.*

Compounds	Colour	Melting point (°C)	D/ temperature (°C)	Molar Conductivity ($\Omega^{-1}cm^2mol^{-1}$)	Effective magnetic moment (BM)
Ciprofloxacin	White	255		-	-
$[Mn(Cip)_2Cl_2]$	Yellow	-	300	10.07	5.5

The conductivity as presented in Table 1 was measured in DMSO (10.07 $\Omega^{-1}cm^2mol^{-1}$) which fall within the range of non-electrolytes in DMSO [8] which was frequently used to elucidate the geometry of the complex.

The suggestion of the likely geometry of complexes can also be provided by their magnetic moment. The magnetic moment of 5.5BM as in Table 1 is tentatively proposed high spin octahedral geometry since the value lies within the range that correspond to spin-only value magnetic moment for high spin octahedral geometry around Mn (II) ion as reported in the literature [9].

Table 2. *The elemental analysis data of the complex.*

Compounds	Molecular formula (Molar Mass)	Elemental analysis: found (calculated)%			
		C	H	N	M
$[Mn(Cip)_2Cl_2]$	$C_{17}H_{18}FN_3Cl_2Mn$ (789)	25.99 (25.86)	2.80 (2.28)	4.00 (5.32)	15.29 (15.97)

3.1. Elemental Analysis

The elemental analysis data obtained are presented in Table 2 in which both the percentage of C, H, N and Metal ion proved the proposed structure of the complex $[Mn(cip)_2Cl_2]$ [10].

3.2. Infrared Spectra

The infrared spectra for both the free ligand of ciprofloxacin (Cip) and metal complex are given in *Figure 2* and *Figure 3* respectively, while the IR data are presented in Table 3 and compared [11].

Table 3. *The IR Spectra Data of Ciprofloxacin and its Metal (II) complex.*

Compound	υ(O-H) cm^{-1}	υ(COO) cm^{-1}	υ(C=O) cm^{-1}	υ(C-O) cm^{-1}	M-O	M-Cl
Ciprofloxacin	3403.99	1628.81	1724.95	1473.82	-	-
$[Mn(Cip)_2Cl_2]$	3530.56	1625.40	1707.92	1495.43	478.20	750.39

Keys: υ=Wave number, M= Metal, O= Oxygen, Cl=Chlorine.

Table 4. *Electronic spectra in DMSO solvent for the ciprofloxacin and metal complex with the suggested geometry.*

Compounds	Electronic Spectra			Suggested Geometry
	Wavelength (nm)	Energy (cm^{-1})	Assignments	
Ciprofloxacin	205	48780	$n \rightarrow \pi^*$	-
	210	47619	$\pi \rightarrow \pi^*$	
$[Mn(Cip)_2Cl_2]$	221	45248	$^6A_{1g} \rightarrow {}^6A_{1g}$	Octahedral
	237	42194	MLCT	

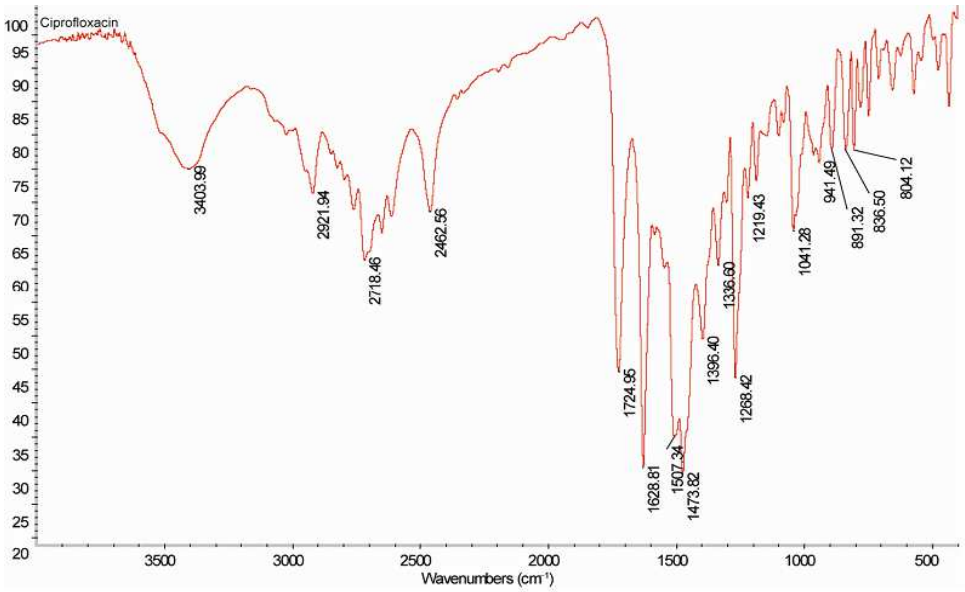

Figure 2. *Infrared Spectrum of Ciprofloxacin.*

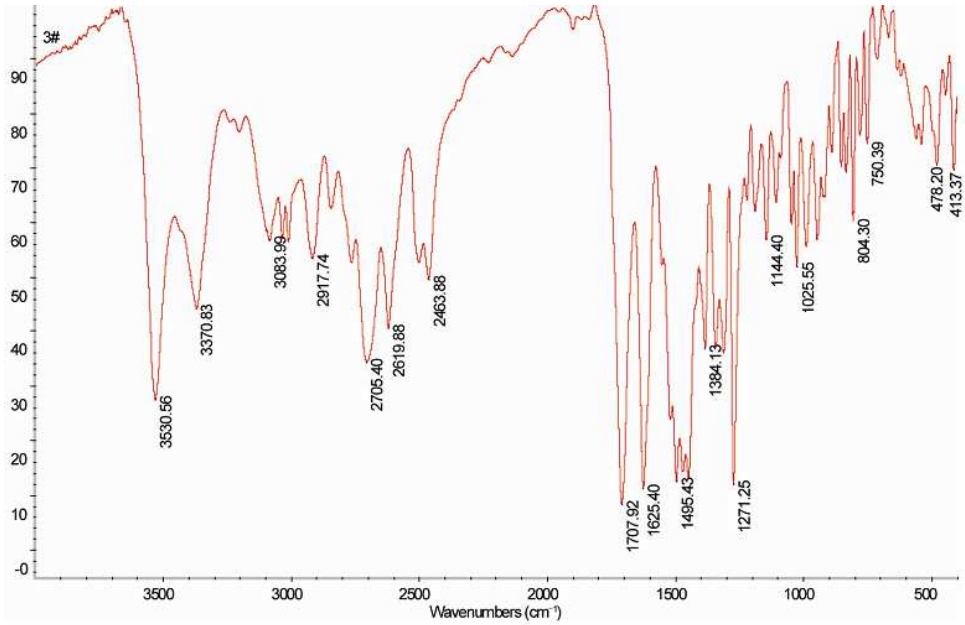

Figure 3. *Infrared Spectrum of Ciprofloxacin Manganese.*

The infrared spectral of the ligand (ciprofloxacin) shows the bands at 1724. 95 cm^{-1} and 1628.81 cm^{-1} which was both assigned to υ(C=O) and υ(COO) vibrational frequency and re-appeared at 1707.92 cm^{-1} and 1625.40 cm^{-1} in the complex which is difference in the free ligand as it provide evidence of coordination through both the carbonyl groups, as presented in the literature [12]. The new bands which are not present in the spectrum of the ligand at 478.20 cm^{-1} and 750.39 cm^{-1} is assigned to M-O and M-Cl vibration which support the involvement of O and Cl atoms in the complexation with metal ion under investigation. Similar results were reported by [13].

3.3. Electronic Spectra

Electronic spectra are presented in Table 4 in which the ligand ciprofloxacin shows two bands at 205nm and 210nm which were assigned to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ [14], while in the complex the bands re-appeared at 221nm and 237nm is assigned to $^6A_{1g} \rightarrow {}^6A_{1g}$ and MLCT transition. This transition is within typical of octahedral geometry around metal ion [14].

3.4. Biological Activity

Biological activity test is presented in table 5.

Table 5. *Anti-bacterial Activity Test of Ciprofloxacin and its Metal (II) complex.*

Compounds	Concentration (µg/ agar-well)	Inhibition Zones		
		S. aureus (mm)	E. coli (mm)	S. typhi (mm)
Ciprofloxacin	5	13	15	18
	10	17	20	19
	20	24	25	22
$[Mn(Cip)_2Cl_2]$	5	29	19	-
	10	32	26	19
	20	35	32	26
Standard (Gentamycin)	20	27	37	44

S. aureus = Staphylococcus aureus, E. coli = Escherichia coli, S. typhi=Salmonella typhi.

The complex is active against bacteria isolates in both higher concentration of 10µg and 20µg while inactive against 5µg *Salmonella Typhi*. Generally, the complex shows significant antibacterial strength and these values are compared with the standard of Gentamycin [15].

4. Conclusion

These results revealed that metal-drug complexes can be prepared mechanochemically. The spectral studies also revealed the coordination of the ligand to the metal ion through both the carbonyl groups in the ligand making the ligand to be bidentate and the complex to be octahedral geometry. Elemental analysis proved the proposed structure of the complex and biological activity of the complex shows increases compared with the ligand.

5. Recommendation

Of all solid-state techniques, mechanochemistry is becoming the focal point of efforts to design solid-state syntheses. Often found to lead to shorter reaction times and higher yields than its solution counterparts.

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