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# Synthesis of New Cadmium(II) Antipyretic Drug.

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**ABSTRACT**

A new Cd(II) complex of diclofenac (Diclo) anti-inflammatory drug has been prepared and characterized using elemental analysis, IR spectra, molar conductance and thermal analysis (TG). Thermal stabilities and the decomposition steps have been designed using thermogravimetric analyzer. The antimicrobial assessments were performed used an official method.

**Keywords:** Diclofenac sodium, cadmium(II) complex, antimicrobial, spectroscopic studies.

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## INTRODUCTION

Diclofenac sodium (Diclo-Na) is a sodium salt of aminophenyl acetic acid (see Fig. 1) and is a well-known representative of non-steroidal anti-inflammatory drugs (NSAIDs) [1,2].

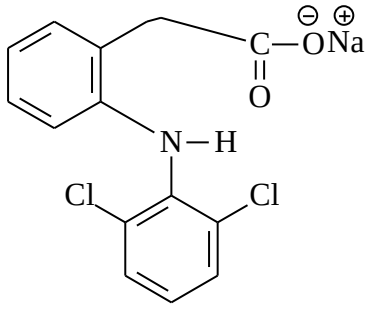


**Fig 1: Schematic structure of diclofenac sodium**

Like other NSAIDs diclofenac sodium is clinically prescribed as an antipyretic, analgesic and anti-inflammatory agent [3-5]. Knowledge of the structure of Diclo-Na molecule is essential to understand its pharmaceutical action. Diclo-Na is a potent inhibitor of cyclo-oxygenase in vitro and in vivo, therapy decreasing the synethesis of protaglandins, prostacyclin, and thromboxane products. Lanthamide ion probe spectrofluorometry (LIPS) introduced by Horrocks and Sunduick [6] employs this technique for determination of diclofenac sodium using (LIPS). The structure of diclofenac consists of phenyl acetic acid group, secondary amino group, phenyl ring, both ortho position of which are occupied by chlorine atom. The secondary amino group precipates in bifurcate intermolecular hydrogen bond interacting with the adjacent acceptor chlorine atom [7-9]. The interaction of diclofenac with cyclodextrin has been reported [9,10]. The nature of inclusion complex in the solid state was studied by X-ray crystallography, IR, and NMR spectroscopy. In this paper we reported the synthesis and spectral characterization of cadmium(II) complex of diclofenac drug. This complex has been structurally characterized in the solid state by IR, $^{1}$H-NMR, electrical conductivity measurement, thermally studied and biological evaluation.

## EXPERIMENTAL

### Material and instrumentation

Diclofenac sodium was purchased from (Aldrich Chemical Company) and all other chemical involved in sample preparation was purchased from (Aldrich) as analytical pure reagent. Carbon and hydrogen content were determined using Perkin-Elmer CHN 2400. FT-IR spectra were recorded on Bruker FT-IR Spectrophotometer (400-4000 $cm^{-1}$) in KBr pellets. $^{1}$H-NMR spectrometer was recorded using DMSO as a respected solvent chemical shift are given in ppm relative to tetramethysilane. The absorption spectra were recorded using Perkin-Elmer lambda or 4B Spectrophotometer in the range 200-600 nm. Molar conductivity of freshly prepared $10^{-3}$ M using Jenway 4010 conductivity meter. Thermo gravimetric analysis (TG/DTG) were carried out in nitrogen atmosphere (30 ml/min) with hearting rate of 10°C/min using Schimadzu TGA-50H thermal analyzer.

### Synthesis of Cd(II) diclofenac complex

The mentioned complex was prepared with employing a molar ratio 1:2. The resulting solution was stirred and refluxed on hotplate of 60-70 °C for 3 hours. The volume of the obtained solution was reduced to one-half by evaporation one day later, the precipitation was settle down, filtered off and washed several time by small amount of hot $CH_3OH$ and dried under vacuum over anhydrous $CaCl_2$. The elemental analyses (Table 1) were in good agreement with those required for the purpose of formula.

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**Table 1: Elemental analyses and physical data of Cd(II) complex**

| Complex | Mwt | Content (Calculate) Found | | | | Λ ($S.cm^{-1}.M^{-1}$) |
|---|---|---|---|---|---|---|
| | | C% | H% | N% | M% | |
| $[Cd(diclo)_2(H_2O)_2].9H_2O$ | 900 | (37.00)<br>(36.89) | (4.00)<br>(3.95) | (3.11)<br>(3.09) | (12.40)<br>(12.32) | 11 |

**Microbiological investigation**

The biological activity of $Cd^{2+}$ diclofenac complex was tested against bacteria and fungi. The antibacterial activity of this complex was applied on more than one tested organism. The organisms used in the present investigation included two bacteria with different kinds as B. subtilis (Gram +ve), E. coli (Gram –ve) and two kinds of fungi (Aspergillus niger, Aspergillus flavus). The results of the bactericidal screening and fungicidal of the synthesized complex were recorded.

## RESULTS AND DISCUSSION

The selected physical properties and characteristic data of the synthesized metal complex were measured and listed in Table 1. The isolated solid complex is $[Cd(diclo)_2(H_2O)_2].9H_2O$. The complex is air-stable, with high melting point. This complex is insoluble in common organic solvent but is soluble in DMSO. The molar conductivity of $10^{-3}$ $mol/dm^{-3}$ solution of respected complex in DMSO (Table 1) indicate that this complex is non-electrolyte. The synthesized complex according to elemental analysis, IR, Uv-Vis and thermogrovimetric data, the cadmium(II) complex has a uni-dentate ligand.

**Infrared spectra**

The IR data of diclofenac and its complex are listed in Table 2 and shown in Fig. 2. The IR spectrum of the Cd(II) complex was compared with those of the free ligand in order to determine the coordination sites that involved in chelation. It is observed from IR spectra, there is no large shifts for ν(NH) and δ(NH) bands in the spectrum of complex compared to those of the ligand indicates that there no interaction between the NH group and the metal ions. The difference of bands of $\nu_{as}$(COO) and $\nu_s$(COO) which characterized the carboxylate ligation. The $\nu_{as}$(COO) and $\nu_s$(COO) bands of diclofenac complex are at 1547 and 1450 $cm^{-1}$, respectively. The difference ($\Delta = \nu_{as}COO - \nu_sCOO$) is 100 $cm^{-1}$ which closed to the ionic value of (sod. diclofenac the Δ value is 170 $cm^{-1}$), as expected for the unidentate mode of carboxylate. Diclofenac complex exhibit band at 3584 $cm^{-1}$ attributed to the presence of coordinated and lattice water [11]. The weak band at 525-530 $cm^{-1}$ in case of the cadmium(II) complex are assigned to the ν(M-O) stretching vibration bands.

**Table 2: IR spectra of diclofenac and its metal complexes**

| Compound | ν(NH) and ν(OH) | δ(NH) | ν(COO) (as) | ν(COO) (s) | ν(M-O) (COO) | Δ | ν(M-O) ($H_2O$) |
|---|---|---|---|---|---|---|---|
| Diclofenac | 3359 | 1500 | 1572 | 1402 | --- | 170 | --- |
| $[Cd(diclo)_2(H_2O)_2].9H_2O$ | 3584<br>3344<br>3288 | 1504 | 1547 | 1450 | 446 | 100 | 528 |

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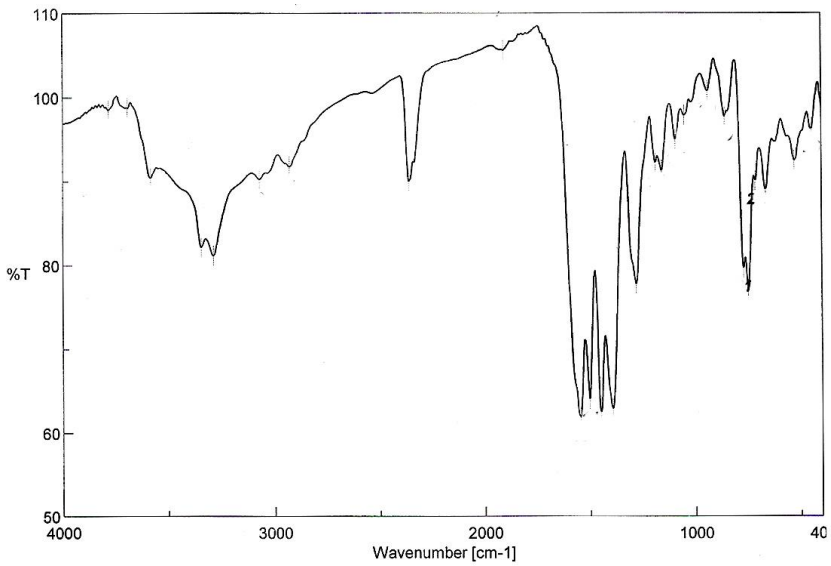


**Fig 2: FT-IR spectrum of Diclo/$Cd^{2+}$**

**$^1$H-NMR spectra**

The $^1$H-NMR spectrum of Cd(II) diclofenac complex is shown in Fig. 3 and assigned in Table 3. The $^1$H-NMR spectrum of Cd(II) complex show signal at $\delta$=3.50 ppm as broad singlet which refer to proton of uncoordinated water molecules. The signal at 2.50 ppm refer to presence of coordinated water. The multiple peaks at 6.2-7.5 ppm) are attributed to the proton of phenyl group of two diclofenac molecule, in the prepared complex. The NH proton appeared as broad singlet at $\delta$= 8.6 ppm in the spectrum of Cd complex, it is unshifted in comparison with sodium salt of diclofenac [12-14]. The resonance of the NH proton appear as broad singlet at $\delta$= 8.6 ppm in the spectrum of Cd(II) complex if compared with sodium salt of diclofenac is due to intermolecular hydrogen bond with respect to the pure salt [12-14]. Based on this discussion, it can be suggested that Cd(II) complex formula as refer in Scheme 1.

**Table 3: $^1$H-NMR spectral data of diclofenac and its Cd(II) complex**

| Compound | $\delta$ (ppm) of protons | | | |
|---|---|---|---|---|
| | 2H; $H_2O$ | H; $CH_2$+$H_2O$ | H; ArH | H; NH |
| Diclofenac | -- | 3.41 | 6.23-7.47 | 10.51 |
| Pb (II) complex | 2.50 | 3.50 | 6.2-7.52 | 8.60 |

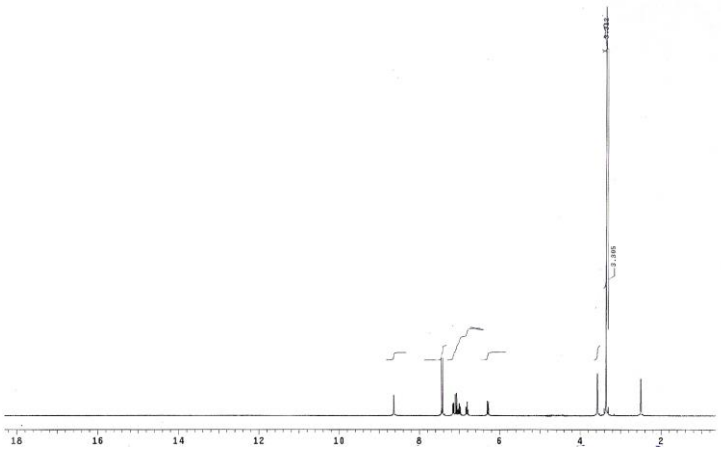

**Fig 3: H-NMR spectrum of Diclo/$Cd^{2+}$**

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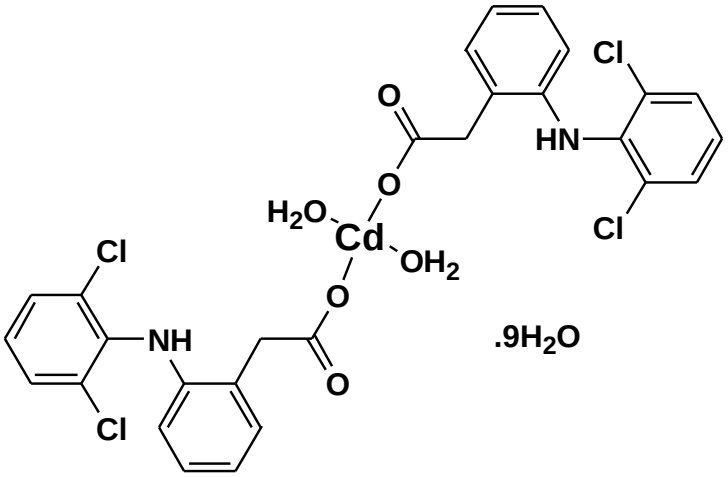


**Scheme 1: The suggested formula of Cd(II) complex**

**Thermogravimetric analysis**

Thermogravimetric analysis of the cadmium(II) diclofenac complex and weight loss was measured from ambient temp up to 1200 °C. The data are listed in Table 4 and shown in Fig. 4. The $[Cd(diclo)_2(H_2O)_2].9H_2O$ complex decomposed in three steps. The 1st step occurs at 120-190 °C which is corresponding to the loss of $H_2O$ molecule, representing a weight loss of 2.055% and its calculated value is 2.00%. The 2nd step takes place with the range of 190-360 °C and it is corresponding to the elimination of $9H_2O$ and ($C_{13}H_{10}O_3N_2Cl_2$) organic molecules due to a weight loss of 54.80% in a good matching with theoretical value 53.88%. The 3rd step occurs at 360-690 °C is corresponding to the loss of ($C_{15}H_2OCl_2$) organic molecule, representing a weight loss of 29.86% and its calculated value is 29.88%. The CdO is the final product remains stable till 700 °C.

**Table 4: Thermal analysis (TG) data summary for synthesized diclo complexes**

| Steps | Temp. range (°C) | DTG peak (°C) | TGA weight loss (%) | | Assignments |
|---|---|---|---|---|---|
| | | | Calc. | Found | |
| 1 | 120-190 | 161 | 2.00 | 2.055 | $H_2O$ |
| 2 | 190-360 | 275 | 53.88 | 54.80 | $9H_2O + C_{13}H_{10}O_3N_2Cl_2$ |
| 3 | 300-690 | 640 | 29.88 | 29.86 | ($C_{15}H_2OCl_2$) |
| Residue | | | | | CdO |

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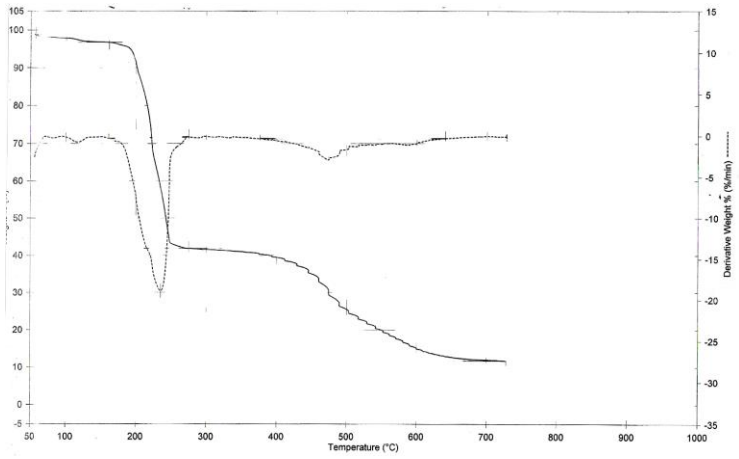


**Fig 4: TGA of Diclo/$Cd^{2+}$**

**Electronic spectra**

The formation of the cadmium(II) complex was also confirmed by Uv-visible spectrum Fig. 5, show the electronic spectrum of the respected complex in DMSO within the range (200-600 nm). The free diclofenac has two essential band. The first at 275 nm may be attributed to ($\pi$-$\pi$*) transition of the aromatic ring and the second observed at 350 nm that attributed to (n-$\pi$*) electronic transition in the spectrum of metal complexes the two band are bathochemically shift, suggesting that ligand coordinated to metal ion through carboxylic group.

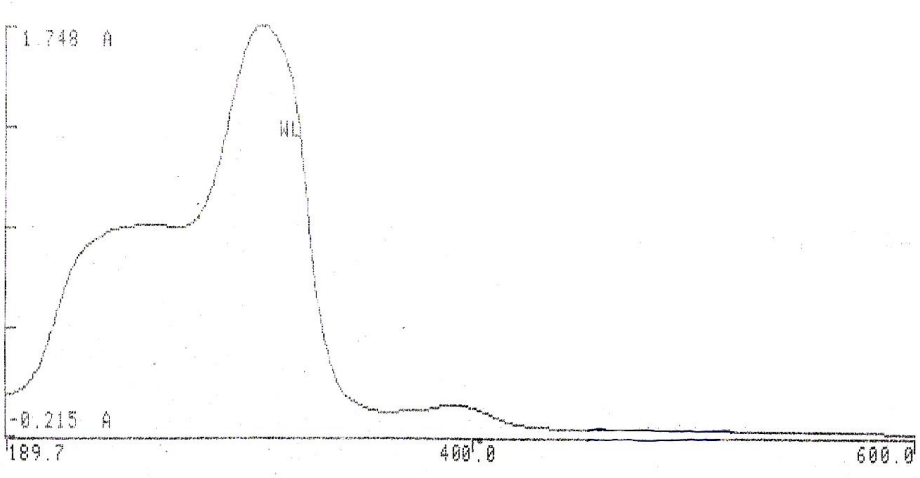


**Fig 5: UV-visible absorption spectrum of Diclo/$Cd^{2+}$**

**Antimicrobial activity**

Antibacterial and antifungal activity of the diclofenac ligand and its Cd(II) complex are carried out against two kind of bacteria, B. subtilis (Gram +ve), Escherichia coli (Gram –ve) and fungal (Aspergillus niger, Aspergillus flavus) in Fig. 6 and Table (5). The antimicrobial activity estimated based on the size of inhibition zone around dishes. The complexes are found to have high activity against Aspergillus niger and flavus.

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**Table 6: Antimicrobial of diclo complexes ($L_3$).**

| | Diameter of inhibition zone (cm) | | | |
|---|---|---|---|---|
| | B. subtilis | E. coli | Aspergillus niger | Aspergillus flavus |
| Control | 0 | 0 | 0 | 0 |
| Diclo-Na | 0.3 | 0.6 | -- | -- |
| Diclo/Cd | 1.8 | 1.5 | 3.1 | 2.2 |

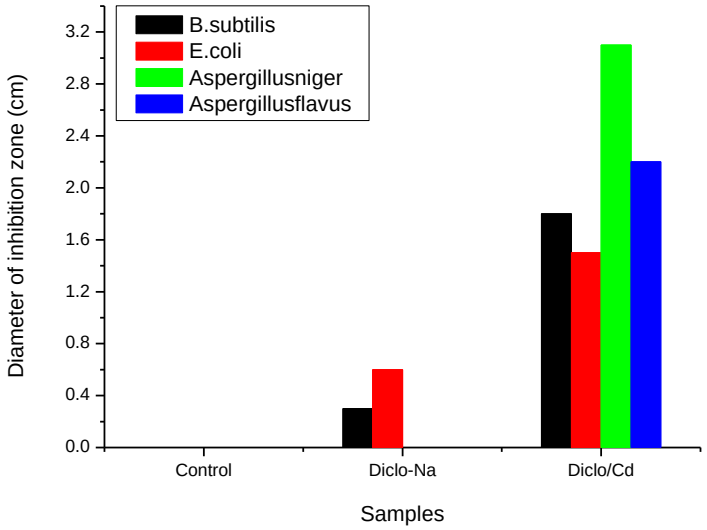


**Fig 6: Statistical representation for biological activity of diclo free ligand and its Cd(II) complex.**

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