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Preparation and Characterization of Aceclofenac Complexes of First Row Transition Metals Mn(II), Co((II), Ni(II), Cu(II), and Zn(II)

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Abstract

A number of complex compounds of aceclofenac with different first-row transition metal ions like Co(II), Mn(II), Ni(II), Cu(II), and Zn (II) were synthesized in an aqueous medium and characterized on the basis of their UV-Visible, FTIR spectra, elemental (C, H, N) analyses, and metal estimation data. Thermogravimetric analysis (TGA) was also done. Conductivity measurement and magnetic susceptibility measurement were also done to have information about the electrolytic behavior of the compounds and oxidation states of the central metal atoms respectively.

Keywords: Aceclofenac, Transition Metals, Thermogravimetric, Spectroscopic.

I. Introduction

Coordination chemistry is the study of compounds consisting of a central metal atom or ion bonded to one or more neutral or charged molecules called ligands containing one or more lone pairs of electrons. One of the most important properties of metallic elements is their ability to act as Lewis acids to form metal complexes with a variety of Lewis bases [1]. Metal complexes are essential in biosystems, and have tremendous significance in life science. Hemoglobin is an iron complex of porphyrin that transports oxygen in our blood [2] and the iron having been coordinated to oxygen in the lungs to form oxyhemoglobin[3] is carried through the circulatory system to the body. Currently metal ion complexes are used in the human body for the transport and storage of oxygen as electron transfer agents, catalysts, and drugs[4]. Many coordination compounds exhibited biological activities against bacteria and fungi[5-7].

The bioavailability of trace metals like Cr, Mn, Fe, Co, Ni, Co, and Zn are responsible for biotoxicity depending on the forms of the metal species and the metal ion concentration. M^{n+} being relatively smaller in size can be more harmful to biotin than its complexes, MLn. Transition metals particularly iron and essential trace metals like Mn Fe Cu Zn etc are present in animal and human bodies and function as metalloenzymes or as enzymatic activators. Copper ion, comparable to iron as an essential constituent and vital oxidative enzyme is involved in the oxygen transport of proteins in marine animals and zinc is the trace element required for the activity of an appreciable number of enzymes like other essential trace elements [8].

For the above reason it is very much important to know about coordinating nature as well as the complexation features of metals with different ligands. Here aceclofenac has been used to react with the metal ions in order to know the coordinating nature of a drug. Aceclofenac ($C_{16}H_{13}Cl_2NO_4$), is a nonsteroidal anti-inflammatory drug (NSAID) analog of diclofenac with anti-inflammatory and analgesic properties and it is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis, and ankylosing spondylitis. It can be used as a ligand which can form a complex with different transition metals. Aceclofenac is a crystalline powder with a molecular mass of 354.19. According to the Biopharmaceutical Classification System (BCS) drug substances are classified into four classes on their solubility and permeability. Aceclofenac falls under BCS Class II, a poorly soluble and highly permeable drug [9].

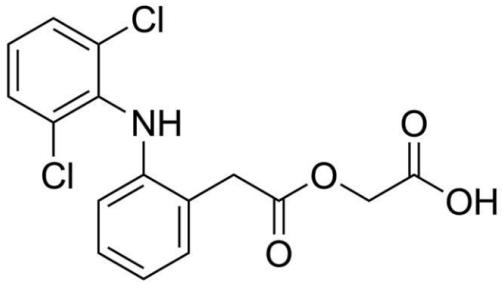

Fig. 1. Structure of Aceclofenac

The study on the interaction of drugs with various transition metals for the last several decades is creating much attention all over the world [10-15]. We have been doing research on metal vitamin B complexes for a few years [16-18]. The present work includes the preparation of solid complexes of some first-row transition metals with aceclofenac. The ligand structure (Fig 1) indicates two main coordinating sites, N and the carboxylic O atom. The characterization of the complexes was done using

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spectroscopic methods, thermal, conductometric measurements, and their various properties studies in order to establish the nature of metal-aceclofenac interactions.

II. Experimental

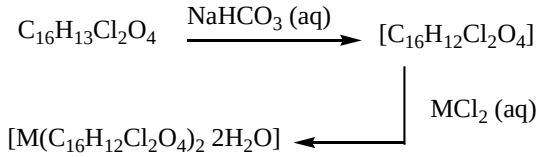
Materials and Methods

Analytical grade reagents (BDH and Aldrich) were used in all preparative and analytical works. Micro-analysis for C, H, and N were performed on an automatic micro-analyzer in the laboratory of BCSIR. The metal content of the complexes was quantitatively determined by the complexometric method[19]. The chloride content of all the complexes was qualitatively tested with an $AgNO_3$ solution. The melting point of all the complexes was measured in a heating device, MEL-TEMP II, Laboratory Devices with a thermometer made in the USA. Infrared spectra of the complexes were recorded on a calibrated Fourier Transformation Infrared Spectrophotometer (Shimadzu, IR-470) in the range 400-4000 cm^{-1} as KBr pellets. The electronic spectra of aceclofenac and its complexes were recorded on a Shimadzu UV-visible recording spectrophotometer (UV-160A), in the wavelength 200-400 nm. The thermo-gravimetric analysis of the complexes was carried out with a computer-controlled TA-60WS thermo-gravimetric analyzer and TGA-50H detector (Shimadzu, Japan). The magnetic properties of the complexes were studied at ambient temperature on a Magnetic Susceptibility Balance (Magway MSB Mk1 Sherwood Scientific Ltd, Cambridge, England).

Preparation and formulation of the metal complexes

All the metal complexes were prepared in the aqueous medium following the same procedure as given below.

About 1mmol of Aceclofenac was taken with 1mmol of $NaHCO_3$ in about 50 mL distilled water and heated for half an hour to neutralize the solution. After complete neutralization, the solution was filtered. Then 2mmol of the chloride salt of metals was dissolved in water and mixed with the neutralized solution dropwise. The resulting coloured precipitate was then filtered, collected, and washed with cold water. The product was kept in a desiccator in normal laboratory conditions for drying. After drying the product was weighed and stored for further analysis. The reaction scheme may be shown as,



The compounds were analyzed to estimate the metal quantitatively. The metal content in the complexes was determined by the complexometric titration method. The percentage of carbon hydrogen nitrogen and the metal contents in complexes are given in Table 1.

Table 1. The % of C, N, H, and M (metal) in the complexes of aceclofenac and their melting temperature

Compound (Molecular Formula)	Physical appearance	Experimental Data (Calculated Data)				Melting Point (°C)
		% Metal	% C	% N	% H	
$Mn(C_{16}H_{12}NO_4)_{2(}H_2O)_2$	White powder	6.90 (7.27)	48.18 (47.64)	3.51 (2.70)	3.54 (3.11)	238-244
$Co(C_{16}H_{12}NO_4)_{2(}H_2O)_2$	Brown powder	7.37 (8.62)	47.94 (48.34)	3.50 (3.82)	3.52 (3.74)	212-220
$Ni(C_{16}H_{12}NO_4)_{2(}H_2O)_2$	Greenish powder	7.31 (8.34)	47.97 (47.47)	3.49 (3.00)	3.51 (3.09)	218-224
$Cu(C_{16}H_{12}NO_4)_{2(}H_2O)_2$	Light greenish powder	7.88 (7.88)	47.67 (47.50)	3.48 (2.64)	3.50 (2.79)	246-250
$Zn(C_{16}H_{12}NO_4)_{2(}H_2O)_2$	White powder	8.05 (9.13)	47.58 (45.36)	3.47 (3.56)	3.50 (2.97)	224-228

III. Results and Discussion

The metal compounds of aceclofenac with a few first-row transition metals were prepared in the aqueous medium and formulated by comparing the elemental analysis result. The agreement between the calculated and experimental results suggests that they are in a pure state. All the metal-aceclofenac complexes are soluble in polar solvents but in non-polar solvents these are mostly insoluble. These compounds decompose at temperatures before melting. This implies the slightly ionic character of the compounds. The study of the spectral properties of compounds was

accomplished using infrared, ultraviolet-visible, and near-infrared spectral analyses.

Infra-red spectral analysis: The important IR bands with their tentative assignments of the ligand and its metal compounds are listed in Table 2. The assignments are done on the basis of some standard references [20-22]. Ciprofloxacin absorbs at 3530 cm^{-1} due to O-H stretching 1709 cm^{-1} for ketonic (>C=O) 1610 cm^{-1} for aromatic (C=C) 1273 cm^{-1} for carboxylic (C-O) 740 cm^{-1} for C-H out of plane bending mode of vibration. The IR spectra of the metal compounds are more or less similar to that of the ligand. The compounds absorb for OH stretching in the range 3650-3070 cm^{-1}. The C-H and N-H stretching vibrations in all the compounds are merged with that of O-H absorption bands. Like the ligand the aromatic C=C absorption band appears near 1600 cm^{-1} (1598-1635 cm^{-1}) In all the compounds the absorption due to C=O is absent indicating the probable participation with metal ions. Aromatic C-H out of plain bending is observed in the range 740-775 cm^{-1}.

Table 2. Tentative assignments of IR peaks of the metal aceclofenac compounds

Metal complexes	νN-H cm^{-1}	νC=C cm^{-1}	νC=O (ester,acid) cm^{-1}	νC-H cm^{-1}	νC-Cl cm^{-1}	νC-N cm^{-1}	δC-O (ester, acid)cm^{-1}	νO-M cm^{-1}
$(C_{16}H_{13}Cl_2NO_4)$	3319	3027	1771 1715	2937	747	1438	1149 1256	-
$Mn(C_{16}H_{12}NO_4)_2(H_2O)_2$	3521	3199	1716 1633	2947	746.4	1450	1142 1244	478
$Co(C_{16}H_{12}NO_4)_2(H_2O)_2$	3360	3199	1727 1604	2947	747	1453	1151 1238	716
$Ni(C_{16}H_{12}NO_4)_{2(}H_2O)_2$	3359	3199	1726 1618	2954	747	1452	1150 1252	520
$Cu(C_{16}H_{12}NO_4)_{2(}H_2O)_2$	3354	3199	1724 1611	2957	727	1450	1184 1307	690
$Zn(C_{16}H_{12}NO_4)_{2(}H_2O)_2$	3450	3199	1733 1613	2950	749	1463	1148 1238	670

Aceclofenac exhibits a strong band at 3319 cm^{-1} due to N-H stretching vibration. Usually absorption less than 3027 cm^{-1} indicates the presence of a sp^2 C=C bond in aromatic stretching, and the weak absorption at about 2937 cm^{-1} might be due to the presence of a C-H bond. The strong absorption at 1771 and 1715 cm^{-1} indicate the presence of C=O of the ester and carboxylic group respectively. The peak at 1439 cm^{-1} was observed due to the presence of C-N (ring stretch) and the peak at 1256 cm^{-1} is due to the C-O. Two peaks at 1149 cm^{-1} and 1056 cm^{-1} may be due to the C-O of the ester group. Aromatic = C-H out-of-plane bending occurs between 900-690 cm^{-1}. The peak at 747 cm^{-1} indicates the presence of a C-Cl bond. Metal-Aceclofenac complex exhibits a strong band in the range 3354-3521 cm^{-1} due to the N-H stretching vibration while in aceclofenac it was observed at 3319 cm^{-1}. Usually, absorption less than 3199 cm^{-1} indicates the presence of a sp^2 C-H in the aromatic ring. The weak absorption at about 2947-2957 cm^{-1} might be due to the presence of the C-H bond for all the compounds. The strong absorption bands of the complexes at 1716 to 1733 cm^{-1} range indicate the C=O of ester shifted towards lower frequency and broad peaks at 1634 to 1604 cm^{-1} for (C=O) of the carboxylic group may be shifted due to other oxygen bonded to metal ions. The strong absorption was observed at 1771 and 1715 cm^{-1} indicating the presence of C=O of ester and carboxylic groups respectively in the case of free legand aceclofenac. The peak at 1450-1463 cm^{-1} may be attributed to the stretching vibration of the C-N bond in different metal complexes. The peaks at 1238-1307 cm^{-1} and at 1143 -1150 cm^{-1} are due to the presence of C-O of the carboxylic group and C-O of the ester group respectively. The bands at 900-690 cm^{-1} may be attributed to the out-of-plane bending vibrational motion of the ring C-H bond. The peaks at 746-749 cm^{-1} are due to C-Cl bonding. Thus, the absorption bands for all the metal complexes and aceclofenac ligand were observed nearly in the similar region except for C=O of ester and carboxylic groups where the absorption shifted to lower frequency indicating the bond formation between the different metals and the ligand.

Electronic Spectral Analysis[23-24]: The ultraviolet spectra of aceclofenac and all the complexes showed a very sharp peak at 269 nm and a relatively broad absorption at 280-281 nm. The sharp peak is the instrumental error, while the broad absorption is an envelope of peaks that may be corresponding to the $n \rightarrow \pi^*$ or $\pi \rightarrow \pi^*$ transition due to double bonds in the aromatic ring and the heterocyclic ring

as well as the nonbonding electron present in >C=O group and on N atom and substituent Cl on the aromatic ring of the ligand moiety both in the free ligand and in the synthesized complexes. No other peaks were observed for other types of electronic transition.

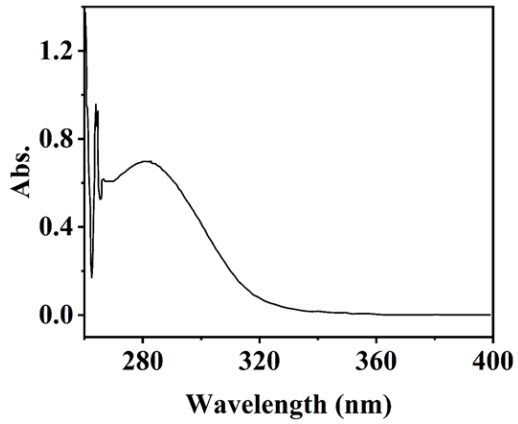


Fig. 2. Electronic spectrum of $Mn(C_{16}H_{12}NO_4)_2(H_2O)_2$

Thermogravimetric Analysis: The TGA data show that for all complexes the weight loss started at 54-57 ˚C except for Zn (at 21.93 ˚C). Before 206 ˚C a certain percentage of weight loss occurs corresponding to moisture and 2 moles of co-ordinated water. The total organic moiety is lost in three steps in all the compounds suggesting that the decomposition pattern in the ligand and the metal compounds are more or less the same. At above 150 ˚C temperature loss of a large percentage of weight corresponds to the loss of most of the organic part of the aceclofenac ligand. Near about 300 ˚C the weight loss corresponds to the loss of chloride from the complexes as Cl2 gas. At about 500 ˚C the weight loss corresponds to the loss of CH_4, NH_3, and H_2 gases, and finally, the residue found was probably due to the formation of metal oxide only.

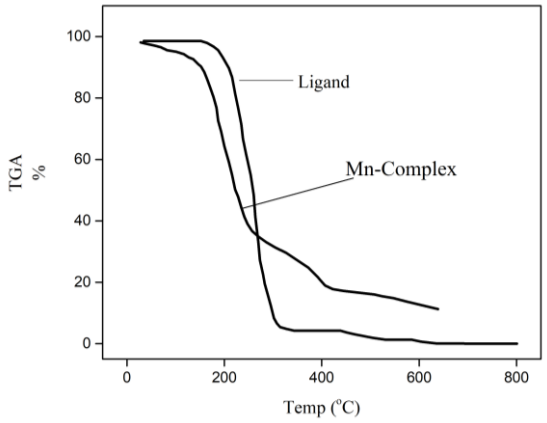


Fig. 3. The thermogram for aceclofenac and its Mn complex.

Conductivity measurement: The specific conductances for the aceclofenac-metal complexes are higher than that of the solvent (DMF). It is found that in all the cases, the molar conductance increases with an increase in dilution of the solution. Specific conductance increases with an increase in molar concentration for all the metal-aceclofenac complexes. It is also observed that the molar conductance decreases exponentially with an increase in $(molarity)^{1/2}$. At very high $(molarity)^{1/2}$ the change of molar conductance remains constant indicating weak electrolytic behavior of the metal complexes in the DMF medium (Fig 4).

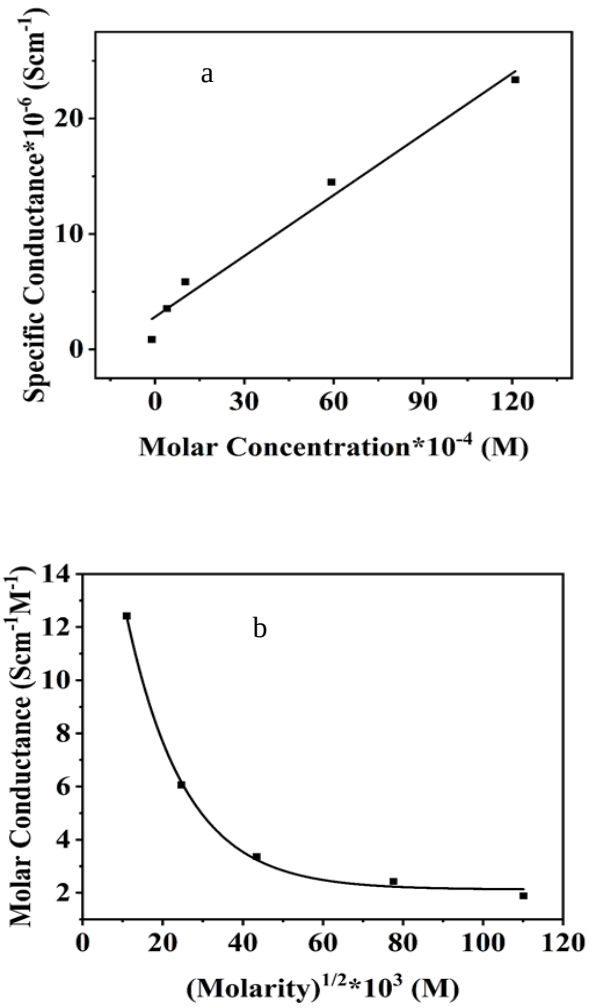


Fig. 4. (a) Specific conductance vs. molar concentration and (b) Molar conductance vs. $(molarity)^{1/2}$of $[Mn(C_{16}H_{12}Cl_2NO_4)_2(H_2O)_2]$

Magnetic properties: The magnetic properties of the complexes were examined by magnetic susceptibility balance, which has been summarized in Table 3.

Table 3. Experimental magnetic properties and value of Band gap energy (eV) for-metal complexes by Kubelka–Munk method

Metal Complex	g (C.G.S. unit) $\times 10^{-3}$	μ_{eff} (BM)	No. of unpaired electrons	Band gap energy (eV)
$[Mn(C_{16}H_{12}Cl_2NO_4)_2(H_2O)_2]$	12.06	5.38	5	1.98
$[Co(C_{16}H_{12}Cl_2NO_4)_2(H_2O)_2]$	4.35	3.23	3	2.74
$[Ni(C_{16}H_{12}Cl_2NO_4)_2(H_2O)_2]$	2.69	2.54	2	2.93
$[Cu(C_{16}H_{12}Cl_2NO_4)_2(H_2O)_2]$	0.07	1.41	1	2.58
$[Zn(C_{16}H_{12}Cl_2NO_4)_2(H_2O)_2]$	negative	-	-	2.82

The magnetic moment measurement study reveals that Mn(II), Co(II), Ni(II), and Cu(II) complexes are paramagnetic whereas Zn(II) complex is diamagnetic in nature. The complexes are paramagnetic because of the presence of unpaired electrons in their 3d orbitals. The magnetic moment of Mn(II), Co(II), Ni(II), and Cu(II) complexes are 5.38 BM, 3.23BM, 2.54BM, and 1.41 BM respectively. The magnetic susceptibility values of Zn(II) are negative due to their diamagnetic behaviour.

Reflectance Analysis: The optical excitation of the electrons from the top of the valence band to the bottom of the conduction band is evidenced by an increase in the absorbance at a given wavelength (band gap energy). The determination of E_g by applying the Kubelka–Munk (K–M or F(R)) method offers great advantages in this case. The K–M method is based on the following equation:

$$F(R) = \frac{(1-R)^2}{2R}$$

Where R is the reflectance; F(R) is proportional to the extinction coefficient. This equation is usually applied to highly light-scattering materials.

The band gap energy for aceclofenac is 3.42eV which indicates the insulating behavior of the ligand. The band gap energy of the complexes of the aceclofenac is below the 3eV in the range of 1.98-2.93 eV

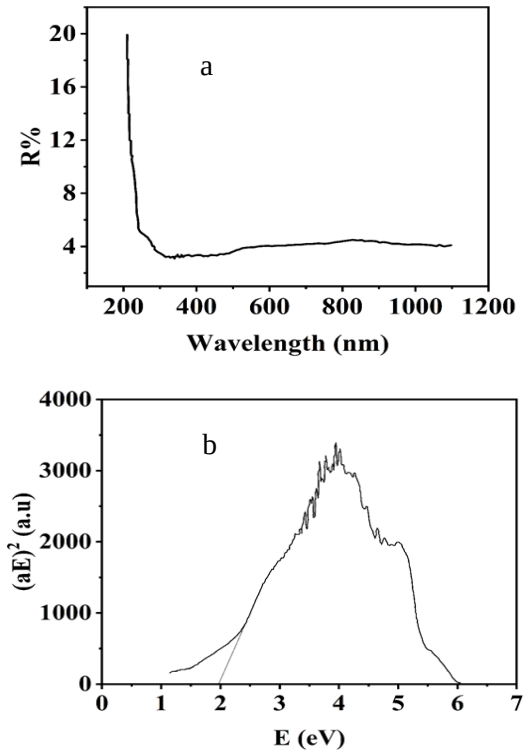


Fig. 5. A plot of (a) Reflectance vs wavelength (nm) and (b) modified Kubelka–Munk $(\alpha E)^2$ vs E of $[Mn(C_{16}H_{12}Cl_2NO_4)_2(H_2O)_2]$ complex

(The individual values are listed in Table 3) which gives an indication of the semiconductor behavior of the complexes. Thus, the modification of the ligand by metal complexation, their insulating or conducting behavior change.

IV. Conclusion

Mn (II), Co (II), Ni (II), Cu (II), and Zn (II) form compounds with aceclofenac with a ratio of 1:2. The spectral analyses (IR, UV-VISIBLE) show that the spectrum of the ligand and those of the metal compounds

are more or less similar, which indicate that the structure of the ligand remains unchanged in the metal compounds. In all the cases, specific conductance decreases and molar conductance increases with decreasing concentration. Therefore, it can be concluded that these compounds behave as weak electrolytes. Findings from the TGA curves are almost similar in all the cases. All of those exhibit two to three regions of melting. All the compounds except Zn complex show paramagnetic properties. From reflectance analysis it was concluded that all the complexes behave like semiconductors whereas the ligand shows behaviour of an insulator. On the basis of all these analyses, we can suggest the structures of the complexes with distorted octahedral geometry as shown in Fig 6.

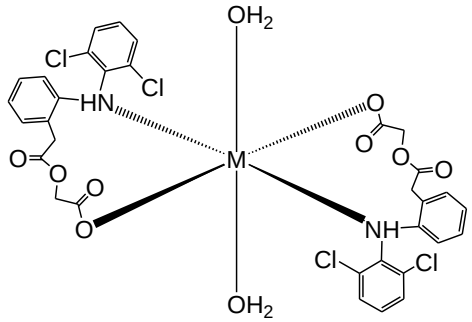


Fig. 6. Octahedral geometry of metal- aceclofenac complexes.

References

1. Cotton, F. A., G. Wilkinson and P. L. Gaus, 1995. *Basic inorganic chemistry*. John Wiley & Sons. **23**

2. Katz, S.A. and H. Salem, 1993. The toxicology of chromium with respect to its chemical speciation: a review. *Journal of Applied Toxicology*, **13(3)**, 217-224.

3. Dayan, A.D. and A. J. Paine, 2001. Mechanisms of chromium toxicity, carcinogenicity and allergenicity: review of the literature from 1985 to 2000. *Human & experimental toxicology*, **20(9)**, 439-451.

4. Rosenberg B. 1969 Platinum Compounds: A New Class Of Potent Antitumour Agents. *Nature* 222 (5191), 385–386.

5. Chohan, Z. H., H. A. Shad, M. H Youssoufi,. & Ben Hadda, T. 2010, Some new biologically active metal-based sulfonamide. *European Journal of Medicinal Chemistry* 45, 2893–2901.

6. Psomas, G., A. Tarushi,., E. K Efthimiadou,., Y Sanakis,., C. P Raptopoulou,., & N. Katsaros, , 2006 Synthesis, structure and biological activity of copper(II) complexes with oxolinic acid, *Journal of Inorganic Biochemistry* 100, 1764–1773.

7. Efthimiadou, E. K., Katsarou, M. E., Karaliota, A. & Psomas, G. 2008 Copper(II) complexes with sparfloxacin and nitrogen-donor heterocyclic ligands: Structure–activity relationship, *Journal of Inorganic Biochemistry* 102, 910–920.

8. Holm R., P. Kennephol and E. I. Solomon, 1996, Structural and Functional Aspects of Metal Sites in Biology, *Chemistry Reviews*, 96, 2239-2314

9. Karmoker, J. R., S. Sarkar, P. Joydhar and S. F. Chowdhury, 2016. Comparative in vitro equivalence evaluation of some Aceclofenac generic tablets marketed in Bangladesh. *The Pharma Innovation*, **5(3,** Part A**)**, 3-7.

10. Pareek, A. and N. Chandurkar, 2013. Comparison of gastrointestinal safety and tolerability of aceclofenac with diclofenac: a multicenter, randomized, double-blind study in patients with knee osteoarthritis. *Current medical research and opinion*, **29(7)**, 849-859.

11. Pezeshk, A., 1986. Drug-metal interactions: an unusual four-membered ring copper phenobarbital complex. *Journal of the American Chemical Society*, **108(26)**, 8285-8286.

12. Pezeshk, A. and V. Pezeshk, 1990. Drug-metal interactions: copper (II) complex of the antidiabetic drug acetohexamide and pyridine. *Journal of inorganic biochemistry*, **38(3)**, 185-197.

13. Kale, A. M., R. Shelke and B Nawale, R., 2014. Zinc-aceclofenac complex: Synthesis, hydrolysis study and antiinflammatory studies. *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry*, **13(1)**, 36-44.

14. Koly S. F., S. P. Kundu, S. Kabir and Md. Z. Sultan, 2015. Analysis of aceclofenac and bovine serum albumin interaction using fluorescence quenching method for predictive, preventive, and personalized medicine. *EPME Journal*, **6**, 24.

15. Leung, C. H., S. Lin, H. J. Zhong and D. L. Ma, 2015. Metal complexes as potential modulators of inflammatory and autoimmune responses. *Chemical Science*, **6(2),** 871-884.

16. Ehsan, M. Q., S. Khatun and M. A. Quyser. 2001. Preparation and Characterization of Pyridoxine Complexes of Mn(II), Co(II), Ni(II), Cu(II), and Zn(II). *J. Saudi Chem. Soc*., **5(1);** 59-66.

17. Rahman, K. Lutfar, M. A. Mamun and M.Q. Ehsan. 2011. Preparation of Metal Niacin Complexes and Characterization using Spectroscopic and Electrochemical Techniques. *Russian Journal of Inorganic Chemistry*, **56(9):** 1436-1442.

18. Shaikh, A. A., M. Begum, A.H. Khan and M.Q. Ehsan 2006. The Cyclic Voltammetric Studies of the Redox Behaviour of Iron (III) Vitamin B_6 Complex at Carbon Paste Electrode. *Russian J. Electrochemistry*, **42**(6): 620-625.

19. "*Vogel's Text Book of Quantitative Chemical Analysis*, 1989, 5th ed, ELBS series, 329, ()

20. Nakamoto, K. 1978, "*IR and Raman Spectra of Inorganic and Coordination Compounds*", 3rd Edn, John Wiley and Sons, N.Y., 211; C. N. R. Rao, 1963 " *Chemical Applications of IR Spectroscopy*", Academic Press, N. Y., 364.

21. Pavia, D. L. G. M. Lampman, and G. S. Kriz, 2001, "*Introduction to Spectroscopy"*, 3rd ed., Harcourt College Publishers,

22. Silverstein, R. M. F. X. Webster and D. J. Kiemle, 2005, "*Spectroscopic Identification of Organic Compounds*", 7th ed., John Wiley and Sons. Inc., New York, ().

23. Lever, A. B. P. 1968, "*Inorganic Electronic Spectroscopy*", 1st ed., Elsevier Publishing Company, ().

24. Sutton, D. 1968 "*Electronic Spectra of Transition Metal Complexes*", 1st ed., McGraw Hill, New York, ().