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A study on the complexes of transition metals with nitazoxanide

[1]Deepak Tayde*, Shruti S. Sarwade[2], W. N. Jadhav[2] and B. C. Khade[2]

[1]Department of Chemistry, Dr. BabasahebAmbedkar Marathwada University Aurangabad, Maharashtra, India
[2]Department of Chemistry, Dnyanopasak Science College, Parbhani, Maharashtra, India

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ABSTRACT

Novel complexes of Nitazoxanide with Mn(II), Fe(III), Cu(II) and Zn(II) have been synthesized keeping in view that some metal complexes are found to be more potent than their parent drug. The synthesized complexes are characterized on the basis of elemental analysis, conductivity, magnetic measurement, UV and IR spectral studies.

Keywords: Nitazoxanide, complexes, UV spectroscopy, IR spectroscopy, Thermo gravimetric studies.

INTRODUCTION

Nitazoxanide [2-(acetyloxy)-N-(5-nitro-2-thiazolyl) benzamide,NTZ] is a potent anti-parasitic and antiviral agent recently approved. The anti-protozoal activity of NTZ is believed to be due to interference with pyruvate: ferredoxin oxidoreductase (PFOR) enzyme dependent electron transfer reaction which is essential to anaerobic energy metabolism [1].Intestinal parasitic infections rank among the most significant causes of mortality in the world today. Nevertheless, it has been ≥ 30 years since the introduction of any new innovative treatment and, for some pathogens there is currently no accepted specific therapy[2]. The thiazole derivative Nitazoxanidefirst described by Rossignol, is a broad spectrum antibacterial and anti-parasitic agent, particularly efficacious against anaerobic bacteria and as an anthelminthic and antiprotozoal agent[3-4]. It is used for the treatment of cryptosporidiosis and giardiasis in immune-competent patients. It is absorbed from gastrointestinal tract following oral administration and is rapidly hydrolyzedto an active desacetyl metabolite (tizoxanide).[5-9]

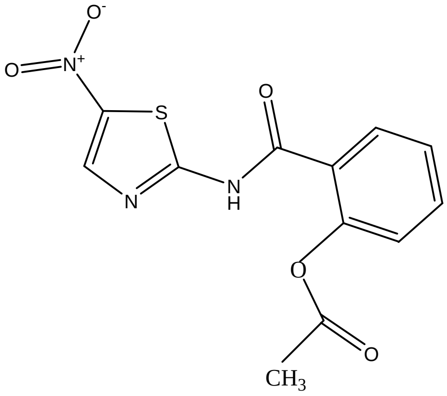

FIG. I STRUCTURE OF NITAZOXANIDE

MATERIALS AND METHODS

Materials:
All chemicals used in this study were of analytical grade. They included Nitaxozanide (NTZ) of the formula $C_{12}H_9N_3O_5S$ and metal salts $MnCl_2 .4H_2O$, $FeCl_3.6H_2O$, $CuCl_2.2H_2O$ and $ZnCl_2.2H_2O$.These chemicals were purchased from Merch or Aldrich. The organic solvent ethanol was purchased from BDH and used without further purification.

Preparation of solid complexes:
The solid M-NTZ complexes were prepared by drop wise addition of 25ml of 1mM metal salt to 25ml of 2mM of NTZ solution.

NTZ 2mM solution in 25 ml ethanol was made by dissolving 0.614gm and metal salts solution by dissolving 0.16gm $MnCl_2 .4H_2O$, 0.278 gm $FeCl_3.6H_2O$, 0.17gm $CuCl_2.2H_2O$ and 0.172gm of $ZnCl_2.2H_2O$ respectively in 25ml ethanol while preparing each complex.

The complexes were synthesized by refluxing Nitaxozanide and metal salts. Nitaxozanide is dissolved in ethanol and to this metal solution in ethanol was added in the ratio 1:2 [M: L], with continuous stirring, refluxed on water bath at 80^0 C. The resulted solution was cooled, filtered and later reduced to a small volume. The concentrated solution was left overnight, which resulted in the formation of crystals.

RESULT AND DISCUSSION

NTZ –M complexes were synthesized with 1:2M ratio. Examination of solubility of these complexes shows that they are insoluble in water and sparingly soluble in DMF and DMSO. The physical characteristics are given in Table I. The structure of the complexes suggested from the elemental analyses agrees well with their proposed formulae**.**

The observed solution conductivity value in DMF ($1*10^{-4}$M) reveals their non-electrolytic nature.

TABLE I:Analytical data of complexes

Sr.no.	Composition of complex	colour	Yield %	M.P(^{0}C)	Molar conductance $\Omega^{-1}cm^2mol^{-1}$
1	$Mn(NTZ)_2(Cl)_2$	Pale yellow	78	219	18.60
2	$Fe(NTZ)_2(Cl)_2$	Reddish brown	86	188	16.20
3	$Cu(NTZ)_2(Cl)_2$	brown	74	172	13.75
4	$Zn(NTZ)_2(Cl)_2$	yellow	81	175	14.60

TABLEII: Elementalanalysis of complexes

Complex	%C found(cal)	%H found(cal)	N% found(cal)	O% found(cal)	S% found(cal)	M% found(cal)
NTZ	46.80(46.90)	2.85(2.93)	13.56(13.68)	26(26.05)	10.34(10.42)	-
$Mn(NTZ)_2(Cl)_2$	42.99(43.05)	2.55(2.69)	12.45(12.55)	23.88(23.91)	9.43(9.56)	8.15(8.21)
$Fe(NTZ)_2(Cl)_2$	42.84(42.99)	2.56(2.68)	12.43(12.54)	23.74(23.88)	9.42(9.55)	8.21(8.33)
$Cu(NTZ)_2(Cl)_2$	42.24(42.50)	2.54(2.65)	12.32(12.39)	23.54(23.61)	9.35(9.44)	9.23(9.37)
$Zn(NTZ)_2(Cl)_2$	42.20(42.39)	2.51(2.64)	12.22(12.36)	23.21(23.55)	9.32(9.42)	9.44(9.62)

IR spectra studies ofcomplexes:
The IR spectra of the free ligand and their metal complexes were carried out in the range of 4000-400cm^{-1}.In order to clarify bonding and the effect of the metal ion on the ligand, the IR spectra of the free ligand and the metal complexes were studied and assigned based on careful comparison of their spectra with that of the free ligand.

The v (N-H) stretching was at 3357cm^{-1} in NTZ drug. This frequency shifted to lower range 3350-3240 cm^{-1} indicating coordination of ligand through amido N-H.

The band observed at 1659cm^{-1} in the ligand NTZ for amido carbonyl group shifted to lower frequencies in range 1634-1655 cm^{-1} in complexes.

The NTZ spectra showed a strong band at 1774cm^{-1} assigned to ester carbonyl group this band got shifted to 1735cm^{-1} in Fe NTZ complex, while in all other complexes it disappeared indicating coordination of carbonyl oxygen in the complexes.

The bands at 450- 500 cm^{-1} in the spectra of the metal complexeshave been assigned to *v* (M-O) cm-^{1}of the amide-O- mode.

Table III: IR spectral assignments of complexes

NTZ/ M-NTZ	*v* N-H cm^{-1}	*v* NH-CO cm^{-1}	*v* COO^{-} cm^{-1}	*v* M-O cm^{-1}
NTZ	3355	1659	1774	-
Mn (NTZ)$_2$(Cl)$_2$	3255	1645	-	493
Fe(NTZ)$_2$(Cl)$_2$	3243	1654	1735	493
Cu(NTZ)$_2$(Cl)$_2$	3345	1655	-	453
Zn(NTZ)$_2$(Cl)$_2$	3312	1634	-	464

UV/VISspectral studies of complexes:

Mn(NTZ)$_2$(Cl)$_2$ complex gave three weak absorption bands at 751nm, 410nmand 376nmwhich are characteristic of Mn (II) .The Mn complex has µeff. of 4.95 B.M which is in the range of octahedral complex.

The observed magnetic moment of Fe(NTZ)$_2$(Cl)$_2$complex is 5.22 B.M , indicating octahedral geometry.The spectrum shows band at 431nm and 361nm which are attributed to charge transfer.

The electronic spectra of Cu (II) complex shows weak band at 430 nm band corresponding to $^2E_g(D){-}{>}^2T_2g$ (D) transition respectively. The band at 430 nm is expected for d-d transition of Cu (II) complex. The broadness of the band could be attributed to the overlapping of several bands as a result of strong Jahn- Teller distortion expected in a d^9 ion. Thus the electronic absorbance data supports a distorted octahedral geometry. The copper complex showed µ eff. value of 1.87 B.M indicative of one unpaired electron.

Table IV: Magnetic susceptibility and electronic absorption spectral studies:

COMPLEX	WAVELENGTH (nm)	WAVELENGTH(cm^{-1})	TENTATIVE ASSIGNMENT	$\mu_{EFF.}$ B.M
Mn (NTZ)$_2$(Cl)$_2$	751 410 376	13316 24390 26596	$^6A_1g{-}{>}4T_1g(G)$, $^6A_1g{-}{>}^4T_2g(G)$ $^6A_1g{-}{>}^4T_2g(D)$	4.95
Fe(NTZ)$_2$(Cl)$_2$	431 361	23200 27700	Charge transfer Charge transfer	5.22
Cu(NTZ)$_2$(Cl)$_2$	430	23300	$^2Eg{-}{>}^2T_2g$	1.87
Zn(NTZ)$_2$(Cl)$_2$	257	38900	LMCT	diamagnetic

Table V:Ligand Field Spilliting Energy- LFSE Nephelauxetic ratio-β=B'/B
B' -Racahinterelectronic repulsion parameter

Complex	LFSE 10 Dq (cm-1)	B' (cm-1)	β=B'/B	*v*2/*v*1	LFSE (kcal mol-1)
Mn (NTZ)$_2$(Cl)$_2$	1331.6	735.86	0.855	1.83	38.02
Fe(NTZ)$_2$(Cl)$_2$	2320	-	-	1.19	66.20
Cu(NTZ)$_2$(Cl)$_2$	2330	-	-		66.51
Zn(NTZ)$_2$(Cl)$_2$	3890	-	-		109

TG/DTA thermogravimetric studies of complexes:

The mode of co-ordination of ligands in complexes has been further supported by their Thermogravimetric studies. The contents of a particular component in a complex changes with its composition and structure. Thus, the content of such compounds can be determined based on Thermogravimetric plots of the complex.

Mn (NTZ) $_2$(Cl)$_2$ complex

The complex shows decomposition at 250^{0}C and 5- nitro -2- thiazolyl molecule seems to be eliminated(49.41% found, 51.79% calculated). At about 450^{0}C to 750^{0}C the organic moiety is completely eliminated(35.34% found, 35.92% calculated) and a residue is left behind(12.45% found, 12.87% calculated), which remains unchanged on further heating in the case of all the complexes.

Fe (NTZ) $_2$(Cl)$_2$complex

The Thermogravimetric studies of the complex showed that it was decomposed in two successive overlapped and unresolved steps. The steps involved the loss of ligand molecule with an overall weight loss amounts to 85.56% found, 85.84% calculated.

Cu (NTZ) $_2$ (Cl)$_2$complex

The complex Cu (NTZ) $_2$(Cl)$_2$, TG- DTA curves of this complex reveal that it remains unchanged upto 180^{0}C. This complex shows gradual decomposition upto 200^{0}C but above this temperature, the rate of decomposition is found in creased, and practically at 280^{0}C the weight loss (37.93 found, 38.40 calculated) is observed which is consistent with the removal of ,5- nitro -2- thiazolyl from the above complex. Further, a slow decomposition has continued and rapid mass loss takes place at 590^{0}C which is evident from the TG curve of the complex. At about 580^{0}C the organic moiety is completely eliminated and the weight of the remaining residue coincides with the weight of CuO (calculated 11-66%, found 12.68%).

Zn (NTZ) $_2$(Cl)$_2$complex : The Thermogravimetric studies of the Zn (NTZ) $_2$(Cl)$_2$ complex showed that it was decomposed approximately with three main degradation stages in 500^{0}C – 900^{0}C temperature range. The first stage of decomposition occurs in 200^{0}C to 320^{0}C range is accompanied by a weight loss of 43.26% calculated (42.34% found). The subsequent step 320^{0}C – 530^{0}C correspond to removal of remaining NTZ ligand leaving behind metal oxide as residue.

CONCLUSION

Reviews on other metal drug complexes have shown that the Nitazoxanide complexes have been successfully synthesized and characterized by spectral and analytical data. Based on this data, octahedral geometry has been assigned to the complexes. In the complexes, Nitazoxanide was proposed to co-ordinate through amide NH and through acetate O.

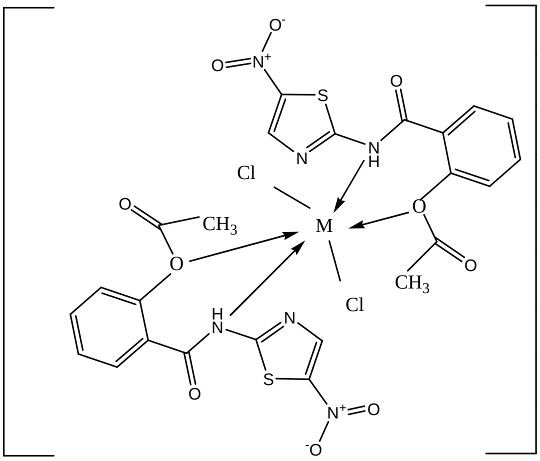

FIG. II PROPOSED STRUCTURE OF COMPLEX

M = Mn (II), Cu (II) and Zn (II)

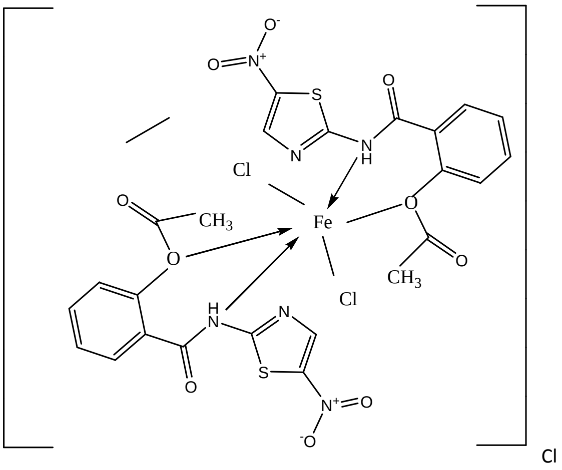

FIG. III PROPOSED STRUCTURE OF Fe (NTZ) $_2$ (Cl)$_3$COMPLEX

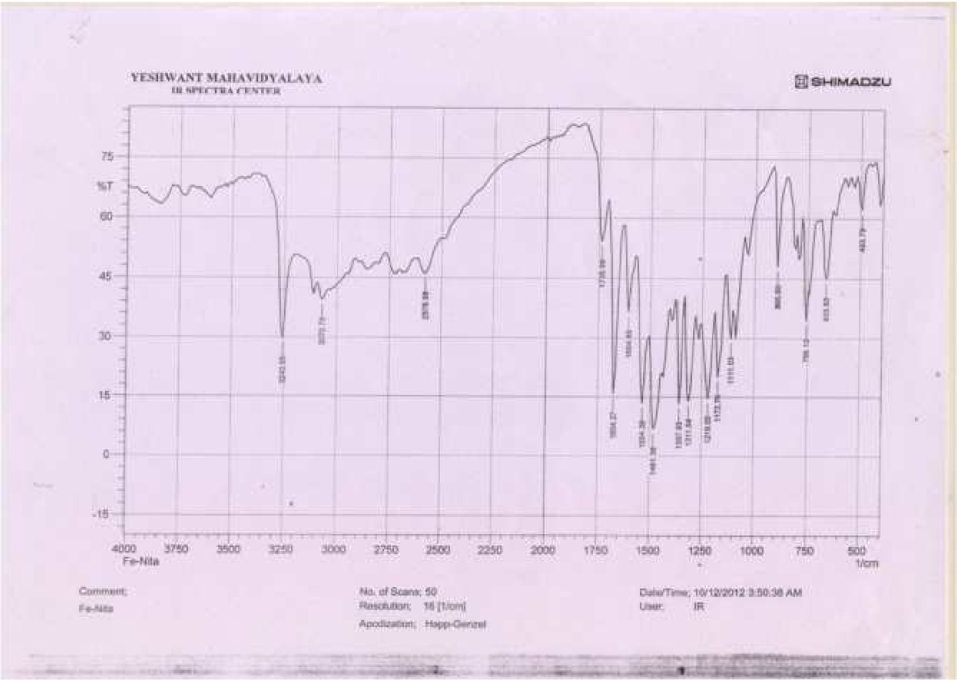

FIG. IV IR SPECTRA OF Fe (NTZ) $_2$ (Cl)$_2$COMPLEX

FIG. V IR SPECTRA OF Cu (NTZ) $_2$ (Cl)$_2$COMPLEX

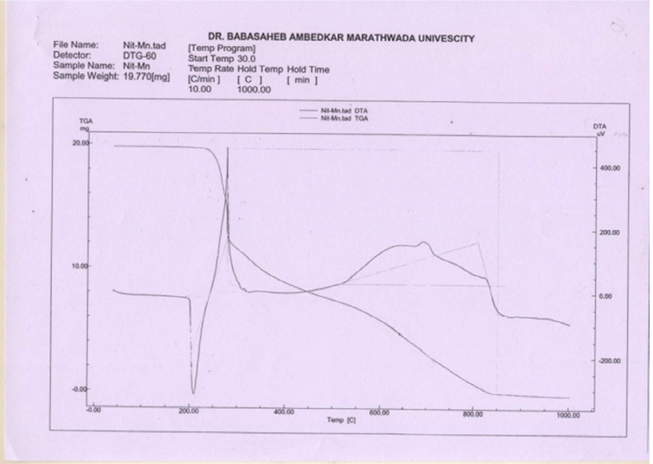

FIG. VI TG /DTA SPECTRA OF Mn (NTZ) $_2$(Cl)$_2$COMPLEX

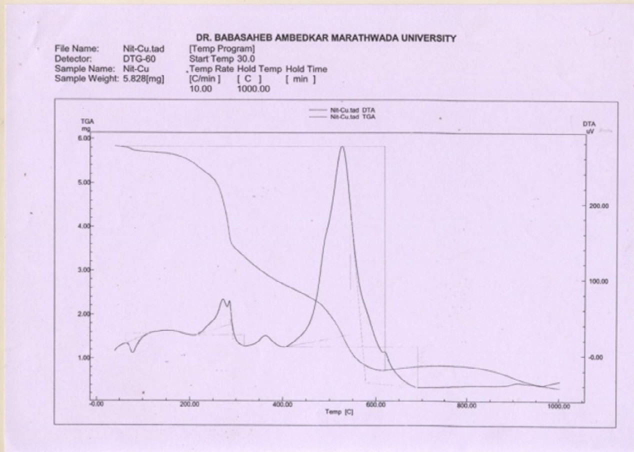

FIG.VII TG /DTA SPECTRA OF Cu (NTZ) $_2$ (Cl)$_2$COMPLEX

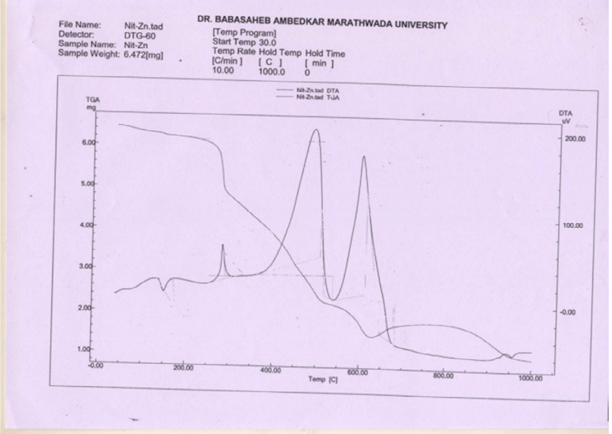

FIG.VIII TG /DTA SPECTRA OF Zn (NTZ) $_2$ (Cl)$_2$COMPLEX

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