Synthesis, Characterisation and Biological Studies of Mn(II) and Ni(II) complexes with Drug Alprazolam [8-Chloro-1-mthyl-6-phenyl-4H-1,2,4-triazolo (4,3-a) (1,4) benzodiazepine]

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Abstract: In the present study, Mn(II) and Ni(II) complexes have been prepared by reacting metal Nitrate with the ligand (Alprazolam), which have the general structural composition [(L) $M(NO_3)_2$], where M=Mn(II) and Ni(II) and L=Alprazolam [8-chloro-1-methyl-6-phenyl-4H-1,2,4-trizolo (4,3-a) (1,4) benzodiazepine].The complexes were characterised on the basis of elemental analysis, molecular weight and IR data. The shift in the characteristic infrared frequencies of the free ligand bands confirm the coordination. The IR data of the complexes reveal the bidentate nature with [N(1) and N(4)] sites of the ligand. All the complexes, ligand and metal salts have been screened for antibacterial and antifungal activities against selected microbes. Biocidal studies show that the Ni(II) complexes is more effective than Mn(II) complexes.

Key words:- Metal complexes, Alprazolam and Biocidal study.

Introduction:

The complexes of 1,4-benzodiazepine with metal ions have immensely been reported in literature[1-5]**.** Alprazolam a benzodiazepine drug is included in the category of tranquillizer drugs. It is used to treat anxiety disorders and as an adjunctive treatment for depression. It has been reported that complexes of 1,4-benzodiazepine also possess anticancer[6-7] and pharmacological[8] properties. Metal complexes of 1,4-benzodiazepines possessing biological activity may be even more active than free ligand [9]. Mn(II) complex of Alprazolam appears to be quite active, having a rapid onset of action and it also prolongs the duration as compared to that of Alprazolam itself. Different coordination modes have been including coordination with the neutral ligand viz. N(4), However, none of the modes has been ascertained. Neutral complexes of 1,4-benzodiazepines such as Nitrazepam where the ligands act as anions through labialization of proton at N(I) atom giving (imido) complexes, have been reported[9-11]. The structure of the ligand Alprazolam (AZ) is given in figure (1).

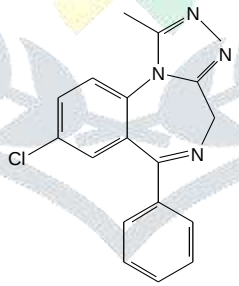


Fig. 1: Alprazolam (AZ)

The proposed work has been taken up to investigate the mode of coordination of the metal ion with (AZ) drug of increased biological activity of the drug on complexation as reported in the literature[12]. The results will throw light on the mode of coordination of the metal ion with the AZ drug as well as on the complex formation of other benzodiazepines in general.

Experimental:

All the chemical used were of AR grade and their solution were prepared in double distilled water. The complexes were prepared by mixing molar solutions of $Mn(NO_3)_2.4H_2O$, $Ni(NO_3)_2.6H_2O$ (dissolved in double distilled water) and the ligand Alprazolam (dissolved in ethanol). The pH of the mixture was adjusted at 7.5-8.5.

The stoichiometry of the complexes of the drug (0.025M) with Mn(II) and Ni(II) (0.025M) metal ions was found by carrying out potentiometric titration against standard (0.1M) NaOH solution in ethanol-water mixture. The pH changes observed during the titration were plotted against moles of alkali (m) added per moles of metal ion and ligand as depicted in figs. 3 and 4. The stoichiometric ratio is confirmed by *Job's method[13]*. The coloured precipitates were filtered, washed several times with hot water followed by ethanol to free it from the soluble impurities. The complex were finally dried in an oven at 100^0C and stored in desicator. The purity of the complexes was checked by TLC. The

complexes were dissolved in benzene: Acetic Acid (2:1) and TLC was carried out in ethanol: Benzene (80:20) system. The Retention factor (Rf value) was calculated by following formula.

$$Rf = \frac{\text{Distance travelled by solute}}{\text{Distance travelled by mobile phase}}$$

The Rf values of the Mn(II) and Ni(II) complexes were given in table.

Table-1: The Rf values of Mn(II) and Ni(II) complexes of Alprazolam

Solvent System	Sample	Rf value	Impurity
Ethanol : Benzene 80 : 20	Mn(II)-AZ complexes	0.75	Not visible
	Ni(II) – AZ complexes	0.65	Not visible

Experimental (Biocidal):

Metal complexes, metal ion and ligand have been tested for their effect on the growth of microbial cultures to study their interactive role with fungi (*Aspergillus flavous, Aspergillus niger, Penicillium, triticena* and *Fusarium species*) and bacteria (*Escherichia coli, Salmonella typhi, Bacillus subtilis, Staphylococcus aureus*) using filter paper disc method[14] and Broth serial dilution method[15] respectively as detailed below –

The complexes were dissolved in DMF (0.5ml) to get a stock solution of 1000 ppm by adding sterilized distilled water. The dilute solution of 750 ppm, 500 ppm and 250 ppm concentration were obtained by further dilution of the stock solution. The activity was studied in all the solutions in the cavity slides by mixing the spore suspension of the test organism separately. Standard drug was used to check and compare the activity of the complexes. It indicated that metal complexes of the drug had a significant activity at a lower concentration and bacteria were incubated at 24 ± 1^0C for 20 hours. The data and results are presented in Table – III.

The IR spectra in KBr matrix were recorded on Perkin-Elemer 842-Spectrometer. Elemental analysis of C,H,N were carried out at CDRI, Lucknow.

Result and Discussion:

The molecular formula of the Mn(II) and Ni(II) complexes correspond to $[(C_{17}H_{13}Cl\ N_4).\ Mn(NO_3)_2]$ and $[(C_{17}H_{13}Cl\ N_4).Ni(NO_3)_2]$. The molecular weights 487.70 and 491.50 respectively for Mn(II), Ni(II) complexes were determined on the basis of elemental analysis. The physical and analytical data of ligand Mn(II) and Ni(II) complexes are given in table-II.

Compound	Mol.Wt.	Elemental analysis found (Calculated) %					Colour	M.P.
		C	H	N	Cl	M		
$[C_{17}H_{13}ClN_4]$	308.8	(66.06) 67.02	(4.21) 3.50	(18.13) 19.50	(11.5) 10.20	--	White	228.5
AZ $Mn(NO_3)_2$	487.70	(41.83) 42.23	(2.67) 1.83	(17.22) 18.40	(7.28) 6.40	(11.26) 12.36	Black	339
AZ $Ni(NO_3)_2$	491.50	(41.51) 43.10	(2.64) 3.20	(17.09) 16.23	(7.22) 6.43	(11.94) 10.53	Brownish cream	258

The IR spectrum of the ligand exhibits bands in the region 1628 cm^{-1}, 1280 cm^{-1}, 1600 cm^{-1}, 740 cm^{-1}, 2960 cm^{-1} and 1355 cm^{-1} which may be assigned to ν(C=N), ν(C-N), ν(C_6H_5), ν(Cl), υ(CH_2) and υ(-CH_3) respectively. The ligand band observed in the range of 1628 cm^{-1} undergoes the lower shifting to 1608 cm^{-1} and 1616 cm^{-1} in Mn(II) and Ni(II) complexes respectively, indicating azomethine nitrogen N(4) atom of Benzodiazepine ring in coordination to the metal ion complexes. The Mn(II) and Ni(II) complexes the band attributed to the vibration mode $\upsilon(\diagdown\!\!\diagup C-N-)$ appear at 1267 cm^{-1} and 1261 cm^{-1} showing lower shifting as compared to the ligand (1280 cm^{-1}), indicating $(\diagdown\!\!\diagup C-N-)$ nitrogen (1) participating in complexation. In IR spectrum of the ligand the bands attributed to vibrational mode υ(-C_6H_5), υ(CH_3), υ(–Cl), υ (CH_2) appears at 1600 cm^{-1}, 1355cm^{-1}, 740 cm^{-1} and 2960 cm^{-1} showing small positive shift in complexation.

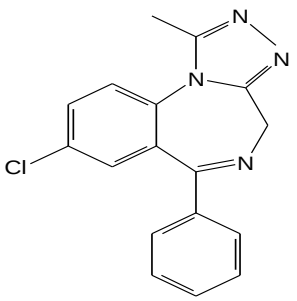
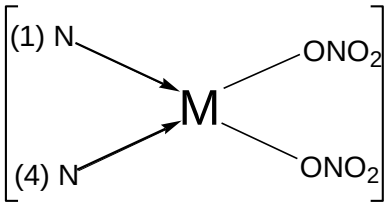


Fig.2

The presence of new bands at 508 cm^{-1} and 480 cm^{-1} in Mn (II) complex and 515 cm^{-1} and 460 cm^{-1} in Ni (II) are attributed to υ (M-N) linkage[16]. Other strong bands at 1360 cm^{-1} and 950 cm^{-1} in Mn(II) complexes and 1355 cm^{-1} and 862 cm^{-1} in Ni (II) complex suggest monodentate nitrate group in complexes[17]. The representative structure of the complex may be shown as



Probable structure of metal complexes
Where M=Mn (II), Ni (II)

Biocidal Activity :The biological activities of Mn(II) and Ni(II) complexes, metal nitrates and ligand were screened against bacteria – *E. coli, S. typhi, B. subtilis* and *S. aureus* and fungi – *A. flavous, A. niger, P. triticena* and *F. species*. The zone of inhibition of Mn(II) and Ni(II) complexes on bacteria and fungal species are presented in Table – III.

Table – III: Antibacterial and Antifungal activities of the Drug, Metal nitrates and Complexes

Compound	Antibacterial Activity zone of inhibition (in mm.)				Antifungal Activity zone of inhibition (in mm.)			
Drug (AZ)	--	--	--	--	--	--	--	--
$Mn(NO_3)_2$	--	--	--	--	--	--	--	--
$Ni(NO_3)_2$	--	--	--	--	--	--	--	--
Mn $AZ(NO_3)_2$	47.84	62.66	62.66	62.66	58.46	56.56	69.13	66.56
Ni $AZ(NO_3)_2$	56.56	62.00	62.66	69.15	56.56	58.46	71.53	64.00
DMF	-	-	-	-	-	-	-	-

The above data indicate that the zone of inhibition at 500 ppm concentration is best as compare to the standard drug. The results show that the Ni(II) complex of Alprazolam is more effective towards all fungi and bacteria as compared to Mn(II) complex of Alprazolam and drug Alprazolam itself.

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Fig. 3

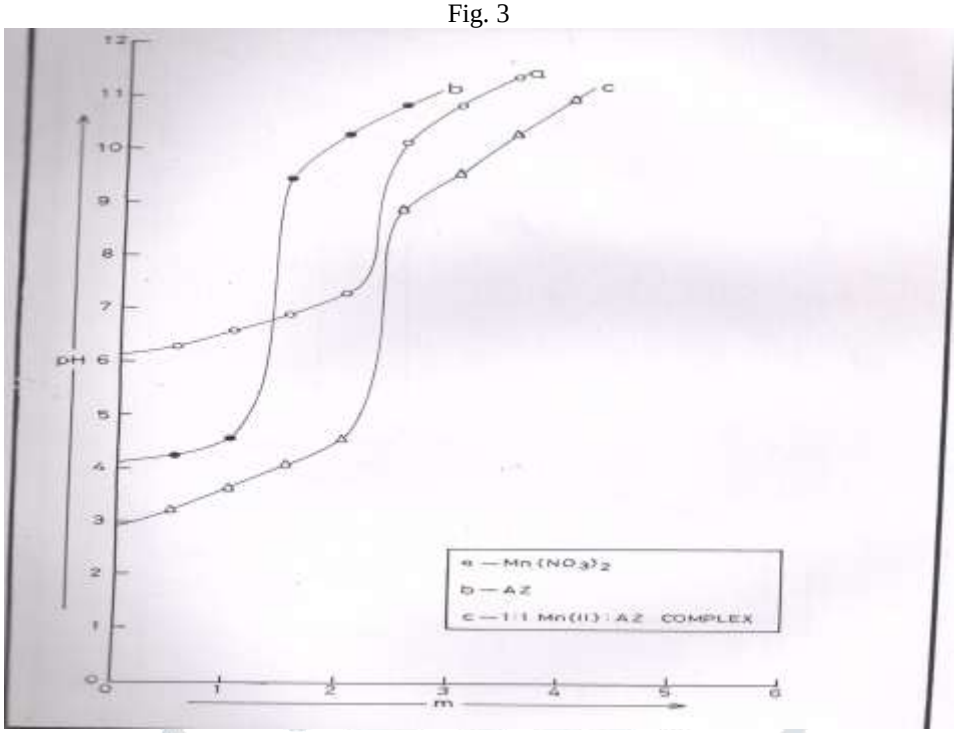
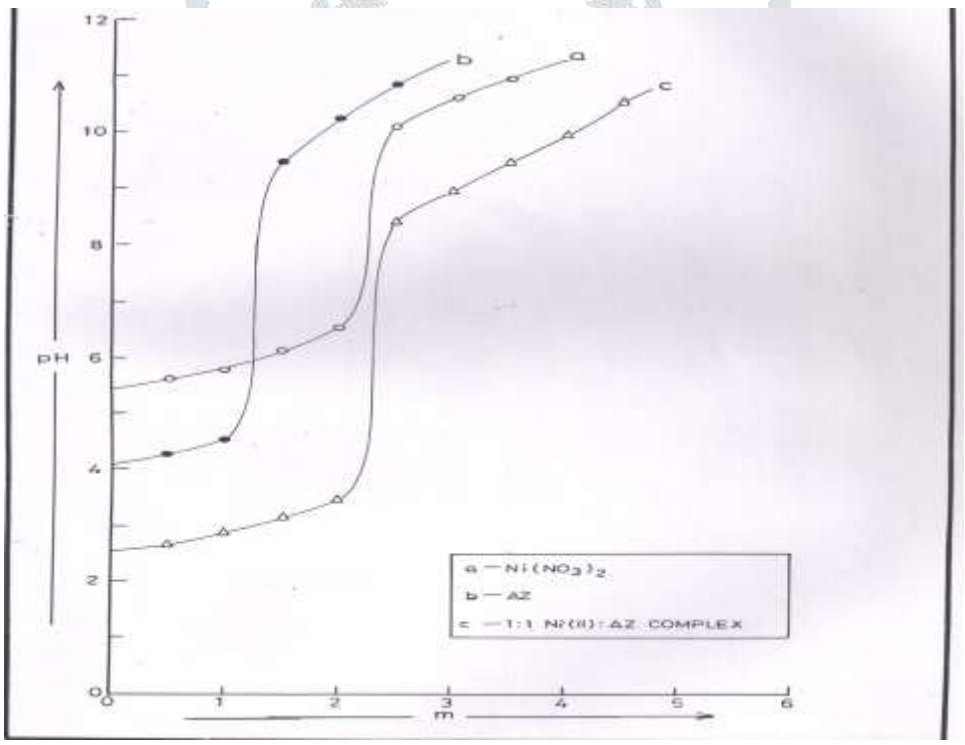

pH
m
a
b
c
a — Mn(NO3)2
b — AZ
c — 1:1 Mn(II):AZ COMPLEX

Fig. 4


pH
m
a
b
c
a — Ni(NO3)2
b — AZ
c — 1:1 Ni(II):AZ COMPLEX

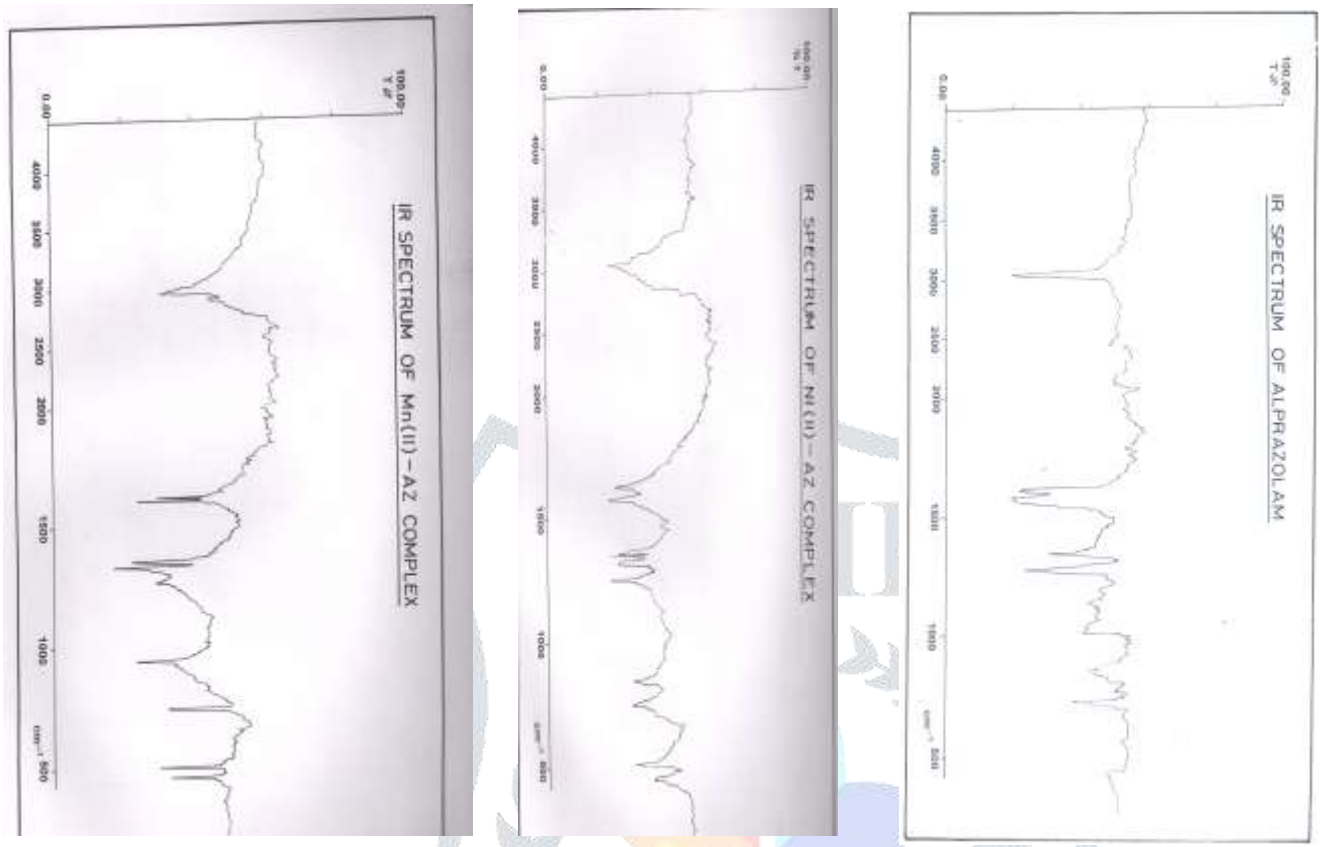

IR SPECTRUM OF Mn(II)-AZ COMPLEX
IR SPECTRUM OF Ni(II)-AZ COMPLEX
IR SPECTRUM OF ALPRAZOLAM

Fig. 5