IJCRT.ORG ISSN : 2320-2882

INTERNATIONAL JOURNAL OF CREATIVE RESEARCH THOUGHTS (IJCRT)

An International Open Access, Peer-reviewed, Refereed Journal

PREPARATION, FTIR, NMR, MASS SPECTRAL, MAGNETIC AND X-RAY CRYSTALORAPHY STUDY OF Co(II) COMPLEX OF N,N-DIMETHYLBIGUANIDE

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Abstract:

N,N-dimethylbiguanide complex of Co(II) is synthesized. Metal ligand ratio is calculated by conductometric titration using monovariation method which is further confirmed by Job's method of continuous variation. According to the elemental analyses, the complex is found to have formula viz. $[(C_4H_{11}N_5)_2Co\ (OH_2)_2]2Cl^-$. The measured high molar conductance values indicate the complex is ionic nature. Geometry of complex is assigned octahedral. Structure have been discussed and suggested upon elemental analyses, IR, ^{1}HNMR spectral data, electronic, magnetic and mass studies. Powder X-ray diffraction data was performed on metal complex. XRD pattern indicate crystalline nature of complex. XRD data have been used to calculate particle size, porosity, volume of unit cell and density of synthesized complex

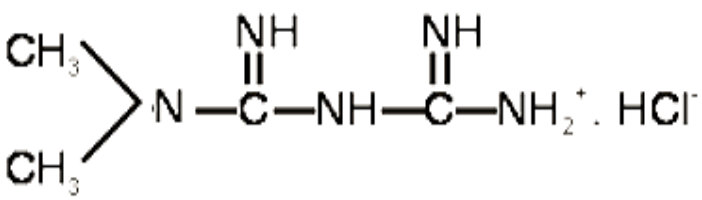
Keywords: *Metformin, Complex, spectroscopy, magnetic moment, and X-ray diffraction.*

INTRODUCTION

Metal ions are fundamental elements for the maintenance of the life of plants, animals and humans. Their role in biological systems was recognized a long time ago. They are essential for the maintenance of life and their absence can cause several disease. Metal ions are required for many critical functions in humans. Scarcity of some metal ions can lead to disease[1]. Well known example is *pernicious anemia* resulting from

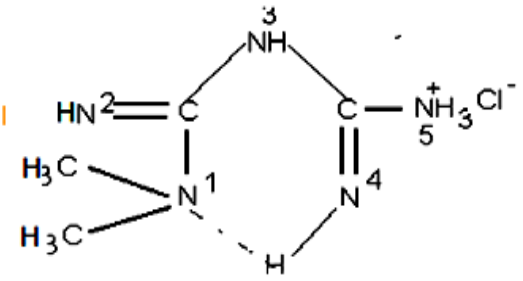
iron deficiency. A large number of metals used as chemotherapeutic agents in *Ayurveda* and *Tibb*, for example, Gold (*Swarn-bhasm - aurous sulphide*) in tuberculosis, arthritis etc., iron (*Kushta-e-foolad = reduced iron sulphide*) in sprue and anaemia, calcium of pearls (*Khamira-e-marvareed*) in gastritis and depressions.

Diabetes is a deceptive disease and if not detected in early stage may cause even death. Several million people are suffering from this disease all over the world (Sadilot and Phatak[2], Bloomgarden[3], Sanger and Thompson[4]). Zinc- insulin was discovered as early as in 1921 and later it proved to be a very efficacious medicine in the treatment of diabetes mellitus. Oral hypoglycemic agents were discovered which has revolutionized the treatment of diabetes. It is worthwhile to mention here that the majority of the essential metallic elements of biological importance are transition metals, whose ability to form coordination complexes and chalets are the characteristic aspects of their chemistry. In recent years much attention is given to the use of sulphonylurea because of their high complexing nature with essential metals. Sulphonylurea are effective for non- insulin dependent diabetes mellitus. These compounds are completely absorbed on oral administration. Complexation of sulphonylurea with lighter transition metals has been studied in detail by Yoshinaga and Yamamotto. [5, 6] Complexation of sulphonylurea and biguanidine by Iqbal *at. el.*, [7-8] and compare its hypoglycemic activity; found that the synthesized complexes are more potent than parent drug. Metformin is also a biguanidine derivative and most useful drug for diabetes, sold under several trade names, including Glucophage XR, Riomet, Fortamet, Glumetza, obimed, Gludormin, Diarber, Diaber, and Diaformin. Broad interest in metformin was not rekindled until the withdrawal of the other biguanides in the 1970s. Genric formulations are now available in several counties and metformin is believed to have become the most widely prescribed antidiabetic drug in the world. Therefore looking the importance of metformin, we have studied metformin complex with Co.



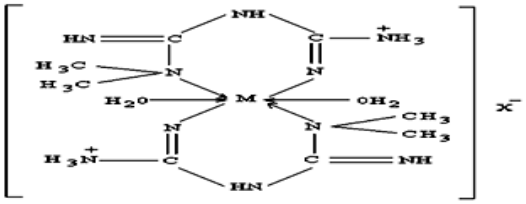
Scheme-I structure of metformin

Let's consider theoretically what will be the structure of these "metformin" complex. If we consider the structure (scheme-I) of active "metformin hydrochloride", we can possibly give tentative structures for metal complexes.



Scheme-I Structure of active metformin hydrochloride

The structure (scheme-I) is shown to be hydrogen bonded and the various places of nitrogen are numbered from 1 to 5. From the above structure it is N^2 and N^4 positions which are capable of protonation and preferably more so at N^4 position because of enolization. Therefore in complex formation metal must be form covalent bond either from N^2 and N^4 positions and coordinate bond from N^1 , for supporting this we have used various spectroscopic technique. If we consider the complex is formed in 1:2 ratios than tentative structure is given scheme-2.



Scheme-II Proposed structure of metformin complex in 1:2 ($M:L_2$) ratio

2. EXPERIMENTAL

2.1 Ligand-Metal Ratio (Mono-variation method)

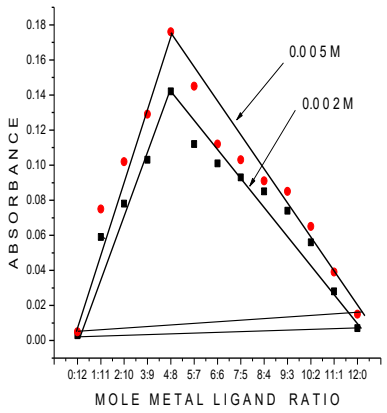
a. Pure "Metformin" 0.828 g (0.005M) was dissolved in 100 ml of ethanol. 0.69 g (0.01M) Ferrous sulphate in 100 ml ethanol and 0.59 g cobaltus chloride was dissolved in another 100 ml of ethanol. 10 ml metformin solution was diluted to 100 ml (ethanol) in a beaker. This was titrated conductometrically against ferrous sulphate solution taken in burette using fractions of 1ml and same procedure was repeated for cobaltus

chloride solution. Conductance was recorded after each addition with proper stirring at temperature 30±1 ^{0}C. Results were plotted in the form of a graph between corrected conductance and volume of metal salt. From the equivalent point in the graph, ratio between metal and ligand was noted to be 1:2.

b. Formation of 2:1 (L_2M) ratio was also confirmed by Job's method [9] of continuous variation as modified by Turner and Anderson[10] (Table-1, figure-1) using absorbance as index property, from these values the stability constant (log k) and free energy change (-ΔF), were also calculated by using formula $k = \frac{x}{(a_1-x)(b_1-2x)^2} = \frac{x}{(a_2-x)(b_2-2x)^2}$ Where, k = Stability constant, x = Conc. of complex and ΔG = -RT Ink respectively.

Table-1: Metformin with cobaltus chloride, Job's method of countinous variation(modified Job's method)

S. No.	Metal:Ligand ratio	Absorbance		Corrected Absorbance	
		.002M	.005M	.002M	.005M
1	0:12	0.003	0.005	0.00	0.00
2	1:11	0.059	0.075	0.056	0.070
3	2:10	0.078	0.102	0.074	0.096
4	3:9	0.103	0.129	0.099	0.123
5	4:8	0.142	0.176	0.137	0.170
6	5:7	0.112	0.145	0.107	0.137
7	6:6	0.101	0.112	0.096	0.104
8	7:5	0.093	0.103	0.087	0.094
9	8:4	0.085	0.091	0.079	0.082
10	9:3	0.074	0.085	0.068	0.075
11	10:2	0.056	0.065	0.050	0.053
12	11:1	0.028	0.039	0.022	0.027
13	12:0	0.007	0.015	0.00	0.00



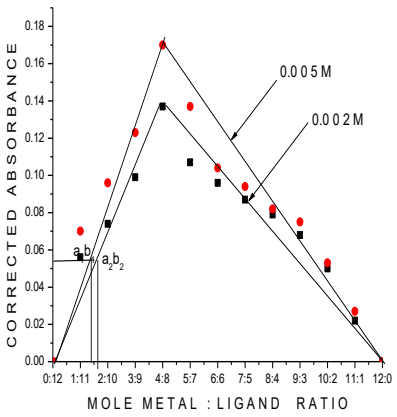


Fig.:1 Metformin with cobalt chloride

(Modified Job's method)

2.2 Synthesis of Complex

The chemicals used in this synthesis were all of analytical reagent grade (A.R.) and of highest purity. A weighed quantity of "metformin" (2 mole) was dissolved separately in minimum quantity of 90% ethanol. The cobalt solution (1 mole) was prepared by dissolving separately in the same solvent. Ligand solution was added slowly with stirring into the solution of metallic salt at room temperature; maintain the pH between 6.0 to 6.5 by adding dilute NaOH solution. On refluxing the mixture for 3-4 h and on cooling, the complexes separated out, which were filtered, washed well with ethanol and finally dried in vacuum and weighed.

2.3 Instrumentation

The elemental analyses of the isolated complexes were carried out using Coleman Analyzer at the Departmental Microanalytical Laboratory C.D.R.I., Lucknow, India. Iron and Cobalt analysis were carried out in Qualichem Laboratory, Nagpur, India by Atomic Absorption Spectroscopy. The IR spectra of the ligand as well as of the complex was recorded on Perkin Elemer Spectrophotometer, ^{1}H-NMR spectra of the ligand as well as isolated complexes were recorded on a Bruker AM-200 spectrometer using d_6-DMSO solvent in C.D.R.I. Lucknow, India. X-ray diffractometer model Rigaku D-max/B with 12KW rotating for X-Ray studies, at Punjab University, Chandigarh, India. The samples were scanned in the range 10.0084

to 79.9804 (2θ) powder data were indexes using computer software (FPSUIT V 2.0). TGA of complexes were carried out in I.I.T, Bombay.

From stoichoimetry and analytical data, the composition of the complex comes out to be $[(C_4H_{11}N_5)_2Co\ (OH_2)_2]2Cl^-$, which favors 2:1 ($L_2M$) ratio. The tentative structure (Scheme-II) assigned to complexes on the basis of analytical data, was further supported by, IR, NMR, and XRD-data[11-12]. Mass spectra of metformin and cobalt complex was recorded at C.D.R.I Lucknow, India which provides information about the complex by examination of the fragmentation pattern and molecular ion peak of the complex which gives the molecular mass of complex.[11-12]

3.0 RESULT AND DISCUSSION

3.1 Physico-chemical Characterstics of "Metformin"-Cobalt complex

Molecular formula $[(C_4H_{11}N_5)_2Co(OH_2)_2]2Cl$, Mol.wt:423.83; Colour:Light pink; Yield:60.20%; m.p:268^oC; –ΔF: 15.55; Log K: 11.23; Anal. Calcd (%) : C22.65; H5.19; N33.03; Cl^- 16.72; Co13.90; Coordinated water 8.93; Found (%): C22.50; H 5.01; N32.90; Cl^- 16.50; Coordinated water, 8.50; Co,12.50.

3.2 Electronic Spectral Studies of "Metformin"- Cobalt complex

Bands observed at 320 cm^{-1} attributed to charge transfer while the value 417 cm^{-1} and 715 cm^{-1} are assignment to the $^6A_{1g} \rightarrow {}^4E_g$, $^6A_{1g} \rightarrow {}^4T_{1g}$ and $^6A_{1g} \rightarrow {}^4T_{2g}$ transition respectively suggest octahedral environment around "Metformin"-Fe(II) complex and bands observed at 210 cm^{-1} attributed to charge transfer while the value 300 cm^{-1} and 372 cm^{-1} are assignment to the $^4T_{2g}(F) \rightarrow {}^4T_{1g}(F)$, $T_{2g}(F) \rightarrow {}^4T_{1g}(F)$ and $^4T_{1g}(P) \rightarrow {}^4T_{1g}(F)$ transition respectively suggest a octahedral environment around "Metformin"-Co(II) complex .

3.3 Magnetic moment studies

The hysteresis curve is given in Figure 2 for metformin- cobalt complex respectively, shows the magnetic behavior of complex. The magnetic measurements of complex was carried out on Vibrating Sample Magnetometer (mode 155) which directly gives the μ_{eff} values without diamagnetic correction with the help of the following equation.

$$\mu_{eff} = 2.84\sqrt{\frac{RTM}{W.H}} \quad \ldots\ldots\ldots\ldots \quad (1)$$

where,

R = reading of magnetic moment on magnetometer, *T*=absolute temperature, *M* = molecular weight of the compound, *W* = weight of the sample, *H* = magnetic field.

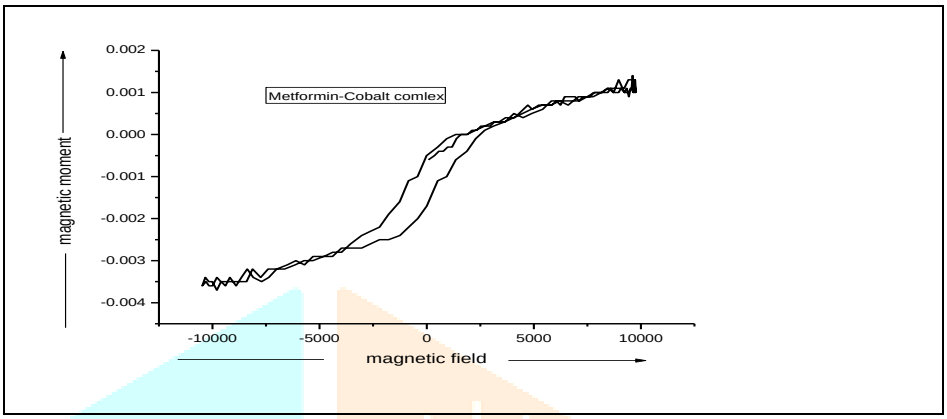


Fig.2 hysteresis curve of metformin-cobalt complex

Magnetic moment has been calculated and is equal to 4.38 B.M for metformin- cobalt complex and hysteresis curve give the information about magnetism i.e "metformin-cobalt complex is paramagnetic.

3.4 Infra-red Specta

Figure. 3 for infrared spectra of metformin- cobalt complex. Assignments of the infrared spectral bands are based on literature.[13-16] IR spectrum shows important bands due to IR(ν,cm^{-1}, KBr ν(M-N) 500±20 cm^{-1}, ν(N-H wagging in ligand as well as complex) 770±10 cm^{-1}, ν(C-N-C) 1215±10 cm^{-1}, ν(-C=N) 1620±10 cm^{-1}(C=N Streaching frequency. The most significant difference in the IR spectrum of the ligand and the complex was the shift of (C=N) stretching frequencies to lower frequencies due to metal-ligand coordination and frequency of chelae ring.) , (amine salt) 2360±10cm^{-1}, ν(C-H) 2910±20 cm^{-1}, ν(NH_3 frequency in ligand and complexes, Similar to amino acid) 3020±10cm^{-1} ν(N-H) 3200-3400 cm^{-1}, ν(coordinate water molecule) 3550±20 cm^{-1}.

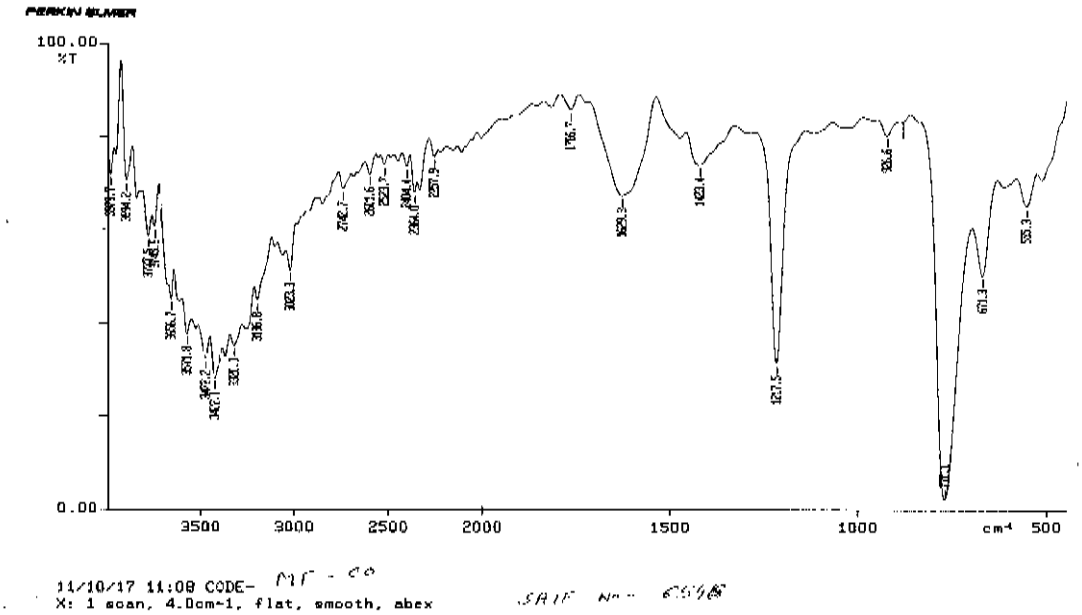


Fig.3 IR spectra of metformin-Cobalt complex

3.5 ^{1}H NMR spectra

NMR Spectra of complex is studied in DMSO. The chemical shift (ppm) of proton for the detected peaks are assigned as for "Metformin"-Cobalt complex, molecular formula $[(C_4H_{11}N_5)_2Co(OH_2)_2]2Cl$ (molecular mass=423.83), ^{1}H-NMR(δ, ppm) δ7.207 (s,2H, Due to amine salt), δ6.788 (s,2H,1C=NH,1C-H-C, J=2.014 H_z), δ2.912 (s,6H,2 methyl-CH_3 J=3.134 H_z) δ2.49(s), δ3.369(s) water of solvent & residual solvent of the DMSO-d_6 respectively. The proposed structure for the isolated complexes is also supported by various auther.[17-19]

3.6 Mass Spectra

Mass spectrum of the compound (Fig.4) has been applied in order to confirm the molecular mass of the complex. Molecular formula of Metformin-Cobalt complex $[(C_4H_{11}N_5)_2Co(OH_2)_2]2Cl$ (molecular mass=423.83), Molecular ion peak ($m^{+\cdot}$); m/z 419 due to $[Co(C_4H_{10}N_5)_2(OH_2)_2\ Cl_2]^{+\cdot}$ or $(ML_2{\cdot}2H_2O.Cl_2)^{+\cdot}$ Molecular ion peak ($m^{+\cdot}$); m/z 372 due to $[Co(C_4H_{10}N_4)_2Cl_2)]^{+\cdot}$ or $[Co(L_2)]^{+\cdot}$, m/z 315(Loss of H_2O,NH_3) due to $[C_8H_{17}N_9Cl_2]^{+\cdot}$ or $[(L_2)]^{+\cdot}$ radical ion, m/z 130 due to $[C_4H_{12}N_5]^{+\cdot}$ base peak ion 100% relative abundance. It is clear that the molecular mass obtained by elemental analyses and signals observed in mass spectra are harmony to each other and confirms the molecular mass of complex[20].

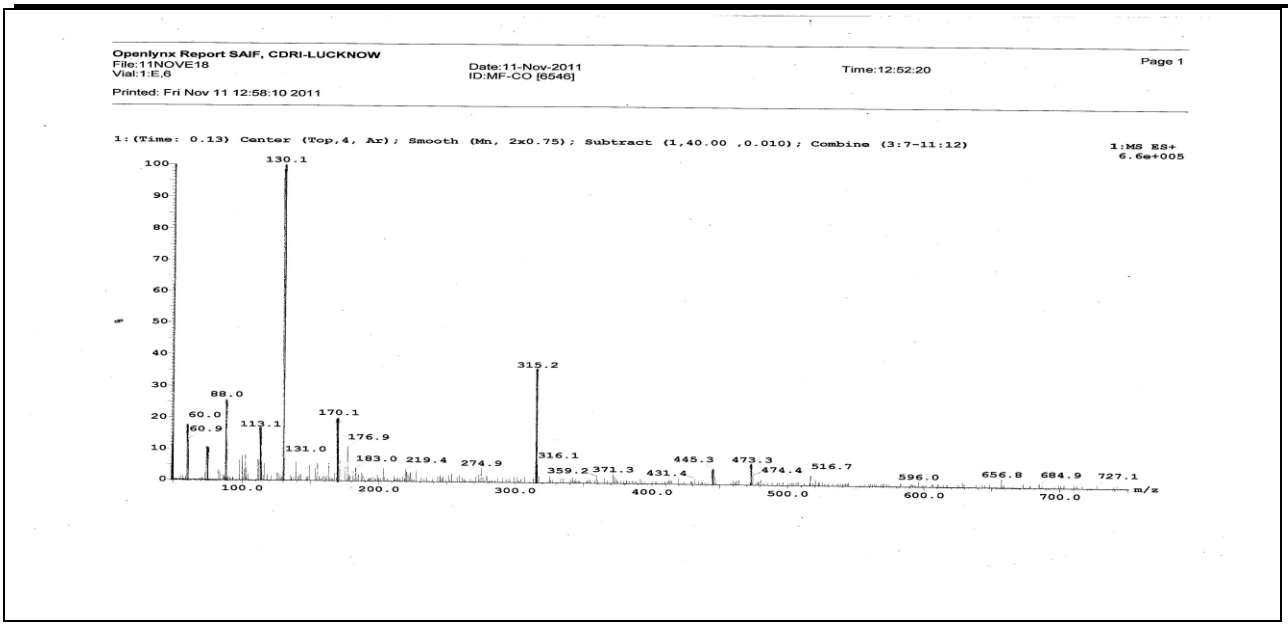


Figure 4:- Mass Spectrum of metformin-cobalt complex

3.7 X-Ray Diffraction Study

X-ray diffraction study also support the complex and formation of new bonds.[21-25] The number of peaks in "metformin" (ligand) are 13 while that of " Metformin"-Cobalt complex is 15 as shown in X-ray difractogram **(**Fig.5 **)** respectively and indicating that complex formed are a well kit one, moreover all the reflections are new ones and the patterns are fairly strong. The X-ray pattern have been indexed (table-2) by using computer software (FPSUIT 2.0V) and applying interactive trial and error method keeping in mind the characteristics of the various symmetry system, till a good fit was obtained between the observed and the calculated $Sin^2\theta$ value. The unit cell parameters were calculated from the indexed data, from cell data and crystal lattice parameters of Co(II) indicates complex attributed to monoclinic crystal system. Powder x-ray diffraction patterns indicate that the synthesized complexes are monoclinic structure.

The particle size were calculated by using the Deby-Scherrer formula $Dhkl = \kappa\lambda/\beta hkl \cos\theta$, where D is the particle diameter in ångstroms, κ is a coefficient and is equal to 0.89 here, β is the half-maximum line width, and λ is the wavelength of x-rays. The other parameters(Table-3) like porosity, volume of the unit cell, and density were calculated by well known formula for "metformin"-cobalt complex.

Table-2: X-ray diffraction data of Metformin with cobalt chloride complex

2θ	I/I$_0$	D$_{(Obs)}$	D$_{(Cal)}$	*h*	*k*	*l*
15.5414	49.42	5.70183	5.68705	2	1	4
20.4673	100	4.33932	4.24260	-4	0	4
21.9046	31.21	4.05773	4.04331	5	2	1
26.3299	87.93	3.38494	3.37778	1	1	8
31.1795	52.91	2.86863	2.86707	6	0	6
32.5514	22.28	2.75079	2.74867	-5	5	5
34.4680	29.20	2.60210	2.59975	-5	4	7
41.4352	10.37	2.17925	2.17734	6	7	6
47.4751	16.01	1.91414	1.91347	11	2	3
51.3930	16.10	1.77797	1.77637	7	10	5
61.2645	9.12	1.51305	1.51174	-14	0	4
62.2343	8.90	1.49178	1.49064	-14	0	5
66.2318	3.00	1.41111	1.40997	12	3	12
74.6563	4.66	1.27138	1.27027	11	12	9
78.4659	1.25	1.21791	1.20510	-11	15	4

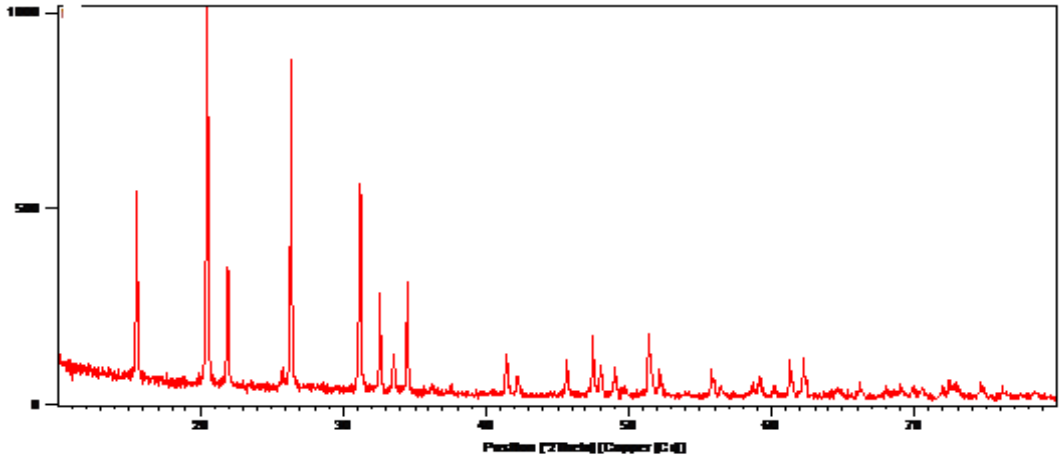
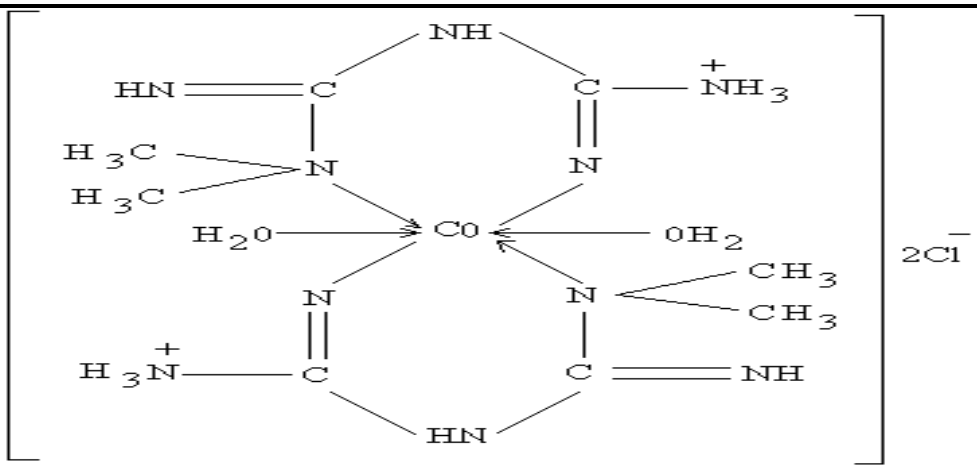


Fig.5 X-ray difractogram of "Metformin"-Cobalt Complex

Table-3 Crystallographic data of complex

Complex	Formula	Particle size, $t = \frac{0.9\lambda}{\beta.cos\theta_B}$	% porosity $= \frac{d_{true} - d_{obs} \times 100}{d_{tru}}$	(Density $= \frac{Weight}{Volume}$ g/cm^3	Volume (A^3)	Space group	Crystal system	Unit dimensions
MF-Co Complex	$[(C_4H_{11}N_5)_2Co(OH_2)_2]2Cl^-$	5.90	0.022	0.0280	14044	Pmmm	Monoclinic	α=90°, β=89°, γ= 0°,a=21.88, b=23.43, c=27.78, λ=1.54 Å



Scheme-III Proposed structure of metformin complex with Cobalt

DISCUSSION

For supporting the proposed structure of cobalt complex with "metformin", initially monovariation method was conducted that indicate 1:2 metal: ligand ratio which was further confirmed by Job's method of continuous variation. Analytical data agree to the molecular formula $[(C_4H_{11}N_5)_2Co(OH_2)_2]2Cl^-$. The proposed structure (Scheme-III) for Co complex of "metformin" was further supported from spectroscopic methods like IR, ^{1}H-NMR, electronic spectra and mass spectral studies etc. We have found a signal at frequency 500±20 cm^{-1}, which is due to linkage of metal-nitrogen. Presence of water molecule is confirmed by getting a medium signal al frequency 3550±20 cm^{-1} .The IR spectral assignments like M-N frequency and the linkage of N^4 to the metal through the covalent bond by the replacement of hydrogen from N^4, while coordinate bond is from N^1 to the metal ion can confirmed by the NMR peak. In complex of biguanidine unit inside the coordination sphere has a positive charge while Cl^- in cobalt complex occupy the outer place of the coordination sphere. Electronic spectra shows charge transfer spectra and mass spectral results gives the molecular ion peak which confirm the theoretically calculated mass of complex. A detailed study of X-Ray also supports the complex formation and the various parameters like particle size, porosity, volume of unit cell, density as well as crystal system was evaluated and we have found that particle size of complex are less than particle size of parent drug.

CONCLUSION

In present paper we have syntheses complex of antidiabetic drug with cobalt and have given its structure which is supported by spectral, kinetics and x-ray parameters which gives the detailed information of the

new structure for coordination chemistry. Moreover in our previous work we have carried out comparative study for hypoglycemic activity of parent drug and its complexes with various transition metals and found that the complexes are more potent than pure drug. If by doing some clinical action it can be used for men and it will be a new drug for diabetes patients.

ACKNOWLEDGEMENT

The authors are thankful to I.I.T Bombay for providing IR spectra, Central Drug Research Institute, Lucknow for providing analytical data, mass spectra and IIT Roorkee for providing magnetic moment of the complex and Punjab University Chandigarh, India for providing X-ray data of complexes.

DECLARATION

No conflict of interest.

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