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Synthesis, Analytical, Spectral and X-ray Diffraction Studies of Cu(II)andNi(II) Complexes with Glipizide, 1-Cyclohexyl3 [[p [2(5methylpyrazinecarboxamido)ethyl]phenyl]sulfonyl]urea, An Oral Antidiabetic Agent

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Complexes of transition metals like Cu(II) and Ni(II) with Glipizide 1-cyclohexyl 3[[p[2(5methyl pyrazine carboxamido) ethyl] phenyl] Sulphonyl] urea were synthesized. Metalcomplexes were characterized byelemental analysis, IR and NMR.The crystal structure of complexeswasdetermined by X-ray diffraction method. The XRD data was used to calculate various parameters like crystal system, volume, density, porosity, particle size etc.based on these studiestetrahedral geometry has been proposed for these complexes.

Key words: Glipizide, Crystal structure, metal complex, IR, NMR, XRD.

Glipizide (trade name, Glucotrol) is one of the most commonly prescribed drug for treatment of type -II *diabetes mellitus*. It is an oral hypoglycemic drug. Chemically, glipizide is a disubstitute darylsulphonyl-urea (Fig.1). Its empirical formula is $C_{21}H_{27}N_5O_4S$, molecular weight is 445.55 and IUPAC name is 1-Cyclohexyl 3[[p[2(5methylpyrazinecarboxamido)-ethyl]phenyl]sulfonyl]urea. It is active at low doses, characterstics feature of second generatio sulphonyl-urea[1]. Oral therapy with glipizide comprises problems of bioavailability fluctuations and may bea ssociated with severe hypoglycemia and gastric disturbances. Although it isclosely related to other sulfonyl-ureas of the same therapeutic classsuchas glibenclamide, blood insulin and glucosetimecourses differ. It also carries much lower risk of hypoglycemia.

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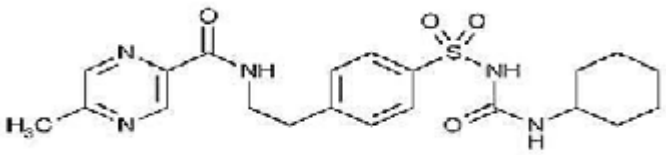
Diabetes mellitus is a chronic metabolic disorder characterized by high blood glucose concentrations (hyperglycemia) causedby insulin deficiency and it is often combined with insulin resistance. Non-Insulin Dependent *Diabetes mellitus* (NIDDM) represents a heterogeneous group comprising milder form of diabetes that occurs predominately in adults and vast majority of diabetic patients possess NIDDM. The analytical parameters of glipizide are given in Table 3 and 4. Glipizide has been in extensive use to treat NIDD Mandacts by increasing the release of endogenousinsulin as well as its peripheral effectiveness; but it has been associated with severe and sometimes fatal hypoglycemia and gastric disturbances like nausea, vomiting, heartburn, anorexia and increased appetite after oral therapy in normal doses[2].Glipizide is bi substituted urea derivative which can exist in keto and enolic forms when dissolved in an organic solvent and react with various metal ions to form intensely colored metal complexes that provide the basis for their use as a sensitive reagent. Many transition and inner transition metal complexes have been synthesized for analytical and commercial

applications, and of medicinal use[3-4].The synthesis and characterization of glipizide complexes with new metal is of great importance for understanding the drug–metal ion interaction and for their potential pharmacological use. Literature survey reveals that the transition and inner transition metal complexes generally show tetrahedral, octahedralgeometry[5,6]. The synthesis and characterization of the glipizide metal complexes is reported in this paper. Different spectroscopic techniques such as infrared spectroscopy, ^{1}H-NMR, elemental analysis and X-Ray diffraction techniques have been used for their characterization[7,8].



Scheme 1. Structure of Glipizide

EXPERIMENTAL

All the chemicals used for the synthesis of complexes are of Hi-media, AR grade and E-Merck quality. Metal complexes were synthesized by adding metal salt solution in appropriate solvent to the solution of the ligand. The mixture was refluxed for 3-4 hours, whereby, the precipitate of metal complexes was obtained. It was filtered, washed and dried in vacuum desiccators.

All selected metals form 1:2 complexes with glipizide which was further confirmed by job's method[9] of continuous variation as modified by Turner and Anderson[10].

Ligand-metal ratio

Mono-variation method

The ligand-metal ratio of complex formation was determined by conductometric titration using mono-variation method on Systronics conductivity meter using dip type electrode. Conductivity water was obtained by distilling laboratory de-ionized water over potassium permanganate. Pure glipizide m.p. 206°C, 0.005 M, was diluted to 100 ml as required and titrated conductometrically against metal salt solutions at 30±1°C. Results were plotted in the form of a graph which indicate ligand metal ratio as 2:1 (L_2M).

Job s method of continuous variation as modified by Turner and Anderson

0.002M and 0.005 M solutions of ligand glipizide and metal salt were prepared in DMF and alcohol respectively. The solution of metal salt and reagent were mixed in varying proportions as under:

Metal (ml)	0	1	2	3	4	5	6	7	8	9	10	11	12
Ligand (ml)	12	11	10	9	8	7	6	5	4	3	2	1	0

pH of the solution was adjusted to 6.5, the precipitated complex was filtered and dried. The absorbance was measured at 630 nm. The absorbance was recorded and given in table 1 and 2 and Jobs plot is given as fig. 1a, 1b and fig. 2a, 2b. It is evident from the graph that absorbance increases up to molar composition of metal to the ligand and after that it decreases indicating 1:2 stoichiometry of the complex[11-13].

Synthesis of metal complexes

Metal complexes were synthesized by adding metal salt solution in appropriate solvent to the solution of the ligand. The mixture was refluxed for 3-4 hours. Then the precipitate of metal complexes was obtained. It was filtered, washed and dried in vacuum desiccators. All selected metals form 1:2 complexes with glipizide, was confirmed by Jobs method[9] of continuous variation as modified by Turner and Anderson[10].

RESULT AND DISCUSSION

The elemental analysis of the isolated complexes was carried out using Elementer Vario EL III analyzer at STIC Kerala, India. The IR spectrum of the ligand as well as of the complexes were recorded on Perkin Elmer Spectrometer at CDRI Lucknow and ^{1}H NMR spectra of the ligand and isolated complexes were recorded on a Bruker DRX-300 Spectrometer at CDRI, Lucknow and $CDCl_3$ was used as a solvent and X-Ray diffractrogram from Punjab University, Chandigarh.

From stoichiometry and analytical data, the composition of the complexes comes out to be $(C_{21}H_{25}N_5O_4S)_2M$, which favors 2:1 (L_2M) ratio. The tentative structure (I) has been assigned to complex on the basis of analytical data, IR, NMR and X-ray diffraction studies.

Infrared spectral studies of the complexes

The IR spectra of pure drug Glipizide[14-16] and its complexes with Cu and Ni were recorded in the range 4000 cm^{-1}-450 cm^{-1}. Assignments of the infra-red spectral bands are based on literature:

Table 1. Glipizide with cupric chloride

Glipizide-0.002M,0.005M — Cupric chloride-0.002M,0.005M
Solvent: Ethanol — Temperature: 30±1^{0}C
Wavelength: 630 nm — pH: 5.9

S. No.	Metal: Ligand ratio	Absorbance 0.002M	Absorbance .005M	Corrected Absorbance 0.002M	Corrected Absorbance 0.005M
1	0:12	0.006	0.009	0.00	0.00
2	1:11	0.021	0.031	0.015	0.02
3	2:10	0.045	0.066	0.039	0.057
4	3:9	0.096	0.126	0.09	0.12
5	4:8	0.156	0.224	0.15	0.218
6	5:7	0.132	0.185	0.126	0.176
7	6:6	0.098	0.162	0.092	0.153
8	7:5	0.076	0.128	0.070	0.119
9	8:4	0.064	0.126	0.058	0.117
10	9:3	0.041	0.1	0.037	0.91
11	10:2	0.025	0.085	0.019	0.076
12	11:1	0.019	0.049	0.013	0.04
13	12:0	0.021	0.00	0.00	0.0

Table 2. Glipizide with nickel chloride

Glipizide-0.002M,0.005M — Cupric chloride-0.002M,0.005M
Solvent: Ethanol — Temperature: 30±1^{0}C
Wavelength: 630 nm — pH: 5.9

S. No.	Metal: Ligand ratio	Absorbance 0.002M	Absorbance .005M	Corrected Absorbance 0.002M	Corrected Absorbance 0.005M
1	0:12	0.011	0.017	0.00	0.00
2	1:11	0.026	0.046	0.015	0.029
3	2:10	0.059	0.075	0.048	0.058
4	3:9	0.085	0.108	0.074	0.091
5	4:8	0.114	0.151	0.103	0.134
6	5:7	0.098	0.146	0.087	0.129
7	6:6	0.081	0.127	0.070	0.11
8	7:5	0.074	0.092	0.063	0.075
9	8:4	0.059	0.071	0.048	0.054
10	9:3	0.048	0.067	0.037	0.057
11	10:2	0.032	0.046	0.021	0.029
12	11:1	0.029	0.031	0.018	0.014
13	12:0	0.017	0.021	0.006	0.004

The proposed structure for the isolated complex is supported by the above given IR absorption bands. The shift of the C=O and S=O by decreased frequencies in the complex indicates that these groups are involved in the complexation. The linkage through amide -O- and sulphone –O atom was further supported by the appearance of a band in the 1636cm $^{1.}$ And at 1665cm ^{1} in both the complexes that may be assignable to M-O frequency[17]. Additional band in the complex region of Cu(II) at 1417cm^{-1} and in Ni(II) at 1416cm ^{1}compared with IR spectra of the free ligand has tentatively been assigned to six member enolic ring structure modified to chelate ring formation in the complexes[18,19].The proposed structure for the isolated complex is also supported by IR absorption

Table 3. Physico-chemical characteristics of Glipizide complexes

S. No.	Metal complex	Metal ligand ratio	colour	% yield	m.p.	Stability constant Log K	Free Energy (-ΔF)
1.	$(C_{21}H_{25}N_5O_4S)_2Cu$	1:2	bluish-green	66	234	11.52	-7.2161
2.	$(C_{21}H_{25}N_5O_4S)_2Ni$	1:2	green	61	206	9.821	-13.842

Table 4. Analytical data of Glipizide complexes

Metal complex	% C	%H	%N	%S	% metal
$(C_{21}H_{25}N_5O_4S)_2Cu$	47.24(48.7)	5.04(6.06)	8.66(9.23)	10.8(11.01)	12.12(12.95)
$(C_{21}H_{25}N_5O_4S)_2Ni$	44.31(42.7)	5.62(4.86)	11.10(9.70)	7.91(7.21)	11.13(11.55)

Table 5. IR Absorption bands of Glipizide Metal Complexes

Complexes	Main IR Absorption in cm^{-1}
Glipizide	538.26w 606.61vw 671.96w 770.48vs 837.84w 902.93w 1032.55s 1085.83w 1156.99s 1217.85s 1330.3s 1370.39m 1442.2s 1529.09vs 1646.48vs 1686.79vs 2855.77s 2939.57s 3023.85s 3247.81vs 3322.01vs
Glipizide-Cu	473.24vw 627.09w 669.66w 772.02v 928.8w 1047.18s 1162.3s 1218.11s 1417.63s 1636.58vs 2143.78s 2400.6s 3020s 3436.87vs
Glipizide-Ni	468.21vw 669.65vw 771.87vw 928.77vs 1047.7w 1166.3s 1217.96w 1416.04m 1665.21vw 2400.07m 3019.24vw 3445.15w

Table 6. NMR- Assignments of Glipizide and its Metal Complexes

Compounds	δ and multiplicity
Glipizide	δ 9.245(s,pyrazine), δ 8.33 (s,1H NH-CO, J=1.12), δ7.8-7.82(d,benzene,J=3.42), δ7.24-7.4(s,SO_2-NH, J=3.20), δ6.44-6.46(d, aromatic,J=1), δ3.77(q,O-CH), δ 3.05(t,NH,J=2.29), δ2.63(s,CH_3gp attached to benzene,J=3.35), δ1.64-1.83(q,CH_3 group,J=7.92), δ 1.11-1.33(CH_3, J=7.6)
Glipizide-Cu	8.11-8.15(s,NH-CO,J=1.21), δ7.87-7.92(d, benzene,J=3.32), δ7.30-7.53(s,SO_2-NH, J=3.12), δ 6.40-6.49(d, aromatic, J=2.10),ä3.54(s, NH-CO-Cu ,J=2.19), δ1.571(q,CH_3, J=5.50) δ 1.13-1.44(CH_2, J=1.165)
Glipizide-Ni	8.033(s, NH-CO,J=1.44), δ7.806(d, benzene,J=3.32), δ7.395(s,SO_2-NH, J=2.14), δ 3.604(s, NH-CO-Ni ,J=3.214), δ1.601(q,CH_3, J=4.50) δ 1.224(CH_2, J=1.015)

S=singlet, d= doublet, t= triplet, q= quadrate, m= multiplet

and has been reported by Rao, Bellamy and Weissberger[20-22].

H^1-NMR Studies

We have observed imides (NH) proton around (d8.35) in the spectrum of the ligand that has disappeared in the spectra of the complexes molecule due to formation of M-O bond. This also confirms the de-protonation of imide NH group through enolisation.

X-ray diffraction study of Glimepiride complexes

The X-ray diffraction of Cu(II) and Ni(II) complexes with glipizide were obtained and summarized in following tables. All reflections has been indexed for h, k, l values using reported

Table 7. Cell data and crystal parameter of GLP-Cu complex

a(Å) = 21.54020	VolumeA^o= 14518.848
b(Å) = 24.34860	Dcal=5.41003g/cm^3
c(Å) = 27.68270	Dobs= 5.39873g/cm^3
α=90°, β=89.4°, γ=90°	Density = 0.07531gm/cm^3
Particle size = 7.0418microns	Porosity (%) = 0.208 %
Standard deviation = 0.002%	Crystal system = Orthorhombic
Space group = Pm	Mass of unit cell=1.8156×10^{-25}

2θ	I/I_0	$D_{(obs)}$	$D_{(cal)}$	h	k	l
16.3852	100.0	5.41003	5.39873	0	1	5
19.1435	5.10	4.63631	4.63984	4	2	2
17.7813	2.06	4.48825	4.48719	4	3	0
26.1407	3.54	3.40901	3.40777	1	7	1
27.6165	1.90	3.23010	3.22664	5	5	0
31.1410	9.01	2.87209	2.86542	2	8	2
31.9204	40.78	2.80372	2.802213	3	8	0
32.5086	63.29	2.75432	2.75055	0	1	10
39.8902	48.74	2.26002	2.25952	7	2	8
45.6683	4.84	1.98662	1.98537	9	3	7
50.1700	10.31	1.81841	1.81681	11	5	0
53.4450	7.06	1.71445	1.71312	9	7	8
56.6559	3.04	1.62468	1.62324	0	15	0
68.6636	4.24	1.36582	1.36574	10	4	15

Table 8. Cell data and crystal parameter of GLP-Ni complex

a(Å) = 21.54020	Volume Å= 14518.848
b(Å) = 24.34860	Dcal=9.23828g/cm^3
c(Å) = 27.68270	Dobs = 9.22757g/cm^3
α=90°, β=89.4°, γ=90°	Density= 0.0862gm/cm^3
Particle size = 10.171microns	Porosity(%) = 0.114 %
Standard deviation = 0.0034%	Crystal system = Orthorhombic
Space group = Pm	Mass of unit cell=2.079×10^{-25}

2θ	I/I_0	$D_{(obs)}$	$D_{(cal)}$	h	k	l
9.5738	100.0	9.22757	9.23828	0	0	3
21.4043	30.25	4.15144	4.18672	4	1	4
31.9560	31.38	2.80068	2.79694	4	6	5
33.9560	17.73	2.66888	2.67178	-1	9	1
45.6859	14.55	1.98590	1.98427	-7	9	3
59.8858	15.40	1.54326	1.54341	3	15	4

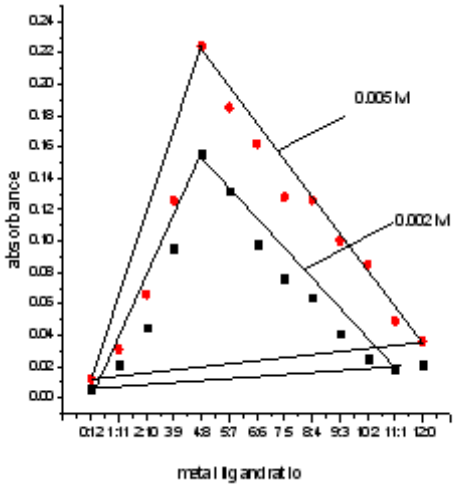


Fig. 1(a)

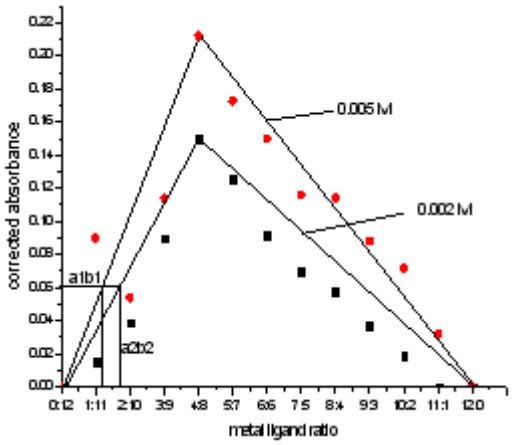


Fig. 1(b)

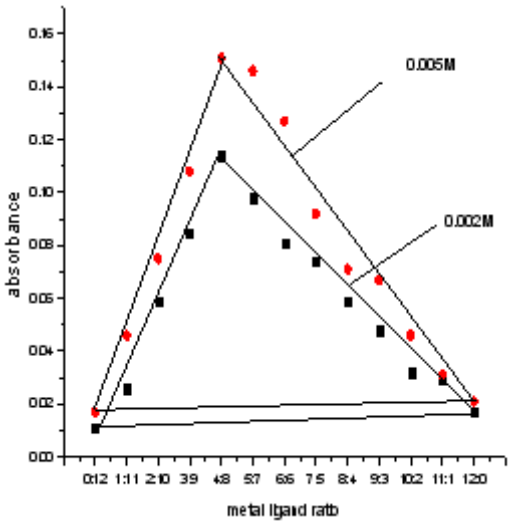


Fig. 2(a)

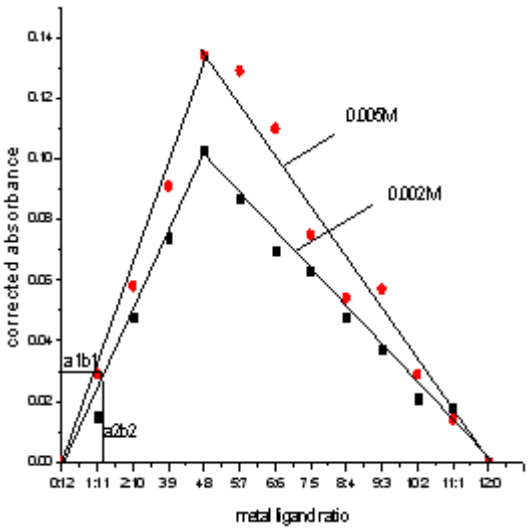


Fig. 2(b)

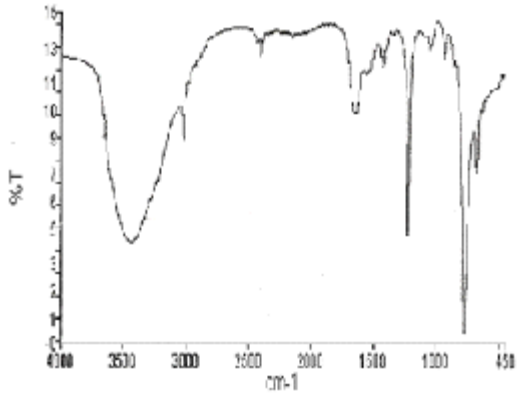


Fig. 4. FT-IR Spectra of Glipizide-Cu complex

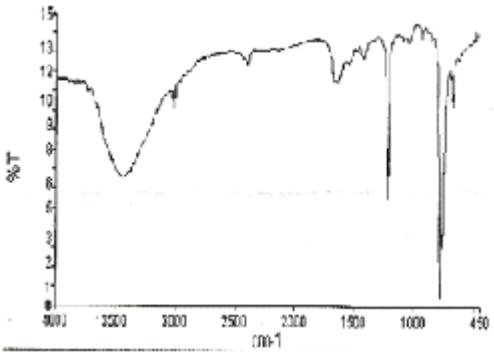


Fig. 5. FT-IR Spectra of Glipizide-Ni complex

literature[23-26] and full proof suit XRD software v.2.0by using foolproof suite XRD software the d-values of metal complexes were obtained. The X-ray diffraction pattern of Cu(II) and Ni(II) complexes has been determined 2θ range from9.5738 to 68.6636°,diffractograms (Fig-6,7) and data has been summarized in the following tables:

X-ray diffraction studies also confirm the complexes and formation of new bonds.In the X-ray diffractrogram of pure glipizide, a sharp peak is presented at a diffraction angle (2θ), and it confirms that the drug is in the crystalline form. Glipizide diffractrogram shows sharp peaks at 7.49, 11.08, 15.67, 18.67 and 21.86 2θ. While no. of peaks in $(GLZ)_2Cu$, and $(GLZ)_2Ni$ are 14 and 6 respectively. Thus indicating that complexes formed are a well kit one, moreover in the X-ray pattern of complexes of glipizide all the reflections present are new ones and the patterns are fairly strong. On comparing the pattern obtained with available Literature. It is evident that its pattern is not in good agreement with available information and thus confirms the formation of totally new complexes. The X-ray pattern have been indexed by using computer software (FPSUIT 2.0V) and applying interactive trial and error methods keeping in mind the characteristics of the various symmetry system, till a good fit was obtained between the observed and the calculated Sin2θ values. The unit cell parameters were calculated from the indexed data, from cell data and crystal lattice parameters of system. $(GLZ)_2Cu$ and $(GLZ)_2Ni$ complexes attributed to Orthorhombic crystal system having tetrahedral geometry.

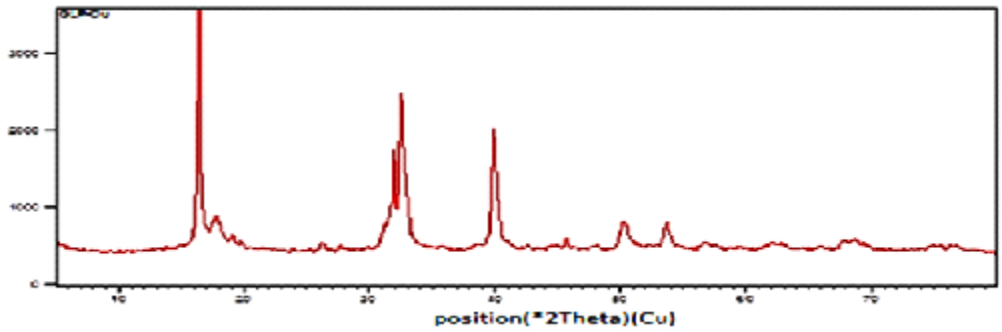


Fig. 6. X-ray diffractrogram of Glipizide-Cu complex

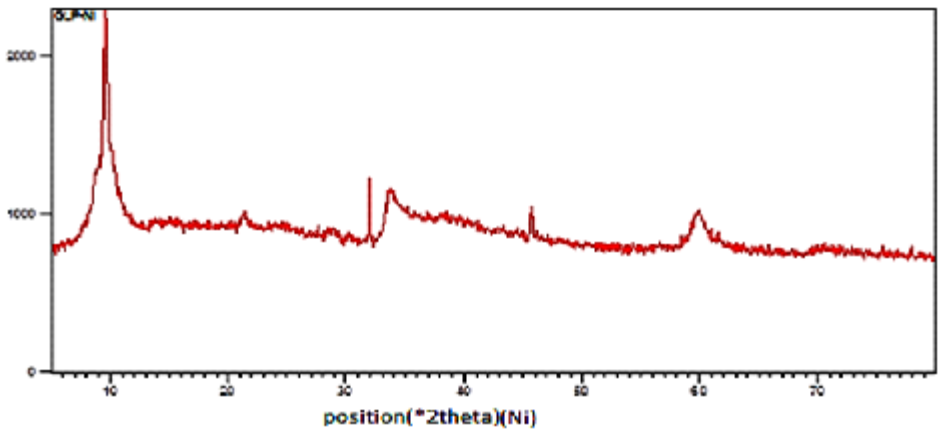
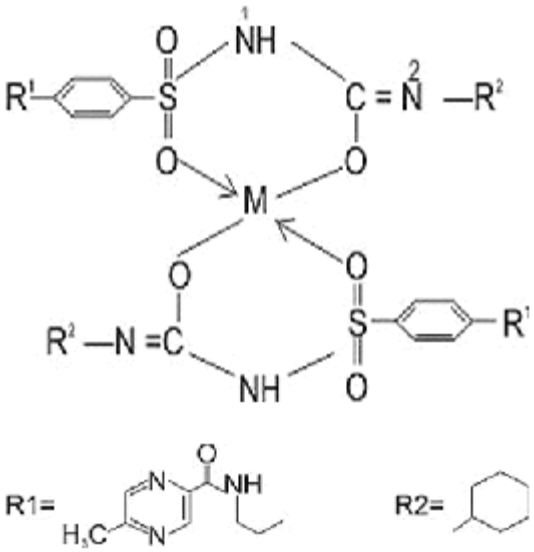


Fig. 7. X-ray diffractrogram of Glipizide-Ni complex



Proposed structure I

DISCUSSION

For supporting the proposed structure (I) of glipizide Cu(II), and Ni(II) complexes, initially job's method of continuous variation as modified by Turner and Anderson(table 1,2 and fig.1a, 1b and fig 2a ,2b)was conducted which indicates 2:1 ligand metal ratio of the complexes. Moreover, stability constant and free energy change was also calculated. Analytical data agrees to the molecular formula$(C_{21}H_{25}N_5O_4S)_2Cu$ and $(C_{21}H_{25}N_5O_4S)_2Ni$. For determining the proposed structure on the basis of stoichiometry and analyzing the complexes, advanced spectrophotometric methods like IR, NMR(table 5 and 6) were conducted which suggest the co-ordination of the metal atom with enolic oxygen of the carbonyl group on one side and oxygen of the sulphonyl group from the other side. These observations were further supported from the IR and NMR values of M-O and the appearance of N-H linkage in NMR respectively. A detailed study of X-ray diffraction (table7 and 8) also supports the complex formation and various values like particle size, porosity, and volume of unit cell, density as well as the crystal system was evaluated and discussed. Moreover looking to the higher electronegativity of the oxygen as compared to nitrogen, N^2 enolisation is strongly supported.

Hypoglycemic activity

The isolated glipizide-metal complexes were found to be more potent than the parent drug. Hence as compared to standard synthetic drug, the glipizide- metal complexes are having more hypoglycemic activity.

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