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Synthesis and Characterisation of Glimeperide Complexes of Copper, Magnesium, Nickel and Cadmium

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ABSTRACT

Glimeperide, 3-ethyl-4-methyl-N (4[N(1r, 4r)-4-methyl cyclohexyl carbamoyl) sulfamoyl] phnethyl)-2-Oxo-2, 5-dihydro-1-H-pyrrole-1-Carboxamide the recently used hypoglycemic agent is active in NIDDM. Metal complexes of glimeperide have been synthesized by reaction with different metals such as Copper, Magnesium, Nickel and Cadmium in the form of their chloride salts. These complexes were characterised by their physical and analytical data, IR, ^{1}H NMR and atomic absorption studies.

Key words: Antidiabetics, Glimeperide, transition metals, ^{1}H NMR, IR, AA-studies.

INTRODUCTION

Glimeperide, 3-ethyl-4-Methyl-M-(4-[N(1r, 4r)-4Methyl Cyclohexyl Carbomoyl Sulfamoyl]-phenerhyl-2oxo-2,5-dihydro-1H-Pyrrole-1-Carboyamide, a sulphanyl Urea derivative (fig 1) having melting point 163-169^{0}C is a while or almost white crystalline, odourless powder, practically tasteless, insoluble in water, sparinsly soluble in methylene chloride, slightly soluble in ethanol and insoluble in solvent ether. It dissolves in dilute solutions of alkali hydroxide as well as DMF, DMSO.

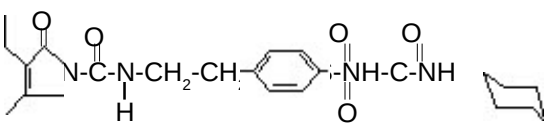


Fig. 1:

Glimeperide is a third generation oral hypoglycemic agent which is more potent than those of insulin sensitizers (Biguanides)[1-5], and is used to assist in the control of mild to moderately severe type-II *Diabetes mellitus* (adult maturity onset) thus does not require insulin, but it can be adequately controlled by diet alone. It is a drug of choice for irritating treatment in non-insulin dependent diabetes when diet and weight control falls. It stimulates the secretion and enhances the utilization of insulin by appropriate tissues.[6] It is 99% absorbed in gastrointestinal tract.[7] The maximum concentrations of the drug were found in liver and kidney. While small amount of concentrations were detected in other body tissues. Glimeperide shows no significant antihepatoprotective activity in man.

Glimeperide is claimed to have a significantly lower risk of hypoglycemia than older agents, Glimeperide therapy is thought to be more effective with lower plasma insulin level and to maintain physiological suppression of insulin secretion in response to lower blood glucose levels. Glimeperide in contrast to glyburide, does not ischemic preconditioning.[8-10]

A number of drug interactions of glimeperide have been reported may of which are potentially toxic. Glimeperide binds to plasma aproteins by non-toxic forces because of its large non-polar chemical group. Consequently bound glimeperide is less succeptible to displacement by other drugs. During interaction between bacteriostatic antibiotic erythromycin, chloramphenicol succinate, stearate or estolate and cefaloridine with glimeperide these drugs increased the hypoglycemic activity.[11] It is also found influence the metabolism of xenobiotics.[12] Bioavailability of glimeperide is influenced by antacids.[13-14] The hypoglycemic activity of glimeperide remaing same when given with cimetidine.[15-16] While in another study plasma glucose concentrations were higher when glimeperide was administered with renitidine or domperidone.[17-18]

Ligand-Metal Ratio

For determining the ligand-metal ratio, molar solutions were prepared of metal salts and ligand in 1:2 ratio and conductometric titrations were carried out by using monovariation method which indicates that all the four metals in the present work forms 1:2 complexes with the drug glimeperide.

This ratio was also confirmed by way of doing the jobs method of contineous variation as modified by Turner and Anderson and the graphs were plotted which indicates 1:2 metal ligand ratio from these curves the stability constaints and free energy of the complexes were also calculated.[19-20] (In the present work Turner and Anderson method was only applied in case of copper complex)[21-23]

MATERIAL AND METHODS

Pure sample of Glimeperide (Trade name Glimer) with molecular formula ($C_{25}H_{34}N_4O_5S$) was received from M/s Zim Laboratories Limited Kalmeshwar, Nagpur. Solvents and metal salts used were of the analytical grade (E-Merk). Melting point was determined by Parkin Elmer melting point apparatus and are uncorrected. pH values determined on LabIndia pH analyser. The ^{1}H NMR spectra were recorded on 90MHz NMR spectrometer in $CDCl_3$ solution using TMS as the internal indicator in the range of 0 to 10 ppm, IR spectra of ligands and complexes were recorded with perkin Elmer Model 577 Spectrophotometer in the range of 4000-200 cm^{-1} as KBr pellets. Atomic absorption studies were carried out by Parkin Elmer Model 3110 atomic absorption spectrometer.

Synthesis

Ethanolic solutions of metal salts were individually added to ethanolic solutions of Glimeperide (2.4530 gm) slowly with stirring at room temperature maintaining the pH between 6-6.5 by adding dilute NaOH solution and refluxed for 2-4 hours. The solutions were left for crystallization at room temperature for 18-20 hours. Crystals of different colours for different metal complexes were obtained which were filtered, washed, dried and their melting points determined. All selected metals forms 2:1 complex with glimeperide were confirmed by jobs method as modified by Turner and Anderson[24-28] (fig. 1 and 2).

Analysis of Complexes

The resulting complexes so formed were characterised by their elemental analysis, physical characteristics, IR, ^{1}H NMR and Atomic absorptions) studies Table 3,4,5 and 6

Structure Determination

Infrared Absorption studies

The infrared spectrum of glimeperide and metal complexes were recorded as KBr disc method on Perkin Elmer model 577 infrared[29-32] spectrophotometer. The major absorption bands for the infrared frequencies and the corresponding assignments are listed in Table (4).

The Glimeperide-metal complex showed a prominent IR absorption band in the region 3300-3370 cm^{-1}. A very sharp peak observed at 2901 cm^{-1} due to -CH stretching, 668 cm^{-1} due to metal-oxygen bond, 778 cm^{-1} due to Aromatic, 980 cm^{-1} due to S=O group, 1077 cm^{-1} due to C-O chelating

Table 1: Glimeperide with Copper Chloride (Modified Jobs' Method)

Glimeperide : 0.005 M, $CuCl_2$: 0.005 M
Solvent : 80% Ethanol Temperature - 27+1^{0}C

Mole Metal ligand ratio	**Conductance X 10^{-4} Mohs** M:S C_1	S:L C_2	M:L C_3	**ΔConductance ×10^{-4} Mohs** $C_l+C_2-C_3$	**ΔCorrected Conductance ×10^{-4} Mohs**
0:12	0.005	0.010	0.010	0.005	0.000
1:11	0.010	0.020	0.015	0.015	0.010
2:10	0.015	0.030	0.020	0.025	0.020
3:9	0.020	0.040	0.025	0.035	0.030
4:8	0.025	0.050	0.030	0.045	0.040
5:7	0.030	0.045	0.035	0.040	0.035
6:6	0.050	0.030	0.045	0.035	0.030
7:5	0.040	0.020	0.030	0.030	0.025
8:4	0.035	0.015	0.025	0.025	0.020
9:3	0.030	0.015	0.020	0.025	0.020
10:2	0.020	0.010	0.015	0.015	0.010
11:1	0.015	0.010	0.015	0.010	0.005
12:0	0.010	0.005	0.010	0.005	0.000

M = Metal Solution, L = Ligand Solution, S = Solvent

Table 2: Glimeperide with Copper Chloride (Modified Jobs' Method)

Glimeperide : 0.002 M, $CuCl_2$: 0.002 M
Solvent : 80% Ethanol Temperature - 27+1^{0}C

Mole Metal ligand ratio	**Conductance X 10^{-4} Mohs** M:S C_1	S:L C_2	M:L C_3	**ΔConductance ×10^{-4} Mohs** $C_l+C_2-C_3$	**ΔCorrected Conductance ×10^{-4} Mohs**
0:12	0.010	0.015	0.020	0.005	0.000
1:11	0.105	0.030	0.125	0.010	0.006
2:10	0.130	0.060	0.170	0.020	0.016
3:9	0.135	0.080	0.185	0.030	0.026
4:8	0.125	0.105	0.190	0.040	0.036
5:7	0.105	0.110	0.180	0.035	0.031
6:6	0.095	0.115	0.180	0.030	0.027
7:5	0.075	0.120	0.170	0.025	0.022
8:4	0.060	0.125	0.165	0.020	0.017
9:3	0.055	0.130	0.170	0.015	0.013
10:2	0.040	0.135	0.165	0.010	0.008
11:1	0.025	0.140	0.160	0.005	0.003
12:0	0.010	0.145	0.155	0.000	0.000

ring, 1168 cm^{-1} due to SO-N frequency, 1388 cm^{-1} due to six membered[2] enolic ring modified in complex 1168 cm^{-1} due to C=N straching frequency and 718 cm^{-1} due to aromatic-S linkage. For copper complex the band was observed at 1708 cm^{-1} in the form of sharp peak whereas in case of Magnesium the band observed at 1718 cm^{-1} as sharp band. In case of Nickel and Cadium complex at 1720 cm^{-1} and 1730 cm^{-1} as sharp band and in the form of sharp double band respectively.

In Glimeperide the NH stretching appear at 3330-3370 cm^{-1} as a sharp doublet in case of copper and magnesium complexes appeared in the region 3330-3371 cm^{-1} in the form of medium doublet, while in case of nickel it was sharp doublet and in the same range whereas in cadmium complex. It appeared in range 3300-3350 cm^{-1} as small doublet. Their is no absorpting band detected for -C=O and NH due to enolisation.[33-35]

^{1}H NMR Studies

NMR data of all complexes get summarized in Table 5 and their proposed structures are given in Fig. 3. The H-NMR signals in the range of δ 3.00-3.14 due to deshilding of N-bearing proton. The N-NMR of Glimeperide Cu(II). Complex at δ3.00, Glimeperide Mg(II) complex at δ 3.01, Glimeperide Ni (II) complex at δ 3.00 and Glimeperide - Cd (II) complex at δ 3.02.

Atomic Absorption Studies

Atomic absorption studies was carried out by direct method which gave total metal content. A number of reference standard solutions of each metal were prepared having various concentration ranges. Absorbance of these solutions were measured at specific wavelength range of each metal using background correction technique[36]. A graph polotted between absorbance and concentration of each metal solution, which showed a straight line in each case. The concentrations of unknown solutions were calculated from the absorbance of unknown solutions using the standard values. Results of analysis are given in Table 6.

Keeping in view all these observations and results, the following structure of Glimeperide - metal complex can be proposed for the isolated complex.

Table 3: Physico-chemical and Analytical data of Glimeperide with transition metals

S. No.	Composition of complex	Ligand metal ratio	Colour	% yield	Melting point(°C)	% of metal observed (required)	% of carbon observed (required)	% H observed (required)	% N observed (required)	% S observed (required)	Stabily const. log k lit/mole	Free energy change (-ΔF) K.cal/mol
						(required)	(required)	AA spec.)				
01	$(C_{24}H_{34}N_4O_5S)_2$ Cu	2:1	Green	61	235	12.041 (12.952)	47.5 (46.007)	5.501 (6.007)	8.611 (9.231)	11.11 (11.61)	5.343	-7.2110
02	$(C_{24}H_{34}N_4O_5S)_2$ Mg	2:1	White	53	186	4.623 (4.953)	43.36 (44.036)	4.97 (5.221)	7.012 (8.783)	8.99 (9.012)	5.750	-7.864
03.	$(C_{24}H_{34}N_4O_5S)_2$ Ni	2:1	White	51	205	11.025 (11.555)	46.78 (47.26)	5.081 (6.3380)	8.3 (9.390)	10.81 (11.08)	5.912	-7.021
04	$(C_{24}H_{34}N_4O_5S)_2$ Cd	2:1	White	48	185	22.613 (22.91)	48.01 (45.493)	4.615 (5.304)	9.18 (10.015)	10.76 (11.984)	5.468	-7.342

Table 4: IR Absorption bands of Glimeperide Metal Complexes

Compounds	Main IR Absorption in cm^{-1}
Glimeperide (Ref)	443sm, 520sm, 541m, 570m, 611m, 640sm, 683m. 820m, 880-901db, m 1010-1033 db, m, 1091sm, 1120sm, 1163s, 1241-1273 db,m, 1300sm, 1344s, 1450s, 1520s, 1615s, 1703s, 2555-2600db, 2901s,3330-3370db,s
Glimeperide-Cu-complex	443sm, 520sm, 541m, 570m, 611m, 640sm, 683m. 820m, 880-901db, m 1011-1032 db, m, 1092sm, 1121sm, 1164s, 1244-1274 db,m, 1301sm, 1343s, 1455s, 1520s, 1616s, 1708s, 2555-2608db, 2908s,3330-3371db,m
Glimeperide-Mg-complex	443sm, 520sm, 541m, 572m, 612m, 641sm, 683m. 822m, 880-901db, m 1012-1033 db, m, 1092sm, 1121sm, 1163s, 1244-1275 db,m, 1302sm, 1343s, 1455s, 1520s, 1616s, 1718s, 2555-2608db, 2907s,3330-3371db,m
Glimeperide-Ni-complex	440sm, 511sm, 540m, 570m, 611m, 644sm, 680m. 810s,880sm, 900m,1010-1026 db, m, 1091sm, 1120sm, 1155s, 1240s,1271m, 1300sm, 1348s,1520s,1622s, 1720s, 2800-2910db,m, 3304-3350 db,s
Glimeperide-Cd-complex	440sm, 520sm, 544s, 570s, 611s, 640sm, 680m. 822s,880sm, 900s, 1011-1018 db, m, 1099sm, 1122sm, 1150s, 1240m,1277sm, 1304sm, 1344s,1522s,1622s, 1730db,s,2850-2910db,m, 3300-3350 db,m

Table 5: Values of H^1 NMR Spectra of Glimeperide Metal Complexes

Compounds	δ and Multiplicity
Glimeperide (Ref)	1.11-1.44 CH_2, 1.71-1.96 CH_2, 3.00-3.14 NH, 3.77 O-CH, 6.42 Aromatic, 6.84-6.88 aromatic, 7.30-7.53 aromatic, 7.87-7.93 aromatic, 7.97-7.91aromatic, 8.14-8.17 aromatic
Glimeperide-Cu-complex	1.13-1.44 CH_2, 1.72-1.98 CH_2, 3.00-3.17 NH, 3.77 NH-CO-Cu, 6.40 Aromatic, 6.83-6.89 aromatic, 7.30-7.51 aromatic, 7.87-7.90 aromatic, 7.97-7.94 aromatic, 8.11-8.15 aromatic
Glimeperide-Mg-complex	1.20-1.28 CH_2, 1.60-1.67 CH_2, 1.80-2.87 CH_2, 3.01-3.04 NH, 3.67 NH-O-Mg, 6.44 Aromatic, 7.38 aromatic, 7.44-7.60 aromatic, 7.81-7.85 aromatic, 8.14-8.11 aromatic
Glimeperide-Ni-complex	1.18-1.34 CH_2, 1.57-1.69 CH_2, 1.80-1.84CH_2, 3.00-3.05 NH, 3.73 NHC-O-Ni, 3.79-O-CH_3, 6.46 aromatic, 6.84-6.89 aromatic, 7.26 aromatic, 7.36-7.41 aromatic, 7.82-7.86 aromatic, 8.14-8.16 aromatic
Glimeperide-Cd-complex	1.13-1.56 CH_2, 1.64-1.68 CH_2, 1.78-1.85CH_2, 3.02-3.04 NH, 3.68 NHC-O-Cd, 3.79-O-CH_3, 6.41 aromatic, 6.85-6.89 aromatic, 7.25 aromatic, 7.35-7.39 aromatic, 7.82-7.98 aromatic, 8.14-8.15 aromatic

Table 6: Estimation of metals by atomic absorption spectroscopy

Compounds	%Metal Calculated	%Metal Found
Glimeperide - Cu-Complex	12.952	12.041± 0.001
Glimeperide- Mg-Complex	4.953	4.623 ± 0.001
Glimeperide - Ni-Complex	11.555	11.025 ± 0.012
Glimeperide - Cd-Complex	22.911	22.613 ± 0.003

RESULTS AND DISCUSSION

Glimeperide was reacted with different metal salts of essential and trace metals in 1:2 metal ligand ratio forming coloured crystaline complexes. The physico-chemical and analytical data of complexes of given on table (3). The complexes formed with Copper, Magnesium, Nickel and Cadmium are diamagnetic and non-ionic in nitrobenzene.

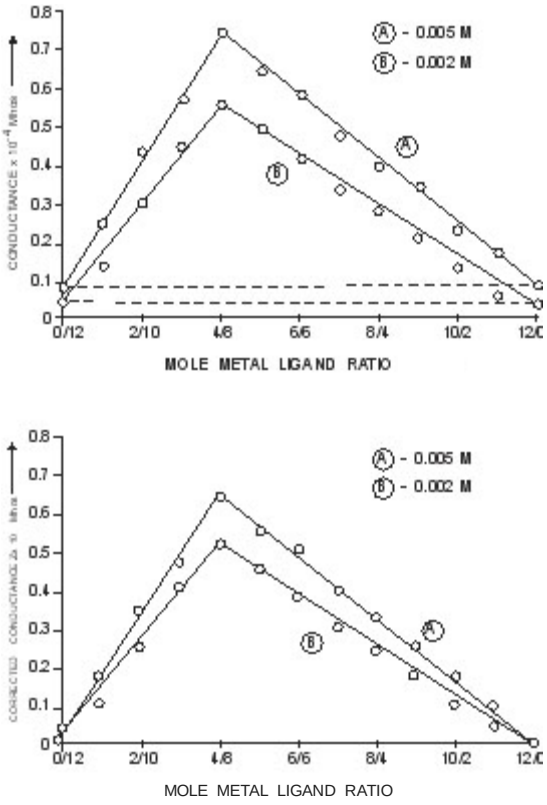


Fig. 2.

CONCLUSION

The differences in melting point of all these complexes as compared to Glimeperide suggested that a new product was formed. The shifts of peaks in IR regtion as well as new signals around at δ 3.00 due to deshielding of N-bearing proton in 4-NMR further confirmed the drug metal complexating. The final proof of metal incorporation in Glimeperide was obtained by the estimating of metals from these complexes by Atomic absorption spectroscopy.

The tentaitve structure of the complexes are further supported from the values of ^{1}H NMR as well as IR frequencies. The magnetic succeptibility studies indicate the glimeperide-metal complexes have octahedral geometry.

Hypoglycemic activity

The isolated glimeperide - Metal complexes were found to be more potent as compared to the parent drug. Hence as compare to standard synthetic drug the glimeperide metal complexes are having more hypoglycemic activity[37].

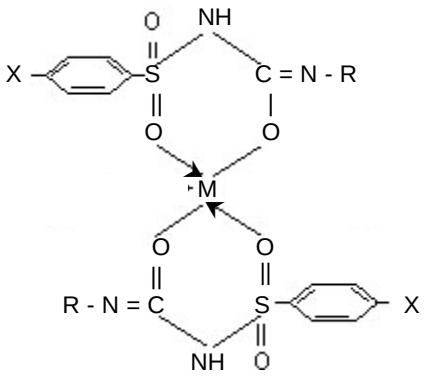
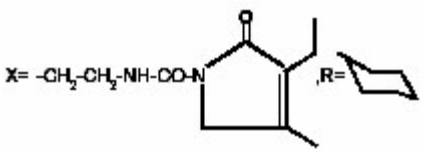


Fig. 2: Glimeperide Metal Complex. (M=Cu, Mg, Ni, Cd)



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