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Synthesis, Physicochemical, Spectral and Pharmacological Studies of Silver Complex of Glibenclamide, An Oral Antidiabetic Drug

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ABSTRACT

Glibenclamide is a current, potent hypoglycemic agent used in NIDDM (Non-insulin dependent diabetes mellitus). Metal complexes of glibenclamide has been synthesised by reaction with silver (I) in the form of its nitrate. The conductometric titration using monovariation method indicates that complex is non-ionic and ML type which was further confirmed by job's method of continuous variation as modified by Turner and Anderson. Analytical data agrees with the molecular formula $C_{23}H_{28}ClN_3O_5S.Ag$. Structure of the complex was assigened as linear in which ligand molecules lies horizontally joining the central silver atom. Infrared spectral, NMR and molar conductance data confirm the co-ordination of sulphonyl oxygen on one side and enolic oxygen attached from other side with the metal ion. Structure assigned to the complex is supported by analytical data and IR spectra.

Key words: Synthesis, Antidiabetics, Glibenclamide, IR spectra.

INTRODUCTION

Man has been in continued search for chemotherapeutic agents right from the earliest times, about 2000 B.C. or even earlier. As a result of this research several naturally occurring substances, plant materials and minerals including Arsenic, Mercury, Bismuth, Gold and Silver as metals or as their salts have been used for several thousand years, especially in Ayurveda and Unani system of medicine. In the early part of the twentieth century, organo-metallic compounds emerged as important agents in the treatment of syphilis tropical diseases etc[1-3]. The discovery of vitamin B_{12} and copper phthalocyanine has given impetus to the development of metal complexes with organic ligands. Silver has been employed medicinally for several thousand years, but it came into prominence only after paracelsus recommended its use for diseases of the nervous system. Until late in the nineteenth century, silver nitrate (Lunar-caustic) was still employed for the treatment of epilepsy[4-7].

Metallic silver has powerful ablugo dynamic action and this might be the basis of use of silver vessels for the storage of water. The use of aqueous solution containing 1.0% $AgNO_3$ as eye drops in conjunctivitis and ophthalmia neonatorum has been superceded by penicillin drops, 41% solutions, however, still being used in the treatment of burns. A survey of literature reveals that metal complexes of some drugs have been found to be more potent than the drug alone therefore in continuation of our previous work[8-12] on metal complexes of oral antidiabetic agents of hypoglycemic activity, the synthesis and structural studies of glibenclamide- Ag complex is described here.

Glibenclamide (Danoil, 1-(4-(2(chloro-2-methoxy benzamido) ethyl)-benzene sulphonyl)-3-cyclohexyl urea) is a sulphonyl urea derivative having melting point 169-174°C is a white or almost white cystalline. odourles powder, partically without taste, insoluble in water and soluble in ethanol, methanol and in alkali solution. It dissolves in diethyl ether also. Glibenclamide is a second generation oral hypoglycemic agent which is more potent than those of first group[13] and is used to assist in the control of mild to moderately severe type (II) diabete smellitus. Complexation of sulphonyl urea with lighter transition metals has been studied in detail[14]. A persual of available literature shows that many drugs possessed modified pharmacological and toxicological properties when administered in the form of metallic complexes.

EXPERIMENTAL

Ligand-Metal ratio

Pure glibenclamide (GBC) (1) Trade name, *Danoil* a sulphonyl urea derivative is supplied by Aventis pharma Ltd; Goa in powdered form 0.005M drug and silver (I) nitrate ($AgNO_3$) 0.01M (Analar grade) were prepared in purified 80% ethanol. Glibenclamide (20ml) was diluted to 200ml and titrated conductometrically against silver nitrate at $27 \pm 1^{o}C$. Results were plotted in the form of a graph which indicates ligand metal ration as 1:1. Fig 2.

Formation of 1:1 (LM) ratio was also confirmed by Job's method[13] of continuous variation as modified by Turner and Anderson[15] using Δ conductance as index property. From these values the stability constant (log K) and free energy change ($-\Delta F$) were also calculated[16-20]. Fig 3. a-b.

Synthesis of Complex

The chemicals used in this synthesis were all of analytical grade. A weighed quantity of glibenclamide (1 mol) was dissolved in minimum quantity of 80% ethanol. The silver (I) nitrate solution was prepared by dissolving it separately in the same solvent. Ligand solution was added slowly

Table 1: Synthesis and physico chemical characteristes of Glibenclamide Silver Complex

Ligand / Complex	Ligend Metal Ratio	Colour	% yield	Stability constant Logk (L/mole)	Free energy change ($-\Delta F$) Kcal/mole
Glibenclamide (Ref)	-	White	-	-	-
Glibenclamide Silver Complex	1:1	Dark grey	66	5.84	8.03

Table 2: Analytical data of complex

Complex	Elemental analyses Found (Calculated)						m.p.^{0}C
	C	H	N	S	Cl	Metal	
$C_{23}H_{28}ClN_3O_5S$	55.87 (55.85)	5.66 (5.64)	8.50 (8.48)	6.47 (6.42)	7.08 (7.04)	-	174
$C_{23}H_{28}ClN_3O_5.Ag$	44.71 (45.77)	4.60 (4.64)	7.20 (6.96)	10.28 (10.26)	5.79 (5.80)	18.08 (18.07)	175

Table 3: IR Absorption data of the complex in cm^{-1}.

Ligand/Complex	υ (NH)	υ (C=O)	υ (S=O)	υ (C-O)	υ (C=N)	υ (M-O)	υ Cl
$C_{23}H_{28}ClN_3O_5S$	3682	1713	1216	-	-	-	541
$C_{23}H_{28}ClN_3O_5Ag$	3682	1708	1216	1018	1529	670	542

with constant stirring into the solution of metallic salt at room temperature maintaining the pH between 6.2 to 6.9 by adding dilute NaOH solution. On refluxing the mixture for 3h at 80°C. On cooling, the complex separated out which was filtered off, washed well with ethanol (80%) and finally dried in vaccum and weighed. The elemental analysis of the isolated complex was carried out using the reported methods[21-22]. In the complex silver was estimated gravimetrically as chloride nitrogen by

Table 4: Values of ^{1}HNMR Spectra of Reference Standard Glibenclamide

Compounds	δ and Multiplicity ^{1}HNMR (300 MH_z, Acetone)
Glibenclamide (Ref.)	8.14 (S,1HNHCO), 7.99(d, benzene J=2.92 H_Z), 7.53(d, benzene J=1 H_Z), 6.29 (S, SO_2NH), 6.26 (Se,CH_2N J = 0.72), 3.74(t, OCH_3 J = 2.08H_Z) 3.68(S, pyrolidine J = 2.08 H_Z), 3.44 (CH_2 attached enolic, OH with benzene J = 1HZ) 3.02 (S, CH_2 attached with carbonyl J = 2.19 H_Z), 1.66 (q, CH_2 attached with Cyclohexane J= 2.14), 1.74 (m, 4H, J = 2.14 H_Z), 1.14 (t, CH_3 group)

S=singlet d=doublet t = triplet q=quatrate m = multiplet

Table 5: Values of ^{1}HNMR spectra of Ag–Glibenclamide Complex

Compounds	δ and Multiplicity ^{1}HNMR (300 MH_z, Acetone)
Glibenclamide	8.58 (S,1HNHCO; J = 1.07 H_Z), 7.83(d, benzene J=0.15 H_Z 7.60 (d, benzene J=0.15 H_Z), 3.52 (q, pyrolidine J = 4 H_Z), 3.40 (m, CH_2 attaached with benzene J = 4H_Z) 3.60 (NHCO-Ag), J = 4H_Z), 3.09 (q , CH_2 attached with carbonyl J = 4H_Z), 1.25 (d, CH_2 attached with Cyclohexane J= 0.45 H_Z).

S=singlet d=doublet t = triplet q=quatrate m = multiplet

Table 6: Antidiabetic activity analysis of metal-ligand/pure drug (Alloxan Induced Antidiabetic Model)

Group	Group Dose	Blood glucose level (mg/dl)			
	mg/Kg	Initial	1 hrs	3 hrs	6hrs
I	Control group +Glucose (2g) +vehicle	222.6± 1.1401	216.2 1.30	271.8 1.78	223 1.58
II	Puredrug Glibenclamide(2mg) Glucose+ Vehicle	223.4 1.8165	193.6 2.07	115.2 1.92	.96 1.5811
III	Silver metal Complex of Glibenclamide (2mg) +Glucose+ Vehicle	223. 1.58	191.2 1.92	110.6 2.07	94.8 1.92

Fig. 1: Structure of Glibenclamide

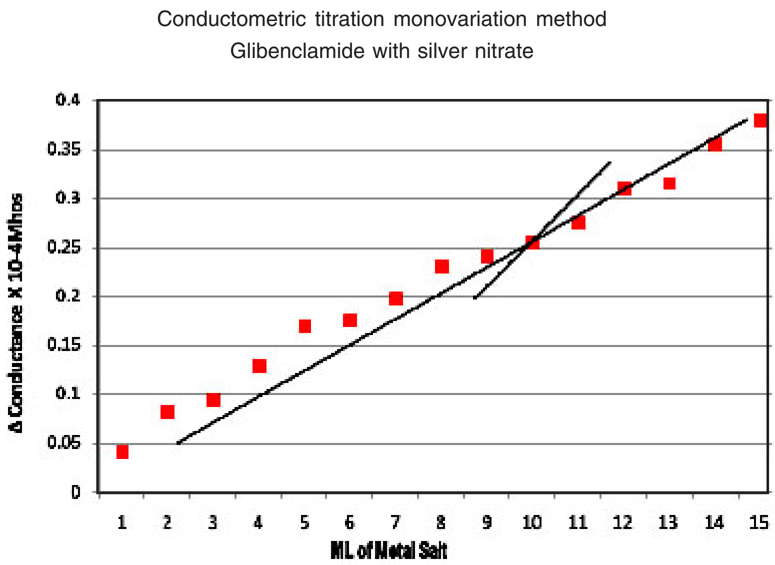

Fig. 2: Conductometric Titration Monovariation Method, Glibenclamide With Silver Nitrate

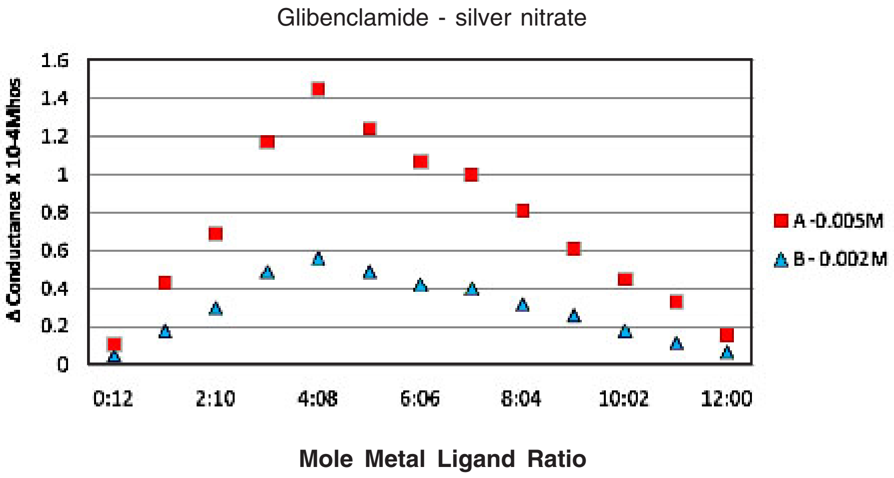

Fig. 3: (a)-Job's Curve

Kjeldhal method and sulphur by Messenger's method, using modified digestion mixture[23-24]. The IR spectrum of the ligand as well as of the complex was recorded on Perkin Elmer Spectrophotometer RX1 (4000-450cm^{-1}) Central Drug Research Institute, Lucknow, India.

Structure determination

Infrared absorption studies

The infrared spectrum of glibenclamide and metal complex were recorded on Perkin Elemer spectrometer RX1 (4000-450cm^{-1}). The major absorption bands for the infrared frequencies and the corresponding assignments are listed in Table5.

The glibenclamide metal complex showed a prominent IR absorption band in the region 1708cm^{-1} due to (C=O) carbonyl group[25-26]. A very sharp peak observed at 2927cm^{-1} due to –CH stretching 670cm^{-1} due to metal oxygen bond, 1216cm^{-1} due to C-O chelating ring, 1529cm^{-1} due to C=N stretching frequency and 3682cm^{-1} due to NH frequency.

^{1}HNMR Studies.

NMR data of the complex get summarized in Table-6 and their proposed structure are given in Fig-IV. the ^{1}HNMR spectra of the ligand was reported on a Bruker DRX-300 spectrometer (CDRI

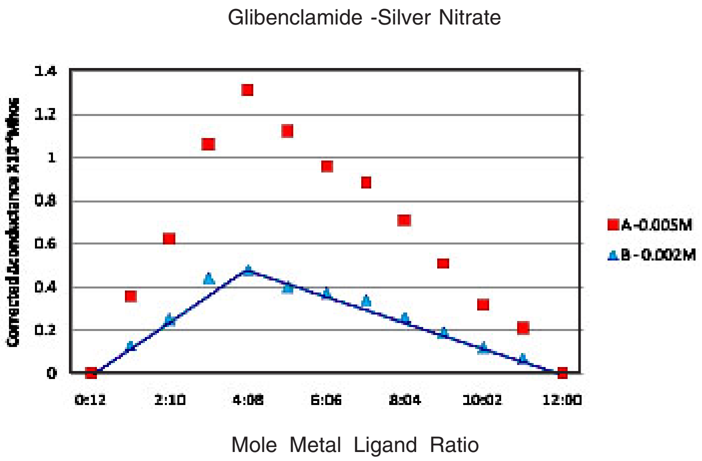

Fig. 3(b): Modified Job's Curv e

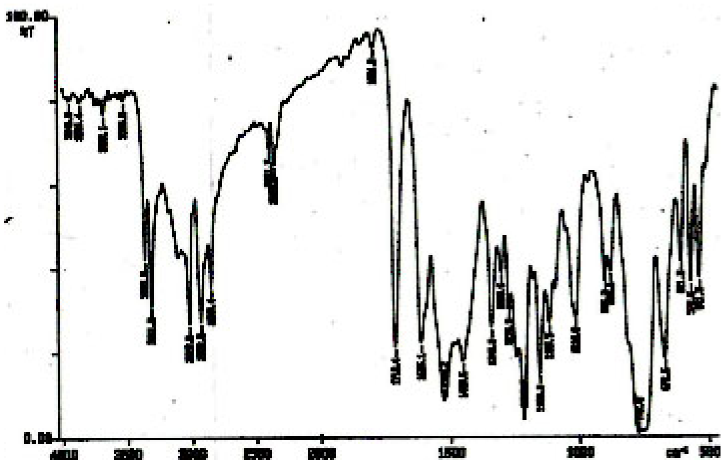

Fig. 4: IR Spectra of Pure Drug Glibenclamide

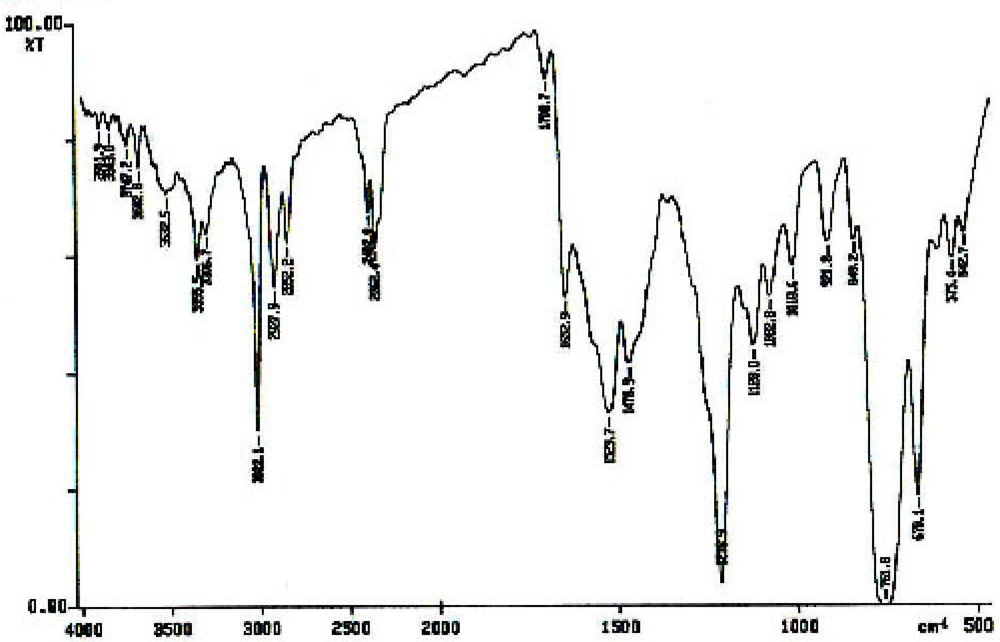

Fig. 5: IR Spectra of Glibenclamide-Silver complex

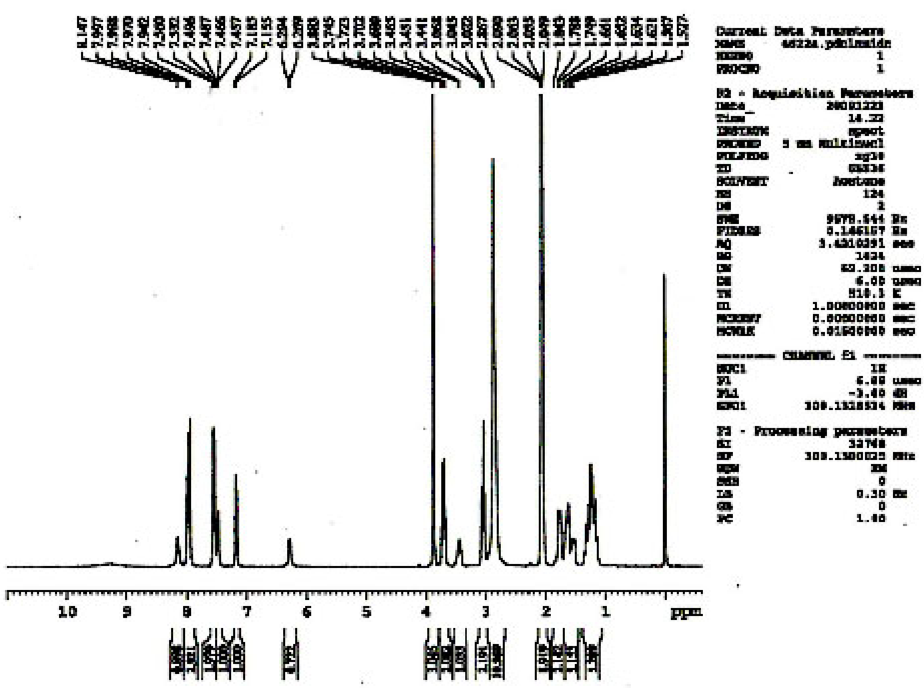

Fig. 6(a): NMR-Spectra of Pure ligand Glibenclamide

Lucknow) and isolated complex was reported on a Bruker Avance II 400 NMR spectrometer (SAIF Panjab University, Chandigarh). DMSO was used as a solvent. The other features of NMR spectrum were the aromatic proton resonances located and the presence of unresolved multiplet is suggestive of excessive deshielding of aromatic protons[27-31]. The NMR signal of enolic OH group is observed in the ligand while absent in the complex indicates the involvement of enolic OH group in complexation. Moreover the enolization of N1 hydrogen is not possible because it is simultaneously attracted from the groups SO_2 from one side and C=O on the other side[32].

Hypoglycemic Activity

The isolated glibenclamide metal complex were found to be more potent as compared to the parent drug. Hence as compare to standard synthetic drug the glibenclamide metal complex is having more hypoglycemic activity[33-36].

The hypoglycemic effect of glibenclamide the well known sulphonyl urea was investigated on the blood sugar levels of male wistar rats by Alloxan induced Antidiabetic model (PBRL Lab, Bhopal). Analysis of data presented in table (VI) reveals that the drug caused a marked decrease in blood sugar level.On comparing the hypoglycemic effect of Silver complex with parent drug it was revealed that in case of

Ag- glibenclamide treated male wistar rats, blood sugar level falls to 94.8 ± 1.9235 mg/dl (on an average) while in glibenclamide treated rats blood sugar level falls to 961.5811 mg/dl (on an average) These results clearly indicate a better hypoglycemic activity of Ag- glibenclamide complex over its parent drug.

From the present study it can be concluded that the study of chemistry and chemical reaction of

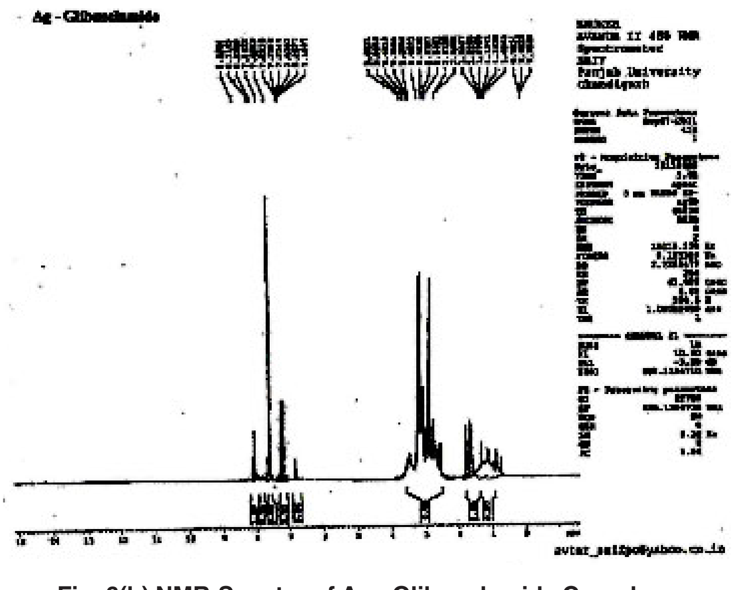

Fig. 6(b) NMR-Spectra of Ag –Glibenclamide Complex

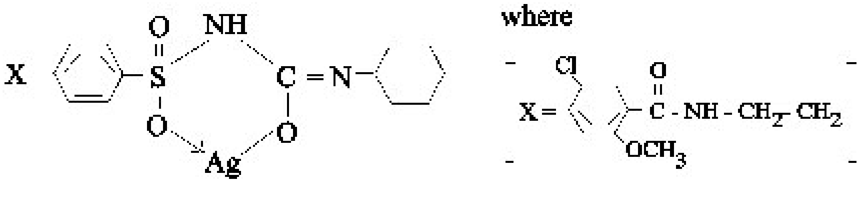

Fig. 7: Structure of Glibenclamide ˘Silver Complex

co-ordination compound help in establishing sturcture activity relationship and it was also been observed that in biological activity metal complex is more potent and less toxic as compared to the free ligand.

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