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X-ray Diffraction and Thermal Characterization Study of Sm^{III} Complex of Sulphonylurea, Glipizide: An Oral Antidiabetic Drug

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ABSTRACT

The present paper deals with the study of sulphonylurea glipizide (GLP) drug in order to give a thought concerning its coordinating potentiality towards some inner transition metals. Metal complex of GLP drug is synthesized and characterized by using analytical data, molar conductance, X-ray diffraction and thermogravimetric analysis (TGA) studies. From the analytical data, the complex is proposed to have general formula$(C_{21}H_{26}N_5O_4S)_2Sm(OH_2)_4$.Low values of molar conductance indicate that complex have non ionic nature. The conductometric titration using monovariation method reveal that complex is L_2M type which is further confirmed by Job's method of continuous variation as modified by Turner and Anderson. Geometery of complex is assigned to be hexagonal in which ligand molecules lie horizontally joining the central metal atom and four water molecules attached vertically and horizontally with the metal, supported by spectroscopic study. Powder X-ray diffraction data have been used to calculate particle size, porosity, volume of unit cell and density of synthesized complex.The thermal decomposition of complex is studied using thermogravimetric (TGA) techniques. The kinetic parameters such as, energy of activation (E_a), enthalpy (ΔH), entropy (ΔS) and free energy change (ΔG) of the complexis evaluated by employing the Freeman-Carroll and Sharp-Wentworth methodsand the relative thermal stability of the complexisalso discussed.

Key words: Glipizide, antidiabetic drug, metal complex,X-ray diffraction,TGA.

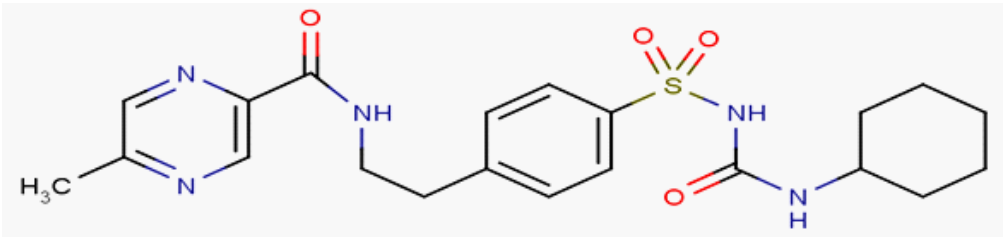
INTRODUCTION

The term *diabetes mellitus* describes a metabolic disorder of multiple etiologies characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both[1]. Currently *diabetes mellitusis* a great threat to the world community with more than 100 million persons suffering from diabetes. The prevalence and incidence of diabetes is increasing in most populations, being more prominent in developing countries as follows, in USA more than 16 million, in Republic of China more than 14 million, in Africa more than 20 million. India leads the world largest number diabetic subjects and is being termed the "diabetic capital of the world" with 40.9 million people currently suffering from diabetes and expected to rise 69.9 million by 2025[2].

For treatment of diabetes, carbutamide became the first clinically useful sulphonylurea but it was later withdrawn because of its undesirable effects on the bone marrow. This compound led

to the development of entirely novel class of oral antidiabetic's viz. sulphonylureas. Tolbutamide and chlorpropamide were the first widely used members of this group. Since then, about 12000 sulphonylureas have been tested[3-4]. The first generation sulfonylureas are still in use, but are less effective than the more recently introduced second generation drugs like gliclazide, glimepiride, glibenclamide and glipizide[5]. An important difference between the older and newer sulfonylureas is a higher specific binding of the latter to pancreatic β-cells. Therefore, the newer sulfonylureas, such as glipizide, are more active[6]. Chemically, glipizide is a substituted aryl sulphonylurea.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-(5-methylpyrazine carboxamido) ethyl] phenyl] sulfonyl] urea[7] scheme 1.It is white to almost white crystalline odourless powder prepared by chemical synthesis. It is practically insoluble in water, alcohol and readily soluble in dimethylformamide (DMF). Its melting range is 208-209°C.

Glipizide is one of the most commonly prescribed drugs for treatment of type 2 *diabetes mellitus*[8]. Its main features are swift and short action with a very high selectivity[9-10].It is about 100 times more potent than tolbutamide in evoking pancreatic secretion ofinsulin[11]. Major effect of glipizide is to enhance insulin availability following meals, whilst it has little influence on nocturnal glucose control[12]. The study of chemistry and chemical reaction of co-ordination compound help in establishing structure activities relationship. It has been reported that in biological activity metal complexes are more potent and less toxic as compared to the free ligand[13-16]. Recently, metals in medicine have been recognized internationally as an important area for research and much attention has been given to the use of sulphonylureas with inner transition metals because of their high complexing nature[17-18].In this account, we have undertaken the Sm^{III} metal complex of glipizide drug for study. The metal complex was characterised by using different physico chemical methods like elemental analyses (C, H, N, S and metal content),



Scheme 1: Structure of Glipizide drug

X-ray diffaractionand TGA techniques.

EXPERIMENTAL

Ligand- Metal ratio

(a) To find out the ligand metal ratio, initially conductometric titration using monovariation method were carried out at 27±1 ºC and 0.005 M solution of glipizide drug was prepared in DMF(dimethylformamide). Similarly, solution of samarium trioxide (Sm_2O_3) was prepared in the ethanol of 0.01M concentration. 20ml of ligand was diluted to 200ml with the same solvent. The ligand was titrated conductometrically against metal salt solution taken in burette using fraction of 1ml. Conductance was recorded after each addition with proper stirring. Results were plotted in the form of graph between corrected conductance and volume of metal salt added. From the equivalence point in the graph, ratio between ligand and metal were noted to be 2:1 (L_2M).

(b) Formation of the complex in 2:1 (L_2:M) ratio was also confirmed by Job's method[19]of continuous variation as modified by Turner and Anderson,[20] using conductance as index property Fig. 1 (a)-(b), from these values the stability constant (log k) and free energy change (ΔF), were also calculated by using formula[21-24];

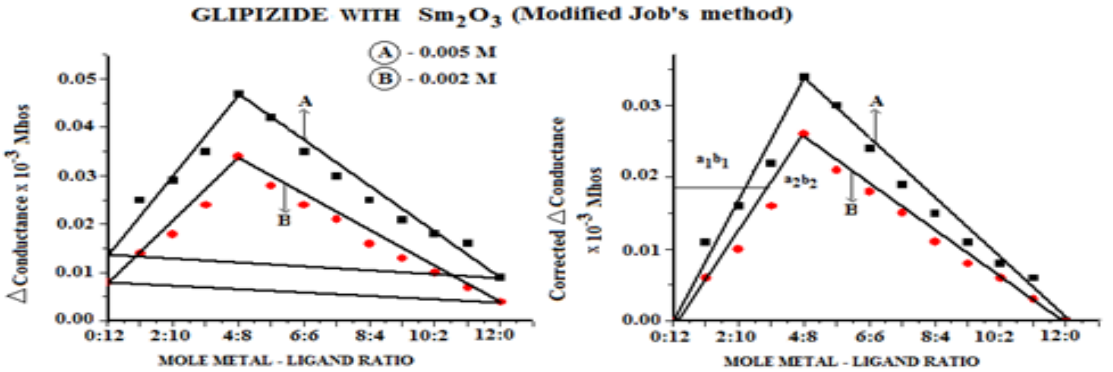


Fig. 1(a). Job's curve **(b) Modified Job's curve**

$$k = \frac{x}{(a_1-x)(b_1-2x)^2} = \frac{x}{(a_2-x)(b_2-2x)^2}$$

MATERIAL AND METHOD

All chemicals used were of the analytical grade (AR) and of highest purity available. They include pure sample of glipizide was received as a gift from M/s Zim Laboratories Limited Kalmeshwar (M.S.) India. The metal salt of (Sm_2O_3)obtained from Hi media Laboratory, Mumbai, India. Organic solvents used included absolute ethanol and DMF. De-ionised water was generally used in all synthesis.

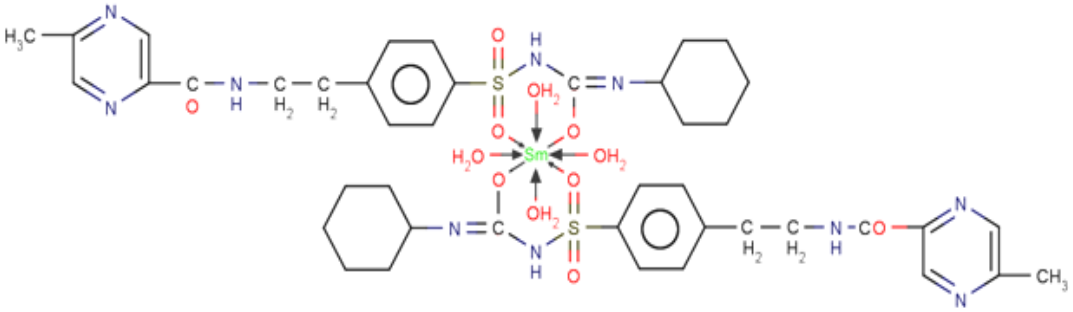
Synthesis of metal complex

A weighed quantity of "Glipizide" (2 mol) was dissolved separately in minimum quantity of DMF. The solution of (Sm_2O_3) was prepared by dissolving separately in the ethanol. 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 at 60°C and on cooling, light yellow crystal was collected by filteration, washed several times with DMF and ethanol finally dried in vacuum and weighed.

Instrumentation

Molar conductance of complex was measured by using Systronics Digital Conductivity meter. Melting point was determined by Perkin Elmer Model melting point apparatus and is uncorrected. The elemental analysis of the isolated complexwas carried out by using Coleman Analyzer Model at the Departmental Micro Analytical Laboratory, CDRI, Lucknow, India. X–ray diffraction studies was carried out by X–ray diffractometer model with 45kV rotating anode and Cuk_{α} (1W=1.54060A°) radiation at Punjab University, Chandigarh, India. The samplewas scanned in the range 10.000° to 79. 9784° (2θ) powder data were indexes using computer software (FPSUIT V2.0).

The thermogravimetric analysis (TGA) were carried out in dynamic nitrogen atmosphere



Scheme 2: Structure of GLP-Sm Complex

(20 ml.min^{-1}) with a heating rate of 10°Cmin^{-1} using shimatzu TGA-50H Thermal Analyzer at IIT Bombay, India.

RESULTS AND DISCUSSION

The synthesized complex is light yellow, being soluble in DMSO and insoluble in water, ethanol etc. Analytical data and conductometric studies suggest 2:1 (L:M) ratio.The proposed structure for the complex is shown in scheme- II.

Composition of metal complex

The isolated solid complex of samarium metal ions with the GLP ligand is subjected to elemental analyses (C, H, N, S and metal content) and molar conductance. The results of physical and analytical data are given in Table 1

X-Ray diffraction studies

The crystallographic data (scattering angles, d-spacings,and relative intensities) for glipizide with Sm^{III} is listed in 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 Sin2θ value. The X-ray diffraction pattern is shown in Fig. 2.It can be seen that the main characteristic scattering peaks for GLP-Sm complex are found at 15°, 29° 40°and 50° positions which indicate that the complex formed is a well knit one[25-26].

From the crystallographic data, unit cell parameters are obtained for GLP-Sm complex which attributed to monoclinic crystal system. The particle size of GLP-Sm complex is 9.418 microns which is calculated from X-ray line broadening using the Scherrer formula $Dhkl=\kappa\lambda/\beta hkl\cos\theta$, where D is the particle diameter in angstroms, κ is a coefficient and is equal to 0.89 here, β is the half-maximum line width, and β is the wavelength of X-rays, porosity is 0.0564% calculated by formula; $\frac{d_{true}-d_{obs}\times 100}{d_{tru}}$ and volume of the unit cell is 14065.752 A° which is calculated by Volume (Å)= abc where a, b and c are lattice parameters. Density = $\frac{Weight}{Volume}$ is found 0.0765 gcm^{-3} respectively. Space group is Pmmm and α=90°, β=90°, γ =89.78°.

Table 1: Physical and analytical data of GLP -Sm complex

Ligand/ Complex	Color (Yield %)	m.p. (°C)	Elemental analysis calculated (found)						A_m ($\Omega^{-1}mol^{-1}cm^2$)	Log K (L/mole)	ΔF (Kcal/mole)
			C	H	N	S	Metal	H_2O			
$C_{21}H_{27}N_5O_4S$	white	208	56.55 (56.45)	6.05 (6.01)	15.71 (15.65)	7.18 (7.13)	-	-	-	-	-
$(C_{21}H_{26}N_5O_4S)_2Sm(OH_2)_4$	lightyellow (56)	217	45.27 (45.18)	4.67 (4.62)	12.57 (12.48)	5.74 (5.60)	13.47 (13.42)	6.46 (6.43)	28.32	11.68	-16.08

Table 2X-ray diffraction data in terms of 2θ, lattice spacing and relative intensities for GLP-Sm complex

2θ	I/I_0	D_{obs}	D_{cal}	*h*	*k*	*l*
16.0753	67.80	5.5136	5.5182	0	0	5
27.9473	54.57	3.1926	3.1918	4	0	7
29.1420	100.00	3.0643	3.0626	7	1	1
40.9482	55.11	2.2040	2.2032	8	6	2
49.5395	31.90	1.8400	1.8390	8	4	10
50.2993	53.63	1.8140	1.8129	9	1	10
57.9217	28.24	1.5921	1.5912	4	6	15
65.9963	15.24	1.4144	1.4145	14	1	8

Table 3: Kinetic parameters using the Freeman-Carroll and Sharp-Wentworth methods for GLP-Sm complex

Compound	Method	Parameter				
		E_a(kJmole^{-1})	ΔS(JK^{-1}mole^{-1})	ΔH(kJmole^{-1})	ΔG(kJmole^{-1})	n
$(C_{21}H_{26}N_5O_4S)_2$ $Sm(OH_2)_4$	FC	23.72	-199.51	2.517	62.370	0.83
	SW	17.90	-207.81	2.512	64.885	-

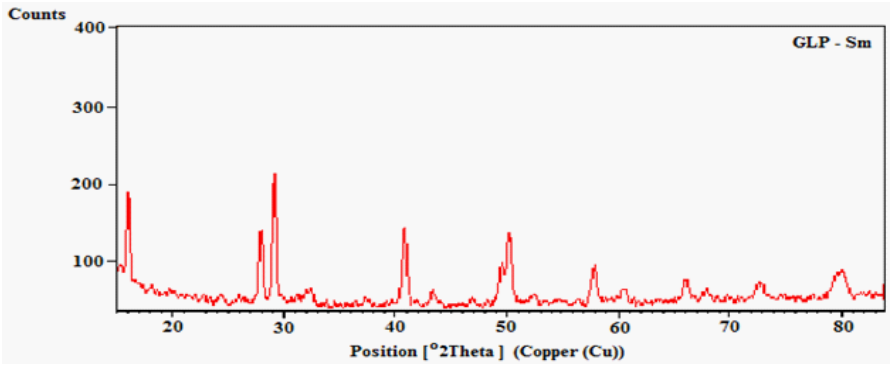


Fig. 2: X –ray diffraction pattern for GLP-Sm complex

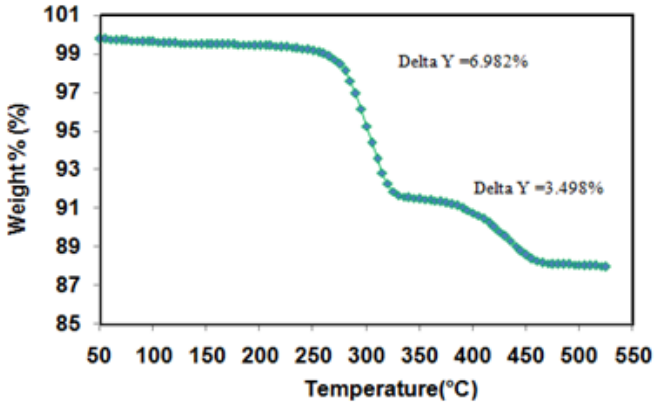


Fig. 3: TGA curve of GLP-Sm complex

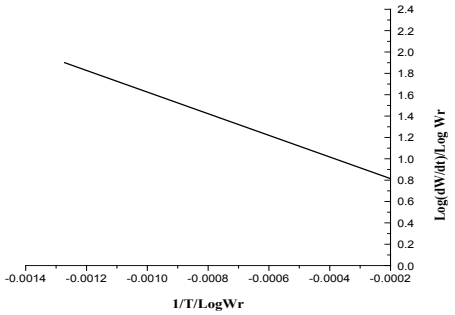


Fig. 4: FC kinetic plot of GLP- Sm Complex using TGA data

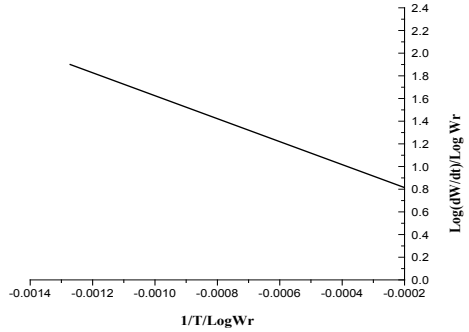


Fig. 5: SW kinetic plot of GLP- Sm Complex using TGA data

Thermal analyses (TGA and DTA)

Thermal analyses techniques (TGA and DTA) are useful in both quantitative and qualitative analyses. Sample can be identified and characterized by investigating their thermal behavior. TGA measures weight changes while DTA measures temperature of transitions and reactions. The TGA curve for the Sm^{III} complex represents two decomposition steps within the temperature range of 50-600°C as shown in Fig. 3.The first step of decomposition with in the temperature range from 350-400°C (Calcd.Wt. loss:6.46%,found,6.98%) is accompanied by the loss of water molecules. The second step of decomposition within the temperature range 450-500°C is 3.49 may accounted for organic moiety in the complex.

Kinetics studies

The Freeman-Carroll and Sharp-Wentworth methods have been employed for the calculation of kinetic parameters of the newly synthesized complex with help of dynamic TG curve.

Freeman-Carroll method[27]

In this method, activation energy and order of reaction are related to following equation as;

$$\frac{\Delta log\frac{dw}{dt}}{\Delta log\ Wr} = n - \frac{E_a}{2.303R}.\frac{\Delta\frac{1}{T}}{\Delta log\ Wr}$$

Where, dw/dt = rate of change of weight with time and Wr =Wc-W, W_c =Wt. loss at completion of reaction, W = Total wt. loss up to time't', E_a=Energy of activation, n=Order of reaction. The plot of the term $\frac{\Delta log\frac{dw}{dT}}{\Delta \log Wr}$ Vs $\frac{\Delta\frac{1}{T}}{\Delta \log Wr}$ is a straight line with a slope of (-E_a/2.303R) as shown in Fig. 4. Energy of activation (*E*a) is determined from the slope and order of reaction (n) obtained with the help of intercept.

Sharp-Wentworth method[28]

In this method E_a can be evaluated by the following expression;

$$\frac{\Delta log\frac{dc}{dT}}{(1-c)} = log\ \frac{A}{B} - \frac{Ea}{2.303\ R}.\frac{1}{T}$$

Where, dc/dt = Rate of change of fraction of weight with change in temperature. β = Linear heating rate dT/dt. Fig.5 shows a plot of the left-hand side of the above equation against 1/*T* gives a slope from which E_a was calculated.

The entropy of activation (Δ*S*), enthalpy of activation (Δ*H*) and the free energy change of activation (Δ*G*) were calculated using the following equations;

$$\Delta S = \left[\frac{Int}{1} - \frac{log kR}{h\varphi Ea}\right] \times 2.303 \times R \qquad \Delta H = E_a - RT$$

$$\Delta G = \Delta H - T\Delta S$$

The calculated values of kinetic parameters such as energy of activation (E_a), enthalpy (Δ*H*), entropy (Δ*S*) and free energy change (Δ*G*) are given in Table 3.

According to the kinetic data Sm^{III} complex

have negative values of entropy, which indicate that complex have more ordered systems [29]. The values of ΔG is found to be positive for the complex which reveals that the free energy of the final residue is higher than that ofthe initial compound and all the decomposition steps are non-spontaneous processes. Positive value of ΔH means that the decomposition processes are endothermic.

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