Introduction

Glipizide is one of the most commonly prescribed drugs for the treatment of type 2 Diabetes mellitus. It is about 100 times more potent than tolbutamide in evoking pancreatic secretion of insulin. It is absorbed rapidly, uniformly with good mean oral bioavailability. It offers several advantages such as swift and short action with a very high selectivity. It is a white or almost white crystalline, odourless powder, practically tasteless, insoluble in water and alcohols, but soluble in 0.1 N NaOH; it is freely soluble in dimethylformamide. It exhibits slow gastrointestinal absorption rate and inter individual variation of its bioavailability. A survey of literature reveals that metal complexes of some drugs have been found to be more effective than the drug alone therefore, much attention is given to the use of sulphonylureas due to their high complexing nature with essential metals.

The complexation of sulphonyl-urea with metals has been studied in detail by Yoshinaga and Yamamoto and Iqbal et. al. A persual of available literature shows that systematic study on complexation of cerium with “glipizide” is relatively scanty. It is interesting to have an insight into the synthesis of cerium complex with glipizide and to
diagnose various structural aspects of the isolated complex. Present study describes the synthesis and characterization of cerium with glipizide.

**EXPERIMENTAL**

**Ligand- Metal Ratio**

Pure glipizide m.p. 208°C (Lit. 179-180), 0.005 M, were diluted to 100 ml as required and titrated conductometrically against cerium nitrate at 27°C ±1. Results were plotted in the form of a graph which indicate ligand metal ratio as 2:1 (L:M). This ratio was also confirmed by Job’s method of continuous variation as modified by Turner and Anderson. The graphs were plotted which indicates 2:1 ligand metal ratio, Fig.2(a, b); from these curves the stability constant (Log k) and free energy (-ΔF) of the complex was also calculated and reported in table 1.

**MATERIALS AND METHODS**

Pure sample of glipizide with molecular formula (C_{21}H_{27}N_{5}O_{4}S) was received from M/s Zim Laboratories Limited Kalmeshwar (M.S.). Solvent and metal salt used were of the analytical grade (E-Merk). Melting point was determined by Perkin Elmer melting point apparatus and is uncorrected. The elemental analysis of the isolated complex was carried out using Coleman analyzer at the Departmental Micro analytical Laboratory CDRI Lucknow, India. From stochiometry and analytical data, the percentage of each element of complex has been given in table 2. IR spectra of the ligand and isolated complex was recorded on Perkin Elemer Spectrophotometer Model 577, range 4000-450 cm⁻¹ and the probable assignments are given in table 3. The proposed structure for the isolated complex is supported by IR absorption bands and characterized by the prominent band in region of 3331±10 due to N-H stretching, a very sharp peak observed at 770 cm⁻¹ due to -CH stretching of aromatic ring. The carbonyl group (C=O) band was observed at 1688 cm⁻¹ in ligand; but in complex this stretching frequency got shifted downward at 1664 cm⁻¹ region. At 1222 cm⁻¹ a strong absorption band was obtained in complex due to SO₂-N frequency while the peak at 663 cm⁻¹ arises due to metal rotating anode and CuKα (1W=1.54060A°) radiation (Punjab University) Chandigarh, India.

**RESULTS AND DISCUSSION**

The synthesized complex is pale yellow and stable being soluble in DMSO, and insoluble in water, ethanol etc. Analytical data and conductometric studies suggest 2:1 (L: M) ratio.

**IR absorption analysis**

The IR spectra of the ligand and the isolated complex was recorded on Perkin Elemer Spectrophotometer Model 577, range 4000-450 cm⁻¹ and the probable assignments are given in table 3. The proposed structure for the isolated complex is supported by IR absorption bands and characterized by the prominent band in region of 3331±10 due to N-H stretching, a very sharp peak observed at 770 cm⁻¹ due to -CH stretching of aromatic ring. The carbonyl group (C=O) band was observed at 1688 cm⁻¹ in ligand; but in complex this stretching frequency got shifted downward at 1664 cm⁻¹ region. At 1222 cm⁻¹ a strong absorption band was obtained in complex due to SO₂-N frequency while the peak at 663 cm⁻¹ arises due to metal rotating anode and CuKα (1W=1.54060A°) radiation (Punjab University) Chandigarh, India.

### Table 1: Physico-chemical characteristics of Glipizide with Ce complex

<table>
<thead>
<tr>
<th>Ligand/complex</th>
<th>Ligand Metal Ratio</th>
<th>Color</th>
<th>% Yield</th>
<th>Melting Point (°C)</th>
<th>Log K (L/mole)</th>
<th>-ΔF (K cal/mole)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glipizide</td>
<td>2:1</td>
<td>Pale</td>
<td>57</td>
<td>212</td>
<td>11.72</td>
<td>-16.14</td>
</tr>
<tr>
<td>Ce Complex</td>
<td></td>
<td>Yellow</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Table 2: Analytical data of Glipizide complex with Cerium

<table>
<thead>
<tr>
<th>Ligand/Complex</th>
<th>Mol. wt (g/mole)</th>
<th>Elemental analysis calculated</th>
<th>Elemental analysis found</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>C</td>
<td>H</td>
</tr>
<tr>
<td>C_{21}H_{27}N_{5}O_{4}S</td>
<td>445.55</td>
<td>56.60</td>
<td>6.05</td>
</tr>
<tr>
<td>(C_{21}H_{27}N_{5}O_{4}S)<em>{2}Ce(OH</em>{2})_{2}</td>
<td>1067.22</td>
<td>47.08</td>
<td>4.87</td>
</tr>
</tbody>
</table>

### Table 3: IR absorption data of Ligand and Cerium complex in cm\(^{-1}\)

<table>
<thead>
<tr>
<th>Ligand and complex</th>
<th>(\nu) (N-H)</th>
<th>(\nu) (C=O)</th>
<th>(\nu) (SO_2N)</th>
<th>(\nu) (S=O)</th>
<th>(\nu) (-CH_2)</th>
<th>(\nu) (M-O)</th>
<th>(\nu) (H_2O)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand (C_{21}H_{27}N_{5}O_{4}S)</td>
<td>3352 (m)</td>
<td>1688 (vs)</td>
<td>1216 (vs)</td>
<td>1029 (vs)</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Complex (C_{21}H_{27}N_{5}O_{4}S)<em>{2}Ce(OH</em>{2})_{2}</td>
<td>3331 (s)</td>
<td>1664 (s)</td>
<td>1222 (s)</td>
<td>1011 (m)</td>
<td>770 (vs)</td>
<td>663 (s)</td>
<td>3640 (vw)</td>
</tr>
</tbody>
</table>

vs- very strong, s-strong, m-medium, w-week, vw-very weak

### Table 4: \(^1\)H NMR –Assignments of Glipizide and its Cerium complex

<table>
<thead>
<tr>
<th>Glipizide (C_{21}H_{27}N_{5}O_{4}S)</th>
<th>Glipizide-Cerium complex (C_{21}H_{27}N_{5}O_{4}S)<em>{2}Ce(OH</em>{2})_{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.59 (CH_3 attached with pyrazine ring, J=1.00Hz), 7.78 (d, benzene, J=2.067Hz), 7.439 (d, benzene, J=2.101Hz), 6.318 (s, SO_2NH, J=9.282Hz), 3.605 (q, CH_3, J=2.035Hz), 3.250 (t, CH_2 attached with benzene ring, J=1.031Hz), 2.98 (t, CH_2 attached with carbonyl, J=2.078Hz), 1.84 (m, CH_3, J=5.286Hz).</td>
<td>8.59 (CH_3 attached with pyrazine ring, J=0.5312Hz), 7.73 (d, benzene, J=1.883Hz), 7.429 (d, benzene, J=1.898Hz), 3.573 (q, CH_3, J=5.955Hz), 3.11 (t, CH_2 attached with benzene ring, J=5.041Hz), 2.96 (t, CH_2 attached with carbonyl, J=21.33Hz), 1.605 (CH_3, J=2.955Hz).</td>
</tr>
</tbody>
</table>

s- singlet, d- doublet, t-triplet, q-quartate, m-multiplet.

### Table 5: Cell data and crystal parameter of GLP-Ce complex

<table>
<thead>
<tr>
<th>a (Å) = 21.762</th>
<th>b (Å) = 23.427</th>
<th>c (Å) = 27.274</th>
<th>(\alpha = 90^\circ), (\beta = 90^\circ), (\gamma = 90^\circ)</th>
<th>V (Å^3) = 13904.78 Å^3</th>
<th>(D_{\text{cal}}=3.1423, D_{\text{obs}}=3.1459)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density =0.079 gcm(^{-3})</td>
<td>Space Group= Pmnnm</td>
<td>Crystal System = Monoclinic</td>
<td>Porosity= 0.1141%</td>
<td>Particle size= 4.445 microns</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2(\theta)</th>
<th>(I_0)</th>
<th>(D_{\text{obs}})</th>
<th>(D_{\text{cal}})</th>
<th>(h)</th>
<th>(k)</th>
<th>(l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>28.3708</td>
<td>100.00</td>
<td>3.1459</td>
<td>3.1423</td>
<td>3</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>32.9520</td>
<td>56.19</td>
<td>2.7182</td>
<td>2.7514</td>
<td>3</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>47.3375</td>
<td>78.64</td>
<td>1.9203</td>
<td>1.1919</td>
<td>6</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>45.8850</td>
<td>49.37</td>
<td>1.6452</td>
<td>1.6441</td>
<td>12</td>
<td>0</td>
<td>7</td>
</tr>
</tbody>
</table>
Fig. 1: Structure of Glipizide

![Glipizide Structure](image1)

GLIPIZIDE WITH Ce(NO₃)₂

(A) - 0.005 M
(B) - 0.002 M

Fig. 2: (a) Job’s curve (b) Modified Job’s curve

![Job's Curve](image2)

Fig. 3(a): IR spectra of pure drug Glipizide

![IR Spectrum](image3a)

Fig. 3(b): IR spectra of Glipizide and its Cerium Complex

![IR Spectrum](image3b)

Fig. 4: Structure of Glipizide – Cerium Complex

![Glipizide Cerium Complex](image4)
Fig. 4(a-b): X-ray diffraction pattern of GLP and GLP-Ce complex

**1H NMR Analysis**

1H NMR data of complex is summarized in (Table-4), and their proposed structure is given in Fig. 4. It is observed that the singlet due to the (SO2NH) proton around (d 6.318) in the spectrum of the ligand present but disappeared in the complex due to formation of M-O band. This also confirms the deprotonation of amide NH group through enolization. Other features of NMR spectrum were the aromatic ring of unresolved multiplet suggestive protons. Slichter22, Akit 23, Siewers 24 and Afridi 25.

**X-ray diffraction studies**

X-ray diffraction studies also confirm the complex formation due to new bonds26-33. The number of peaks in glipizide are 15 while (GLP)2Ce are 4 (fig 4.(a), (b)), thus indicating that complex formed is a well kit one. All the reflections present are new ones and the pattern are fairly strong. On comparing the pattern obtained with available literature, it is evident that their patterns is not in good agreement with available information and thus confirm the formation of totally new complex. The X-ray pattern have been indexed 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 Sinθ value. The unit cell parameters were calculated from the indexed data, from cell data and crystal lattice parameters of (GLP)2Ce, indicate complex attributed to Orthorhombic crystal system given in table 5.

**CONCLUSION**

The proposed structure of glipizide-cerium complex, initially Job’s method of Continuous variation as modified by Turner and Anderson was conducted which indicate 2:1ligand metal ratio. Moreover, stability constant and free energy change were also calculated. Analytical data agree to the molecular formula \((C_{21}H_{26}N_5O_4S)_2Ce(OH_2)_4\) (L2M). For supporting the proposed structure, given on the basis of stoichiometry and analysis of the complex, advance spectroscopic methods like IR, 1H NMR, were conducted which suggest the coordination of metal atom with enolic oxygen of the carbonyl group on one side and oxygen of the sulphonyl group from the other side. These observation were further supporting from the IR and NMR values of metal-oxygen linkage in IR and disappearance of N-H linkages in NMR. In complex...
A detailed study of X-Ray also supports the complex formation and the various values like particle size, porosity, volume of unit cell, density as well as crystal system was evaluated and discussed. Moreover, looking to the higher electronegativity of oxygen as compared to nitrogen, it appears that enolization will be through C=O group and not from NH group. Moreover, the enolization is possible from N² nitrogen rather than N¹ because the alkyl group of sulphonyl urea is electron releasing in which N² is attached, while N¹ is attached from one side of C=O group, while on other side from O=S=O group, both of which have high electronegativity and are proton attracting.

ACKNOWLEDGEMENTS

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REFERENCES

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