SYNTHESIS, CHARACTERISATION AND ANTIDIABETIC SCREENING OF Co(II),Cu(II),Zn(II) AND La(II) COMPLEXES OF GLIMEPERIDEA STANDARD SYNTHETIC ALLOPATHIC DRUG.

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Abstract:

Metal complxes of Glimeperide drugs were prepared and characterized based on elemental analysis, FT-IR, Molar conductance and thermal analysis (TGA and DTG) technique. From elemental analysis data, the complexes were proposed to have general formulae (GLM)2Co2H2O, (GLM)2Cu, (GLM)2Zn, and (GLM)2La2H2O. The molar conductance data reveal that all the metal complexes are non-electrolytic, IR spectra shows that GLM are coordinated to metal ions in a neutral bidentate manner from the ESR spectra and XRD-spectra. It is found that the geometrical structures of these complexes are tetrahedral Cu(II) ,Zn(II) and octrahedral Co(II), La(II). The thermal behavior of these complexes studied using thermogravimetric analysis (TGA and DTG) techniques. The results obtained shows that the hydrated complexes lose water molecules of hydration followed immediately by decomposition of the anions and ligand molecules in the successive unseparate steps. Thermogravimetric analysis was carried out to study the decomposition and various kinetic parameters. Freeman Carroll and Sharp Wentworth method have been applied for calculation of kinetic parameters. While data from freeman Carroll method have been used to determine various thermodynamic parameters such as order of reactions, energy of activation, frequency factor, entropy change, free energy change and apparent entropy change and order of reaction..

Keywords:

FTIR Spectra, TGA, DTG, , Glimeperide,HPMC-5CPS

Introduction:

Glimeperide, is a bi-substituted urea derivatives can exist in keto and enolic form when dissolved in an organic solvent and react with various metal ions to form intensely coloured metal complexes that provide the basis for their use as a sensitive reagent. The thermal degradation study of complexes has become a subject of recent interest. It is important property of complexes, which decides the thermal stability and processability of the complexes. The study of thermal

behaviour of complexes in air at different temperature provides important information about its practical applicability. Iqbal S.A. et.a11., (2005) synthesized the metal complexes of glimeperide characterized by FTIR, elemental analysis and TGA-DTG parameters. The thermal analysis (TGA) was performed at the heating rate of 10°C/min. in nitrogen atmosphere. Wilma Cyril et.al2., (2011) studied kinetics and Thermal decomposition of Cu(II) complex of of hydroxyl quinoline-5-sulphonic acid Thermal data have been analyzed by Freeman Carroll and Sharp-Wentworth method. Thermal analysis (TGA and DTG) is a typical analytical technique to describe the relationship between physico-chemical changes and temperature.1-2 In order to synthesize complexes having practical applications. There is a need to investigate the effect of heat on complexes in order to establish thermal stability. Iqbal and co-workers3-4 have synthesized and characterized complexes of tolbutamide and glimeperide by FTIR, elemental analysis and TGA-DTA technique. Thermal studies of complexes were carried out to determine their mode of decomposition, the activation energy (Ea), order of reaction (n), frequency factor(Z), entropy change (S), Free energy (ΔF) and apparent entropy change (*S). Thermal decomposition curves were discussed with careful attention of minute details. The freeman Carroll and Sharp-Wentworth methods have been used to calculate thermal activation energy and thermal stability. However, very little work has been carried out on the synthesis and characterization and thermal degradation studies of the metal complexes of glimeperide. Hence in this work we prepare complexes of Cu(II), Co(II), Zn(II) and La(II) transition and inner transition metals with glimeperide drug molecule. The solid complexes were characterized using different physico-chemical methods, like elemental analysis (C, H, N, S and metal content), IR and thermal analysis (TGA and DTG)

Material and Method:

All chemicals used were of analytical reagent grade (A.R.) and of highest purity. They included glimeperide (Zim laboratories, Nagpur), Copper(II) Chloride ,Zinc(II) chloride,Cobalt(II) chloride and Lanthanum(II) Chloride heptahydrate (Hi media Lab, Mumbai) organic solvents used absolute ethyl alcohol, DMF. These solvents were spectroscopic pure from BDH, hydrogen peroxide, hydrochloric and nitric acid (E.Merck) were used. De-ionized water was used in all preparations. 2.2 INSTRUMENTS Molar conductance of solid complexes in DMF was measured using Systronics conductivity meter, elemental microanalyses of the isolated solid complexes for C,H,N were performed at CDRI, Lucknow, using (HMS-932CLECO) Vario elemental analyzers. Infrared spectra were recorded on Perkin-Elmer, FTIR type 1650 spectrophotometer in wave number 400-4000 cm-1. The spectra were recorded as KBr pellets. The thermogravimetric (TG and DTG) analysis was carried out in dynamic nitrogen atmosphere (20 ml.min-1) with a heating rate of 10°C/min. using shimatzu TGA-50H Thermal Analyzer at IIT Bombay (Mumbai) Electronic spectra recorded at Qualichem Laboratory, Nagpur. 2.3 SYNTHESIS OF METAL COMPLEXES Metal complexes are 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 forms 1:2 complexes with glimeperide, were confirmed by Jobs method of continuous variation5 as modified by Turner and Anderson6. 2.4 ESTIMATION OF METALS IN COMPLEXES An accurately weighed portion of the different complexes ranged from 10 to 30 mg was placed in Kjeldhal flask. A measured volume of concentrated nitric acid ranged from 5 to 10 ml was added initially to the powdered complexes to start the fast wet oxidation digestion. This mixture had been digested with some drops of H2O2 solution using a gradual heating. This treatment was conducted until most of the powdered complexes were dissolved and the remaining solution had the colour of the corresponding metal

salt. This solution was then diluted upto a 50 ml. with distilled water and the metal content was determined by titration against standard EDTA solution at a suitable pH value using the suitable indicator.

Result and Discussion:

3.1 COMPOSITION AND STRUCTURES OF METAL COMPLEXES. The isolated solid complexes of Cu(II), Co(II), Zn(II) and La(II) with GLM ligands were subjected to elemental analysis (C, H, N, S. and metal content), I.R., Molar conductance, thermal analysis (TG and DTG) to support the tentative structure. The results of elemental analysis listed in table (1) suggest the formulae [Co(GLM)2]2H2O, [Cu(GLM)2], [Zn(GLM)2], and [La(GLM)2]2H2O for respective complexes. 3.2 MOLAR CONDUCTANCE The complexes were dissolved in DMF and the molar conductivities of 10-3M of their solutions at 298 K are measured. It is concluded from results listed in table (1) that the complexes are found to have molar conductance values of 13.18 to 30.15Ω-1 mole-1 am-2 indicating that all the metal complexes are non-electrolytes. 3.4 ELECTRONIC SPECTRAL STUDIES Electronic spectra of the ligand shows two high intensity bands at 47431 and 32233 cm-1,indicating n→ n*and π→π transitions respectively of the ligand moity.The electronic spectra of La(II) complex displays band at 32130 and 27393cm-1 The two bands corresponds to 4T1g(F)→4A2g(F), 4T1g(F)→4A1g(P) suggesting octahedral geometry of these complexes. The Cu(II) complex displays a band at 26130cm-1 4E1g(F)→4T2g(F),Zn(II) complex displays single absorption band at 31225cm-1.This is due to Ligand →Metal charge transfer spectra.. 3.3 IR SPECTRAL STUDIES The IR data of the spectra of GLM ligand and there complexes are listed in table (4). The IR spectra of the complexes are compared with those of the free GLM ligands in order to determine the coordination sites that may be involved in complexation7-15 The tautomeric equilibrium depends on the extent of conjugation, nature and position of the substituent, polarity of the solvent etc 3.5 MAGNETIC SUSCEPTIBILITY STUDIES The room temperature

magnetic moment of the complexes was found to be 4.66 B.M. which corresponds to the presence of Co(II), La(II) in octahedral geometry. Zayed et al16., (2000) Cotton et.a17., (1999) In addition to that, the Cu(II), and Zn(II) complexes are found to have magnetic moment value of 4.62 B.M.and 4.72B.M.respectively which indicates the presence of Cu(II) and Zn(II) complexes have tetrahedral structure. 3.6 THERMAL ANALYSIS (TGA AND DTG) In the present investigation, the weight losses for each complex were calculated within corresponding temperature ranges. The obtained data are listed in table (4). All complexes are thermally decomposed in three decomposition steps within the temperature range of 50-600°C .The TGA/DTA data for the complexes are shown in Table-1,2 and 5 The thermoanalytical data are presented in table 1,2 and 5. In studying the decomposition kinetics18-26, three methods mentioned in the literature were used in each case the least square plots were drawn. The first few points that did not fall on straight line were discarded. These types of deviations of points are reported in literature by several research workers. This is explained as due to the failure of obeying as first order kinetics always by the solids in their decomposition in the early stages fig-1 and 2.. Theoretical Consideration To provide further evidence regarding the degradation system of analyzed compounds we derived the TG curves by applying an analytical method proposed by Freeman-Carroll27-28 and Sharp-Wentworth29-30. Freeman-Carroll Method26-27 The straight line equation derived by Freeman and Carroll, which is in the form of (Δlog dw/dt)/(Δlog Wr) = n-E_a/2.303R.(Δ 1/T)/(Δlog Wr) Where, dw/dt = rate of change of weight with time Wr = Wc-W Wc = Wt. loss at completion of reaction W = Total wt. loss upto time 't' Ea = Energy of activation n = Order of reaction The plot between the term (Δlog dw/dT)/(Δ log Wr) Vs (Δ 1/T)/(Δ log Wr) gives a straight line from which slope can be calculated, also we obtained energy of activation (Ea) and intercept on Y-axis as order of reaction (n). The change in entropy (ΔS), frequency factor (Z), apparent entropy (S*) can also be calculated by further calculation. Sharp-Wentworth Method28-29 Using the

equation derived by Sharp and Wentworth (Δlog dc/dT)/((1-c)) = log A/B-Eq/(2.303 R).1/T Where, dc/dT = Rate of change of fraction of weight with change in temperature. β = Linear heating rate dT/dt by plotting the graph between (Δlog dc/dT)/((1-c)) Vs = 1/T, We obtained the straight line which gives energy of activation (Ea) from its slope. The thermodynamic activation parameters of decomposition process of dehydrate complexes namely activation energy (Ea), enthalpy (ΔH), Entropy (ΔS) and Gibb's free energy change of decomposition (ΔG°) are evaluated graphically by employing Free man-Carroll and Sharp-Wentworth relation. The data are summarized in Table 1,2,5. The activation energies of decomposition are found to be in the range 29.70 to 204.7 KJ.Mole-1. The high value of activation energies reflect the thermal stability of complexes. The entropy of activation is found to have negative values in all the complexes which indicate that decomposition reactions process with lower rate than the normal ones31-35 Table-1Thermogravimetric data of Glimeperide-Cu complex by Sharp-Wentworth28-29 method Temp. (°C) °K Temp (T) 1000 T % Mass Loss Change in Wt. 'c' grams 1-c dc dt log(dc/dt) log(1-c) log(dc/dt)/1-c Weight % (%) 30 303 3.30033 0.638 0.00006 0.99994 0.00009 -4.05164 -0.00003 -4.05187 99.362 50 323 3.09598 1.106 0.00010 0.99990 0.00012 -3.92395 -0.00004 -3.92435 98.894 70 343 2.91545 1.534 0.00014 0.99986 0.00017 -3.77705 -0.00006 -3.77758 98.466 90 363 2.75482 2.148 0.00019 0.99981 0.00020 -3.69867 -0.00008 -3.69939 97.852 110 383 2.61097 2.635 0.00024 0.99976 0.00022 -3.65637 -0.00010 -3.65724 97.365 130 403 2.48139 2.958 0.00027 0.99973 0.00024 -3.61347 -0.00012 -3.61444 97.042 150 423 2.36407 3.275 0.00030 0.99970 0.00027 -3.56881 -0.00013 -3.56987 96.725 170 443 2.25734 3.629 0.00033 0.99967 0.00030 -3.52480 -0.00014 -3.52596 96.371 190 463 2.15983 4.017 0.00036 0.99964 0.00033 -3.48241 -0.00016 -3.48368 95.983 210 483 2.07039 4.432 0.00040 0.99960 0.00038 -3.42467 -0.00017 -3.42605 95.568 230 503 1.98807 5.031 0.00046 0.99954 0.00042 -3.38055 -0.00020 -3.38209 94.969 250 523 1.91205 5.594 0.00051 0.99949 0.00050 -3.30383 -0.00022 -3.30551 94.406 270 543

1.84162 6.593 0.00060 0.99940 0.00057 -3.24715 -0.00026 -3.24909 93.407 290 563 1.77620 7.556 0.00069 0.99931 0.00059 -3.23207 -0.00030 -3.23429 92.444 310 583 1.71527 7.969 0.00072 0.99928 0.00061 -3.21413 -0.00031 -3.21645 92.031 330 603 1.65837 8.324 0.00076 0.99924 0.00063 -3.19810 -0.00033 -3.20052 91.676 350 623 1.60514 8.648 0.00078 0.99922 0.00065 -3.18558 -0.00034 -3.18808 91.352 370 643 1.55521 8.917 0.00081 0.99919 0.00067 -3.17559 -0.00035 -3.17817 91.083 390 663 1.50830 9.138 0.00083 0.99917 0.00068 -3.16753 -0.00036 -3.17016 90.862 410 683 1.46413 9.32 0.00085 0.99915 0.00069 -3.16117 -0.00037 -3.16384 90.680 430 703 1.42248 9.467 0.00086 0.99914 0.00070 -3.15540 -0.00037 -3.15812 90.533 450 723 1.38313 9.598 0.00087 0.99913 0.00071 -3.14976 -0.00038 -3.15250 90.402 470 743 1.34590 9.725 0.00088 0.99912 0.00072 -3.14431 -0.00038 -3.14708 90.275 490 763 1.31062 9.849 0.00089 0.99911 0.00073 -3.13884 -0.00039 -3.14164 90.151 510 783 1.27714 9.974 0.00091 0.99909 0.00889 -2.05090 -0.00039 -2.05276 90.026 Table-2Thermogravimetric data of Glimeperide-Cu complex by Freeman and Carroll26-27 method Temp (°C) % Mass Loss Change in Wt. (gm.) Time in Sec. dw/dt log dw/dt wr = wc-w log wr T (K) 1/T(K-1) (Log dt/dt) /(log wr (1/T)/Log wr α = wt/wc gα = 1-(1-α)1-n/1-n T3 x 10-7 gα/T3 x107 1/T x 10-3 log g(α)/T3 30 4.049 0.0002057 90 0.0004250 -3.3717 0.003171 -2.498866 303 0.003300 1.3493 -0.001321 0.06093 0.0628 2.7818 0.001376 3.300330 -86.884856 50 8.566 0.0004352 150 0.0004479 -3.3488 0.002941 -2.531500 323 0.003096 1.3229 -0.001223 0.12891 0.1378 3.3698 0.005272 3.095975 -51.943202 70 9.243 0.0004696 210 0.0004567 -3.3403 0.002907 -2.536609 343 0.002915 1.3169 -0.001149 0.13910 0.1496 4.0354 0.005155 2.915452 -41.678647 90 9.451 0.0004802 270 0.0004616 -3.3357 0.002896 -2.538191 363 0.002755 1.3142 -0.001085 0.14223 0.1532 4.7832 0.004555 2.754821 -34.742302 110 9.558 0.0004856 330 0.0004679 -3.3299 0.002891 -2.539007 383 0.002611 1.3115 -0.001028 0.14384 0.1551 5.6182 0.003970 2.610966 -29.397927 130 9.686 0.0004921 390 0.0004797 -3.3190 0.002884 -2.539985 403 0.002481 1.3067 -0.000977

0.14577 0.1573 6.5451 0.003503 2.481390 -25.051013 150 9.926 0.0005043 450 0.0005039 -3.2977 0.002872 -2.541826 423 0.002364 1.2974 -0.000930 0.14938 0.1615 7.5687 0.003188 2.364066 -21.370558 170 10.413 0.0005291 510 0.0005484 -3.2609 0.002847 -2.545584 443 0.002257 1.2810 -0.000887 0.15671 0.1702 8.6938 0.003067 2.257336 -18.105713 190 11.314 0.0005749 570 0.0006259 -3.2035 0.002801 -2.552623 463 0.002160 1.2550 -0.000846 0.17027 0.1863 9.9253 0.003196 2.159827 -15.099361 210 12.884 0.0006546 630 0.0007092 -3.1492 0.002722 -2.565170 483 0.002070 1.2277 -0.000807 0.19389 0.2151 11.2679 0.003701 2.070393 -12.245875 230 14.603 0.0007420 690 0.0008170 -3.0878 0.002634 -2.579336 503 0.001988 1.1971 -0.000771 0.21976 0.2475 12.7264 0.004275 1.988072 -9.935268 250 16.81 0.0008541 750 0.0013404 -2.8728 0.002522 -2.598228 523 0.001912 1.1057 -0.000736 0.25298 0.2908 14.3056 0.005143 1.912046 -7.922182 270 27.221 0.0013831 810 0.0021815 -2.6612 0.001993 -2.700455 543 0.001842 0.9855 -0.000682 0.40965 0.5243 16.0103 0.013415 1.841621 -4.172467 290 44.295 0.0022506 870 0.0026006 -2.5849 0.001126 -2.948599 563 0.001776 0.8767 -0.000602 0.66660 1.0864 17.8454 0.040583 1.776199 -0.785237 310 53.398 0.0027132 930 0.0027506 -2.5606 0.000663 -3.178407 583 0.001715 0.8056 -0.000540 0.80359 1.6014 19.8155 0.064941 1.715266 0.552733 330 56.805 0.0028863 990 0.0028234 -2.5492 0.000490 -3.309794 603 0.001658 0.7702 -0.000501 0.85487 1.8933 21.9256 0.073819 1.658375 0.953780 350 58.409 0.0029678 1050 0.0028782 -2.5409 0.000409 -3.388795 623 0.001605 0.7498 -0.000474 0.87900 2.0680 24.1804 0.075177 1.605136 1.073373 370 59.567 0.0030266 1110 0.0029243 -2.5340 0.000350 -3.456336 643 0.001555 0.7331 -0.000450 0.89643 2.2169 26.5848 0.074753 1.555210 1.121916 390 60.531 0.0030756 1170 0.0029769 -2.5262 0.000301 -3.521876 663 0.001508 0.7173 -0.000428 0.91094 2.3609 29.1434 0.073794 1.508296 1.141126 410 61.616 0.0031307 1230 0.0030311 -2.5184 0.000246 -3.609834 683 0.001464 0.6976 -0.000406 0.92727 2.5535 31.8612 0.074314 1.464129 1.174889 430 62.737 0.0031877 1290 0.0030755 -2.5121 0.000189

-3.724443 703 0.001422 0.6745 -0.000382 0.94414 4.2660 34.7429 0.115930 1.422475 1.741538 450 63.667 0.0032349 1350 0.0031104 -2.5072 0.000141 -3.849694 723 0.001383 0.6513 -0.000359 0.95813 50.0000 37.7933 1.267597 1.383126 4.446279 470 64.399 0.0032721 1410 0.0031412 -2.5029 0.000104 -3.982297 743 0.001346 0.6285 -0.000338 0.96915 3.3603 41.0172 0.079398 1.345895 1.250144 490 65.042 0.0033048 1470 0.0031720 -2.4987 0.000071 -4.145757 763 0.001311 0.6027 -0.000316 0.97883 3.7101 44.4195 0.081756 1.310616 1.260916 510 65.68 0.0033372 1530 0.0032094 -2.4936 0.000039 -4.408124 783 0.001277 0.5657 -0.000290 0.98843 #REF! 48.0049 #REF! 1.277139 #REF! Fig 1- FC,Kinetic plot of Glimeperide complexes using TGA data.(FC=Freeman and Carroll) Fig- 2 Determination of activation energy by SW method TABLE-(3-ANALYTICAL DATA OF GLIMEPERIDE COMPLEXES Sl. No. Molecular formula of complexes Molecular weight (gm/mol) % Analysis found (calculated) C H N O S Metal H2O 1 (C24H34N4O5S)2Co•2H2O 1076.164 53.18 (53.52) 6.18 (6.13) 10.38 (10.40) 17.82 (17.84) 5.84 (5.94) 5.37 (5.47) 3.54 (3.34) 2 (C24H34N4O5S)2Cu 1044.774 55.14 (55.13) 6.18 (6.31) 10.78 (10.72) 18.30 (18.37) 6.52 (6.12) 6.00 (6.08) - 3. (C24H34N4O5S)2Zn 1044.604 55.10 (55.14) 6.18 (6.31) 10.82 (10.72) 18.48 (18.38) 6.28 (6.12) 6.82 (6.06) - 4. (C24H34N4O5S)2La•2H2O 1156.144 48.88 (49.82) 2.82 (5.70) 9.66 (9.68) 16.80 (16.60) 5.62 (5.53) 11.98 (12.01) 3.28 (3.11) TABLE (4): I.R. SPECTRA (4000-400cm-1) OF THE GLM AND THEIR METAL COMPLEXES Compounds γ (OH) Enolic γ (NH) γ (SO2) Asym γ (SO2) Sym γ (C=O) Amide γ (m-O) (C24H34N4O5S)2Co•2H2O 3100-3320 Br. - 1375 sh. 1100 sh. 1460 sh. 530 m. (C24H34N4O5S)2Cu 3220-3320 br. 3100 br. 1365 sh. 1120 sh. 1481 sh. (C24H34N4O5S)2Zn 3220-3363 br. 3024 br. 1340.8 m. 1160.6 sh. 1481 sh. (C24H34N4O5S)2La•2H2O 3280-3310 - 1305 sh. 1160 w. 1480 sh. 577 m.- Table (5): Thermogravimetric data of Metal complexes of GLM drugs with corresponding to heating rate of 10°C/min. Complexes Decomposition Temp. (°C) %Wt. loss Ea(Kj/mole) ΔS* (Kj/mole) ΔF (Kj/mole) Z S* n F.C. W.W. [CC (C15H20N3O3S)2Cu 30-150 150-350 350-510 9.926 58.408 65.68 32.87

51.21 110.30 31.37 51.01 109.23 -28.85 -64.65 -112.5 -8.708 -27.29569 -69.9772 281.2 269.8 252.7 -44.2681 0.9 (C15H20N3O3S)2Co.2H2O 30-150 150-350 350-510 5.815 51.027 69.718 33.67 55.14 109.37 32.66 54.38 108.38 -33.98 -82.07 -116.8 -10.26227 -34.66047 -72.65703 322.8 268.3 252.3 -48.5380 1.01 (C23H27O5ClN3S)2Zn 30-150 150-350 350-510 10.413 58.409 65.042 29.77 67.76 114.2 28.68 66.14 113.92 -24.59 -67.76 -116.50 -7.421 -29.94992 -72.4653 284.3 263.0 252.0 -43.2123 0.98 (C24H33N4O6S)2La 30-150 150-350 350-510 2.577 61.536 81.344 52.66 85.94 138.23 52.16 85.13 138.14 -43.48 -82.05 -102.2 -13.12178 -39.54421 -43.09237 269.2 269.2 257.6 -44.2381 0.99

Table-1 Thermogravimetric data of Glimeperide-Cu complex by Sharp-Wentworth[28-29] method

Temp. (°C)	°K Temp (T)	$\frac{1000}{T}$	% Mass Loss	Change in Wt. 'c' grams	1-c	$\frac{dc}{dt}$	log(dc/dt)	log(1-c)	log(dc/dt)/1-c	Weight % (%)
30	303	3.30033	0.638	0.00006	0.99994	0.00009	-4.05164	-0.00003	-4.05187	99.362
50	323	3.09598	1.106	0.00010	0.99990	0.00012	-3.92395	-0.00004	-3.92435	98.894
70	343	2.91545	1.534	0.00014	0.99986	0.00017	-3.77705	-0.00006	-3.77758	98.466
90	363	2.75482	2.148	0.00019	0.99981	0.00020	-3.69867	-0.00008	-3.69939	97.852
110	383	2.61097	2.635	0.00024	0.99976	0.00022	-3.65637	-0.00010	-3.65724	97.365
130	403	2.48139	2.958	0.00027	0.99973	0.00024	-3.61347	-0.00012	-3.61444	97.042
150	423	2.36407	3.275	0.00030	0.99970	0.00027	-3.56881	-0.00013	-3.56987	96.725
170	443	2.25734	3.629	0.00033	0.99967	0.00030	-3.52480	-0.00014	-3.52596	96.371
190	463	2.15983	4.017	0.00036	0.99964	0.00033	-3.48241	-0.00016	-3.48368	95.983
210	483	2.07039	4.432	0.00040	0.99960	0.00038	-3.42467	-0.00017	-3.42605	95.568
230	503	1.98807	5.031	0.00046	0.99954	0.00042	-3.38055	-0.00020	-3.38209	94.969
250	523	1.91205	5.594	0.00051	0.99949	0.00050	-3.30383	-0.00022	-3.30551	94.406
270	543	1.84162	6.593	0.00060	0.99940	0.00057	-3.24715	-0.00026	-3.24909	93.407
290	563	1.77620	7.556	0.00069	0.99931	0.00059	-3.23207	-0.00030	-3.23429	92.444
310	583	1.71527	7.969	0.00072	0.99928	0.00061	-3.21413	-0.00031	-3.21645	92.031
330	603	1.65837	8.324	0.00076	0.99924	0.00063	-3.19810	-0.00033	-3.20052	91.676
350	623	1.60514	8.648	0.00078	0.99922	0.00065	-3.18558	-0.00034	-3.18808	91.352
370	643	1.55521	8.917	0.00081	0.99919	0.00067	-3.17559	-0.00035	-3.17817	91.083
390	663	1.50830	9.138	0.00083	0.99917	0.00068	-3.16753	-0.00036	-3.17016	90.862
410	683	1.46413	9.32	0.00085	0.99915	0.00069	-3.16117	-0.00037	-3.16384	90.680
430	703	1.42248	9.467	0.00086	0.99914	0.00070	-3.15540	-0.00037	-3.15812	90.533
450	723	1.38313	9.598	0.00087	0.99913	0.00071	-3.14976	-0.00038	-3.15250	90.402
470	743	1.34590	9.725	0.00088	0.99912	0.00072	-3.14431	-0.00038	-3.14708	90.275
490	763	1.31062	9.849	0.00089	0.99911	0.00073	-3.13884	-0.00039	-3.14164	90.151
510	783	1.27714	9.974	0.00091	0.99909	0.00889	-2.05090	-0.00039	-2.05276	90.026

Table-2 Thermogravimetric data of Glimeperide-Cu complex by Freeman and Carroll[26-27] method

Temp (°C)	% Mass Loss	Change in Wt. (gm.)	Time in Sec.	dw/dt	log dw/dt	wr = wc-w	log wr	T (K)	1/T(K-1)	(Log dt/dt) /(log wr	(1/T) /Log wr	α = wt/wc	gα = 1-(1-α)$^{1-n}$/1-n	T^3 x 10^{-7}	gα/T3 x10^7	1/T x 10^{-3}	log g(α)/T^3
30	4.049	0.0002057	90	0.0004250	-3.3717	0.003171	-2.498866	303	0.003300	1.3493	-0.001321	0.06093	0.06028	2.7818	0.001376	3.300330	-86.884856
50	8.566	0.0004352	150	0.0004479	-3.3488	0.002941	-2.531500	323	0.003096	1.3229	-0.001223	0.12891	0.13078	3.3698	0.005272	3.095975	-51.943202
70	9.243	0.0004696	210	0.0004567	-3.3403	0.002907	-2.536609	343	0.002915	1.3169	-0.001149	0.13910	0.14096	4.0354	0.005155	2.915452	-41.678647
90	9.451	0.0004802	270	0.0004616	-3.3357	0.002896	-2.538191	363	0.002755	1.3142	-0.001085	0.14223	0.15032	4.7832	0.004555	2.754821	-34.742302
110	9.558	0.0004856	330	0.0004679	-3.3299	0.002891	-2.539007	383	0.002611	1.3115	-0.001028	0.14384	0.15051	5.6182	0.003970	2.610966	-29.397927
130	9.686	0.0004921	390	0.0004797	-3.3190	0.002884	-2.539985	403	0.002481	1.3067	-0.000977	0.14577	0.15773	6.5451	0.003503	2.481390	-25.051013
150	9.926	0.0005043	450	0.0005039	-3.2977	0.002872	-2.541826	423	0.002364	1.2974	-0.000930	0.14938	0.16015	7.5687	0.003188	2.364066	-21.370558
170	10.413	0.0005291	510	0.0005484	-3.2609	0.002847	-2.545584	443	0.002257	1.2810	-0.000887	0.15671	0.17002	8.6938	0.003067	2.257336	-18.105713
190	11.314	0.0005749	570	0.0006259	-3.2035	0.002801	-2.552623	463	0.002160	1.2550	-0.000846	0.17027	0.18063	9.9253	0.003196	2.159827	-15.099361
210	12.884	0.0006546	630	0.0007092	-3.1492	0.002722	-2.565170	483	0.002070	1.2277	-0.000807	0.19389	0.21051	11.2679	0.003701	2.070393	-12.245875
230	14.603	0.0007420	690	0.0008170	-3.0878	0.002634	-2.579336	503	0.001988	1.1971	-0.000771	0.21976	0.24075	12.7264	0.004275	1.988072	-9.935268
250	16.81	0.0008541	750	0.0013404	-2.8728	0.002522	-2.598228	523	0.001912	1.1057	-0.000736	0.25298	0.29008	14.3056	0.005143	1.912046	-7.922182
270	27.221	0.0013831	810	0.0021815	-2.6612	0.001993	-2.700455	543	0.001842	0.9855	-0.000682	0.40965	0.52043	16.0103	0.013415	1.841621	-4.172467
290	44.295	0.0022506	870	0.0026006	-2.5849	0.001126	-2.948599	563	0.001776	0.8767	-0.000602	0.66660	1.08064	17.8454	0.040583	1.776199	-0.785237
310	53.398	0.0027132	930	0.0027506	-2.5606	0.000663	-3.178407	583	0.001715	0.8056	-0.000540	0.80359	1.60014	19.8155	0.064941	1.715266	0.552733
330	56.805	0.0028863	990	0.0028234	-2.5492	0.000490	-3.309794	603	0.001658	0.7702	-0.000501	0.85487	1.89033	21.9256	0.073819	1.658375	0.953780
350	58.409	0.0029678	1050	0.0028782	-2.54	0.000409	-3.388	62	0.001605	0.7498	-0.000	0.87900	2.06080	24.1804	0.075177	1.605136	1.073373

370	59.567	0.0030266	1110	0.0029243	09 -2.5340	0.000350	795 -3.456336	3643	0.001555	0.7331	474 -0.000450	0.89643	2.2169	26.5848	0.074753	1.555210	1.121916
390	60.531	0.0030756	1170	0.0029769	-2.5262	0.000301	-3.521876	663	0.001508	0.7173	-0.000428	0.91094	2.3609	29.1434	0.073794	1.508296	1.141126
410	61.616	0.0031307	1230	0.0030311	-2.5184	0.000246	-3.609834	683	0.001464	0.6976	-0.000406	0.92727	2.5535	31.8612	0.074314	1.464129	1.174889
430	62.737	0.0031877	1290	0.0030755	-2.5121	0.000189	-3.724443	703	0.001422	0.6745	-0.000382	0.94414	4.2660	34.7429	0.115930	1.422475	1.741538
450	63.667	0.0032349	1350	0.0031104	-2.5072	0.000141	-3.849694	723	0.001383	0.6513	-0.000359	0.95813	50.0000	37.7933	1.267597	1.383126	4.446279
470	64.399	0.0032721	1410	0.0031412	-2.5029	0.000104	-3.982297	743	0.001346	0.6285	-0.000338	0.96915	3.3603	41.0172	0.079398	1.345895	1.250144
490	65.042	0.0033048	1470	0.0031720	-2.4987	0.000071	-4.145757	763	0.001311	0.6027	-0.000316	0.97883	3.7101	44.4195	0.081756	1.310616	1.260916
510	65.68	0.0033372	1530	0.0032094	-2.4936	0.000039	-4.408124	783	0.001277	0.5657	-0.000290	0.98843	#REF!	48.0049	#REF!	1.277139	#REF!

Conclusion:

Discussion The complexes of Cu,Zn,La and Co were synthesized with oral hypoglycemic agents i.e. glimeperide the formulae suggested for the complexes are well supported by the Jobs method of continuous variation as modified by Turner and Anderson,moreover,the formulae of the complexes further gets supports from the analytical data. The structure of the complexes are supported from variety of spectroscopic technique like I.R,Electronic spectra,TGAmethod whose results are summarized in Tables-3,4,5. All the complexes prove to be formed in 2:1 ligand metal ratio The complexes are formed after enolisation of the drugs which is indicative by the presence of only metal oxygen bonds and not the metal nitrogen. The Cu and Zn complexes shows tetrahedral structures while La and Co complexes shows octahedral structures in which the six co-ordination is fulfilled by two water molecule in which the oxygen of the water is vertically joining to the metal atom, above and below the plane of the molecule. Thus on the bases of analytical data and spectroscopic studies the following structure-1 and 2 may be assign for the

Cu,Zn and La, Co complexes respectively. M=Co,La STRUCTURE 1 and 2 M=Cu,Zn CONCLUSION As the reported metal complexes of Glimeperide drugs are able to dissociate at stomach pH, therefore its dosages, to be given to subject animals should be such that it should not be dissociate in stomach i.e. at pH 1.2 for this complexes prepared enteric coated to make at the drug bioavailable as it is, i.e. at duodenum and small intestinal pH (5.5 to 6.8 pH) Drug is coated with a polymer HPMC-5CPS (Hydroxy propylmethyl cellulose) which does not permit drug to dissolve in stomach (i.e. pH 1.2) and such polymer dissolves rapidly at deodenal pH (5 - 5.5) thus drug releases at 5.5 pH and is available for absorption. At this pH complex is stable, non-dissociatable and absorbable. Therefore dosage forms for animals study is prepared as enteric coated, polymerized in this dosage forms are not soluble at pH 12. This drug delivery system is adopted for further study36 The hypoglycemic effects Glimeperide the well known sulphonyl ureas, were inverstigated on the blood sugar levels of male albino rats by using Folin Wu method.37 . Analysis of data show that thisdrugs caused a marked decrease in blood sugar level to the extent while their complexes reduced the blood sugar level to than the parent drug. This blood sugar lowering effect of sulphonyl ureas seems to be related to the stimulation of insulin secretion on the other hand, many studies have strongly indicated the presence of long term or extra pancreatic action of sulphonyl ureas38. The hypoglycemic activity of sulphonyl ureas may also be attributed to the stimulation of glycolysis and to the inhibition of glycogenesis in the liver by itself or by enhancing insulin action39. On comparing the hypoglycemic effect of these complxes with their parent drugs, it was revealed that in the three groups Glimeperide-Zn(II) treated albino rat had lowest blood sugar level being 49.72 mg/100 ml. respectively on an average. These facts clearly indicate a better hypoglycemic activity of complexes as compared to their parent drugs which is in agreement with the earlier findings of Iqbal and co-workers40. This improved hypoglycemic activity may be related to smaller particle size of metal complexes than drugs as on complexation particle size is

reduced which may promote the ratio of absorption of complexes in gastro-intestinal tract. Results of the present work are also in conformity with the hypoglycemic effect of copper-phenformin complex over parent drug phenformin as mentioned by Piccini et al.,41 These interesting observations on metal-complexes of oral sulphonylureas used as anti-diabetic agents for lowering blood sugar concentration may likely substantiate the use of these complexes after extensive clinical studies.

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