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Metformin HCl chelates of La(III), Pr(III), Dy(III) and Eu(III): Synthesis and spectro-analytical studies

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Abstract:
Metformin hydrochloride (metfHCl) chelates of lanthanides [La(metfHCl)$_3$Cl$_3$]3.5H$_2$O (1), [Pr(metfHCl)$_3$Cl$_3$]3.5H$_2$O (2), [Dy(metfHCl)$_3$Cl$_3$]3.5H$_2$O (3), and [Eu(metfHCl)$_3$Cl$_3$]3.5H$_2$O (4), were synthesized and characterized by elemental analysis, conductance, thermal, LC-MS, IR and UV-Vis. From the findings, the formula structure were proposed with metal to metfHCl ratio as 1:3 and metfHCl as bidentate N,N-ligand.

Key words: *Metformin hydrochloride, lanthanides, chelates, bidentate*

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I. Introduction:

Metformin hydrochloride has proven to be a promising drug during the pandemic of COVID19 increasing the mortality rate [1, 2]. This drug is a biguanide class of antihiperglycemic agent that acts primarily by decreasing hepatic output of glucose by inhibition of gluconeogenesis in the metabolic disorder of Diabetes, in addition to being the first-line treatment for type 2 diabetes. Metformin has a long history of enhancing outcomes in the treatment of infectious disorders like influenza, hepatitis C, in vitro testing for zika and also used to treat PCOS [3]. It is established that, this drug also has neoplastic and anti-microbial activity upon chelation with metals[4].

Synthesis and characterization of binary and ternary metal complexes of metformin and its Schiff bases were well documented, focusing on their biological applications and DNA binding interactions[5-13]. Research onlanthanides has shown that they are useful in a wide range of fields, including material sciences, industry, agriculture, medical diagnosis and treatment [14].They are highly recommended as great spectroscopic probes, sensors, lasers, fluorescent dyes and contrast agents in medical research [15, 16].Lanthanide complexes also exhibit magnetic, catalytic and optical properties[17].

Keeping in view the significance of lanthanides and metformin complexes, the present investigation focusses on the synthesis, characterization of metformin hydrochloride chelates of lanthanides.

II. Experimental

2.1 General:

Analytical-grade chemicals were employed for the synthesis. Suraksha Pharma Pvt.Ltd. provided a free sample of metformin. A Perkin Elmer 240 elemental analyser was used for the microanalysis of the elements C, H, and N. Utilizing Mohr's approach, chloride analysis was performed. A Shimadzu AA-6300 atomic absorption spectrophotometer was used to estimate the metal contents. A Shimadzu LCMS-2010 A spectrometer was used to capture mass spectra. Infrared (IR) spectra were recorded using KBr discs in the range 400-4000 cm−1 with a Perkin Elmer FT-IR spectrometer. Solid-state UV–visible spectra of the complexes were recorded with a Shimadzu 160A spectrophotometer (200-800 nm). Using a TGA Q 5000 V3.13 build 261instrument, thermal analysis was performed.

2.2 Synthesis of metformin hydrochloride- lanthanide chelates

Stoichiometric quantity of lanthanum(III) oxide (0.163g,1mmol) was heated with dropwise addition of conc HCl to convert into its chloride. Excess HCl was slowly removed by heating and allowed to dry out on a hot plate. The residue was dissolved in 10ml methanol. To this solution metformin hydrochloride (0.495g, 3mmol) dissolved in 5ml of 0.1N KOH was added. The reaction mixture was heated for 1 hour on water bath and the complex that separated was filtered and dried.

Similarly Pr(III), Dy(III) and Eu(III) complexes with metformin hydrochloride were prepared.

III. Results & Discussions:

The synthesized chelates are colorless except complex 2 which is light green in color, air stable, and soluble in DMSO, DMF, and hot methanol.

3.1 Mass spectral & elemental analysis

The LC-MS mass spectra recorded at ambient temperature resolve (M+55) adduct peaks from which m/z for all the synthesized complexes are known. The elemental analysis (Table 1) indicates metal to ligand ratio as 1:3. The formulae that emerge from elemental analysis by percentages of carbon, hydrogen, nitrogen, oxygen, chloride, and metal are $LaC_{12}H_{43}N_{15}Cl_6O_{3.5}$, $PrC_{12}H_{43}N_{15}Cl_6O_{3.5}$, $DyC_{12}H_{43}N_{15}Cl_6O_{3.5}$ and $EuC_{12}H_{43}N_{15}Cl_6O_{3.5}$.

Table 1: Analytical data of complexes

Complex	Mol. wt	Colour	Yield (%)	Elements found% (calc)				
				M	C	H	N	Cl
$LaC_{12}H_{43}N_{15}Cl_6O_{3.5}$ **(1)**	805.19	Colour less	95	17.14 (17.25)	17.93 (17.90)	5.36 (5.38)	26.00 (26.09)	26.12 (26.42)
$PrC_{12}H_{43}N_{15}Cl_6O_{3.5}$ **(2)**	807.19	Light green	85	17.38 (17.46)	17.88 (17.86)	5.37 (5.37)	25.99 (26.03)	26.29 (26.35)
$DyC_{12}H_{43}N_{15}Cl_6O_{3.5}$ **(3)**	828.79	Colour less	80	19.59 (19.61)	17.35 (17.39)	5.22 (5.23)	25.36 (25.35)	25.59 (25.67)
$EuC_{12}H_{43}N_{15}Cl_6O_{3.5}$ **(4)**	818.25	Colour less	90	18.52 (18.57)	17.55 (17.61)	5.29 (5.30)	25.62 (25.68)	25.93 (26.00)

3.2 Conductivity measurements

The synthesized compounds has molar conductance values between 11-40 $ohms^{-1}\ cm^2\ mol^{-1}$ for 10^{-3} DMF solutions. In these complexes, the coordination of the anion may be responsible for these values rather than ionic interaction with the lanthanide(III) cations during complex formation, thus supporting the non-electrolytic nature [18].

3.3 Thermal analysis

The stepwise thermal decomposition of the complexes **1**, **2**, **3** and **4** within the range 25-1000^oC was studied by Thermogravimetric analysis. Table 2 lists the initial and final temperatures of decomposition stages as well as the partial mass losses along with the assignments of each decomposition stage[6].

Table 2: Thermo gravimetric analysis data of four complexes

Complex	**Stages**	**Temperature range (˚C)**	**TG Weight loss (%)**		**Assignment**
			Found%	Calc%	
	1	29-150˚C	1.83	2.23	H_2O
(1)	2	150-250˚C	4.15	4.47	$2H_2O$
M.W.805.19	3	250-320˚C	49.14	49.32	$1/2H_2O$, 3HCl, $C_8H_{21}N_9$, Cl $C_4H_{11}N_5$, NH
	4	320-380˚C	17.98	17.91	Cl
	5	380-900˚C	4.78	4.40	LaCl
	6	>1000˚C	22.11	21.65	
	1	29-150˚C	1.79	2.23	H_2O
(2)	2	150-250˚C	9.24	10.10	HCl ,$2.5H_2O$
M.W.807.19	3	250-420˚C	33.36	33.82	$C_4H_{11}N_5$,2HCl,2Cl
	4	420-900˚C	36.93	34.66	$C_8H_{22}N_9$,Cl
	5	>1000˚C	18.68	19.19	PrN
	1	29-100˚C	2.85	3.26	$1.5H_2O$
(3)	2	100-150˚C	2.04	2.17	H_2O
M.W.828.79	3	150-200˚C	4.85	4.11	NH_2, H_2O
	4	200-250˚C	8.31	8.80	2HCl
	5	250-300˚C	7.37	8.03	$2CH_3$,HCl
	6	300-320˚C	3.94	4.28	Cl
	7	320-380˚C	5.31	5.19	CH_3, N_2
	8	380-900˚C	17.76	17.03	$C_5H_{11}N_5$
	9	>1000˚C	47.55	47.13	$DyC_4H_{11}N_7Cl_2$

	1	24-200˚C	9.99	12.33	$3.5H_2O$, HCl
(4)	2	200-400˚C	41.9	41.03	$2(C_4H_{11}N_5)$,2HCl
M.W.818.25	3	400-1000˚C	27.8	27.44	$C_4H_{11}N_4$,3Cl
		Residue	20.25	20.56	EuN

3.4 IR spectral studies

Comparison of the IR spectra of the complexes, **1, 2, 3** and **4**, given in Figure 1, was done with that of the free ligand and presented in Table 3. Imine nitrogen is coordinated to metal during complex formation, as evidenced by the shift in the frequency of the imine υC=N band from 1623 to1625,1627,1629,1626 cm^{-1} in the complexes **1, 2, 3** and **4** respectively and $\delta_{def}(NH_2)$ from 1561 to 1565, 1558 and 1570, 1554 cm^{-1} respectively. The coordination through a M -N (imino) bond is preferable to a M- N (amino) bond[19]. Chelate ring formation by the coordinated ligand revealed an unique band that occurred in the spectra of complexes **1, 2, 3** and **4** at 1397, 1407, 1406 and 1399 cm^{-1}, respectively [5]. As both NH_2(as), and NH groups are unshared during complexation, chelation has no effect on the stretching vibration bands of the ($-NH_2$) and -(NH) of the (primary and secondary) amino group. M-N (imino) bond formation is preferred over M-N (amino) bond as extra stability is attained due to π delocalization of the C-N-C system by imino nitrogen. These results show that metformin binds to metal ions as bidentate N,N-donor via the nitrogen atoms of the imino groups without proton displacement.

Table 3 Assignment of IR spectral bands for Metformin & synthesized metal complexes

	$\upsilon as(NH_2)$	υs (NH)	υ (C=N)	δdef (NH2)	δ(CH3)	υ (C-N)	δ w(NH)	δ def(CNC)	New Chelate ring
metf.HCl	3370 3294	3174	1623	1561	1474 1446 1414	1216 1168 1061	935 799 735	639 599	-
(1)	3370 3293	3174	1625	1565	1474 1450 1416	1168, 1062, 1055	933 821 796 736	638 615	1397
(2)	3370 3293	3174	1627	1558	1480 1449	1219, 1170, 1065	925 827 763	622 603	1407
(3)	3370 3293	3174	1629	1570	1480 1455	1169, 1069, 1047	921 759 739	628 600	1406
(4)	3370 3293	3174	1626	1554	1472 1445	1272, 1166, 1060	937 800 732	631 538	1399

3.5 Electronic spectra

The electronic (UV-Vis) spectra of metformin hydrochloride has π-π* absorption bands at 228, 262, and 284 nm due to the aromaticity of the double bond and at 375 nm which can be due to n-π* transition of the imine (=NH), primary ($-NH_2$), and secondary (-NH) amino groups [6]. The characteristics of the system will alter after complexation with rare earth metal ions as a result of interaction with the metal ion. The changes in these bands and the observed less intense bands of characteristic f-f transitions of lanthanide ions [16, 20] are listed in the Table 4.

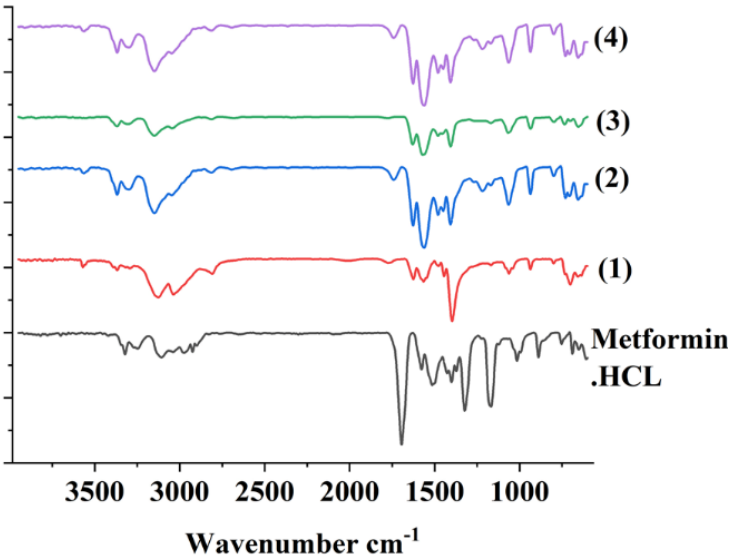

Fig.1. IR spectra of Complexes (**1-4**)

Table 4: Electronic spectral bands (nm) of the Metformin HCl chelates.

Ligand/Complex	λ/nm Transitions			
	π-π*	n-π*	f-f	Assignment of f-f transition
Metf.HCl	228 262 284	375		
(1)	230 262 270	326 332 338	522	$^3H_4 \rightarrow {}^3P_0$
(2)	210 218 245	318 324 337 345	452 476 491 598	$^3P_2 \rightarrow {}^3H_4$ $^3P_2 \rightarrow {}^3P_1$ $^3P_2 \rightarrow {}^3P_0$ $^3P_2 \rightarrow {}^1D_2$
(3)	229 233 245	326 339 354	429 454 478 751	$^6H_{15/2} \rightarrow {}^4G_{5/2}$ $^6H_{15/2} \rightarrow {}^4I_{15/2}$ $^6H_{15/2} \rightarrow {}^4F_{9/2}$ $^6H_{15/2} \rightarrow {}^6F_{3/2}$
(4)	212 220 246	320 323 347	469 530	$^7F_0 \rightarrow {}^5D_1$ $^7F_0 \rightarrow {}^5D_2$

IV. Conclusions

Based on LC-MS, elemental analysis, conductivity, thermal, spectral studies, it is established that metfHCl acts as a N,N-bidentate ligand and metal to ligand ratio is 1:3. The proposed structure is given in Figure 2. The screening of metfHCl and its lanthanide chelates for antimicrobial activities against E.coli, S.aureus, P.aeroginosa are in progress.

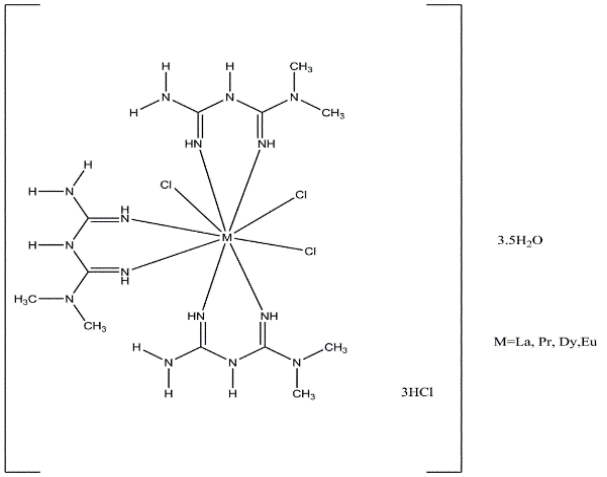

Fig.2 Proposed structure of Metformin HCl chelates of La(III), Pr(III), Dy(III) and Eu(III)

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