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Synthesis, Characterization and Hypoglycemic Activity of Metal Metformin Complexes

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Abstract:

The present study describes the synthesis, characterization, anti-diabetic actions of the Co (II), Ni (II), Cu (II) complexes of metformin hydrochloride. The structure of the complexes were investigated by elemental analysis and infrared spectral studies. These metal complexes are evaluated for their hypoglycemic activities in alloxan induced diabetic rabbits. Metal complexes have shown significant increase in hypoglycemic activity when compared to pure drug. The study of metal complexes is of special interest, owing to their enhanced biological activities.

Key Words: Metformin hydrochloride, anti-diabetic activity, Complexes of Co (II), Ni (II), Cu (II).

1. Introduction:

People focused on metformin in the late 1940s after several reports that it could reduce blood sugar level in human being. In 1957, French physician Jean Sterne published the first clinical trial of metformin as a treatment for diabetes. Metformin is now believed to be most widely prescribed anti diabetic drug in the world. Sterne was the first to try metformin on humans for the treatment of diabetes .He invented the name Glucophage (Glucose eater)for the drug and published his results in 1957.Metfrmin became available in the British National Pharmacy in 1958. Metformin has also been reported to decrease the blood levels of thyroid – stimulating hormone in patients with hypothyroidism.

Metformin hydrochloride is a biguanide; a group of compounds which have great importance in clinical applications [1]. Metformin can produce a hypoglycaemic effect after total pancreatectomy and in complete absence of insulin [2]. Metformin lowers the blood sugar level to the minimum physiological limit and destroys malarial

parasites by attraction. It is used as an antidiabetic, antimaiarial and analgesic [3]. On the other hand, the biguanides are specific antimetabolites for microorganisms that inhibit folic acid metabolism [4].The antihyperglycemic biguanide metformin has been used extensively in the treatment of type 2 diabetes, The work related to biguanides and their metal complexes are very few [5, 6]. Metallopharmaceutical compounds containing vanadium and zinc ions are used to treat both types of diabetes mellitus (DM), by making effective use of the metals.[7]The complexes of V(V/IV), Cr(III), Mo(VI), W(VI), Zn(II), Cu(II), and Mn(III) used as potential oral drugs against type 2 diabetes[8].A comparison study of anti-hyperglycemic effect amongst vanadium, molybdenum and other metal maltol complexes has been done by Thompson et.al[9]. Biguanide derivatives such as 1,1-dimethyl biguanide (metformin), phenylethyl biguanide (phenformin), *N*-(4-chlorophenyl)-*N′*-(isopropyl)-imidodicarbonimidic diamide (proguanil) were used as antihyperglycemic and antimalarial drugs[10] .

The aim of our work was to synthesize the complexes of Co(II); Ni(II), Cu(II) ions with metformin hydrochloride and to characterize them by elemental analysis, IR, electronic, ^{1}H- NMR and mass spectra, in order to throw more light on their structure and geometry. Metal complexes preparation has been the focus because of enhanced biological activities of the corresponding drug-metal complexes in comparison to the pure drug. Biguanide-metal interactions are stabilized by extensive p-electron delocalization. A comparative study of hypoglycemic activity of metal metformin complexes with pure drug has been reported.

2. Experimental:

2.1 Preparation of Complexes:

The complexes were prepared by mixing aqueous solution of metformin hydrochloride (0.01 mol,1.659g) with metal chloride (M= Ni(II), Co(II),Cu(II) (0.005 mol).The reaction mixture was stirred for few minutes and 5 ml 0f 2(M) NaOH solution was added to it. Then it was refluxed for one hour. Colored precipitates were formed on cooling. Filtered, washed with water and recrystallized from ethanol. The resulting Ni- complex was yellow, Cu-complex was pink and Co-complex was reddish orange.

2.2 Structure of the Complexes:

On the basis of analytical data obtained (Table 1),the prepared complexes were formulated as $[M_2(L)_4]$ where M = Co(II), Ni(II), Cu(II).The mode of bonding between metformin and metal ions was deduced from the results of the following investigations.

(a) On comparing the IR spectra of the solid complexes with that of metformin, the following conclusion can be drawn.

(i) The two bands located at 3393, 3273 cm^{-1} due to the V(NH) of primary and secondary amines in positions I and III suffer obvious shifts to lower frequency by 30-50 cm^{-1}'on complex formation.

(ii) One of the two bands due to the imino groups located at 3497 and 3273 cm^{-1} disappears on complex formation, probably the one present at position II, which indicates that metformin is bonded to the metal ion through proton displacement to one NH group. The other imino group, probably that present at position IV, displays an obvious shift to lower frequency by 15-20 cm-1 on complex formation.
(iii) The two new bands observed at 1609-1623 and 374-367 cm^{-1}(Table 2) for all solid complexes, which are not present in the spectra of the free ligand ,are assigned to v(C=N) and v(M-N), respectively.
(b) The absorbance spectra of the complexes under under investigation exhibit a broad maximum with λ_{max},, at 805, 760, 740 nm for Co(H), Ni(II),Cu(II) complexes respectively.

Table-1:Analytical data for Co (II), Ni (II) and Cu (II)-Metformin Complexes.

Complex	$[Co_2 (L)4]$	$[Ni_2 (L)4]$	$[Cu_2 (L)4]$
Analytical Data (%)			
C	30.28 (30.1)	30.57 (30.2)	29.85 (29.80)
H	6.98 (6.0)	6.36 (6.10)	6.88 (5.9)
N	44.14 (44.1)	44.59 (44.20)	43.51 (43.5)
M	18.57 (18.2)	18.51 (18.0)	19.74 (19.4)
Mass	634.53	634.04	643.75

Table-2: IR and UV data for Co (II), Ni (II) and Cu (II)-Metformin Complexes.

IR (cm^{-1})	$[Co_2 (L)4]$	$[Ni_2 (L)4]$	$[Cu_2 (L)4]$	L
νNH_{III}	3206	3217	3230	3273
νNH_{I}	3339	3342	3344	3393
νNH_{II}	3410	3457	3459	3497
ν C=N	1623	1609	1610	1658
ν M-N	374	368	367	
Electronic (nm)	805	760	740	

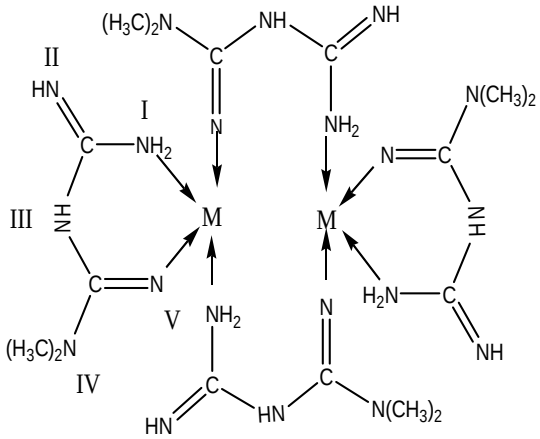

Fig 1:Proposed structure of M-metformin complexes.

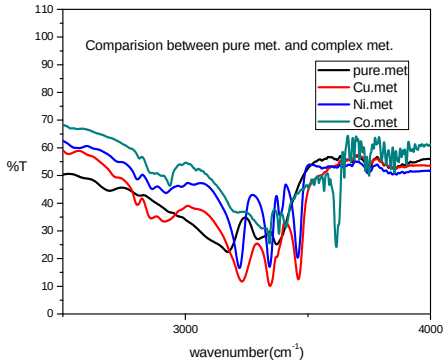

Fig 2: I R Spectra of Pure Metformin and M-metformin complexes.

3. Study of Anti-diabetic activity:

3.1Animals:

The healthy Wistar albino rats, weighing 150-200 g body weight of either sex were selected and housed in acrylic cages in standard laboratory conditions and were fed standard rodent diet with water *ad libitum.* The experiments on animals were conducted in accordance with the experimental protocol duly approved by the Institutional Ethical Committee of the School of Pharmaceutical sciences, Siksha O' Anusandhan University, Bhubaneswar, Orissa with registration no IAEC 1171/C/08/CPCSEA.

3.2 Study on alloxan induced diabetic animals:

The acclimatized animals were kept fasting for 24 h with water ad libitum and injected intraperitoneally a dose of 140 mg/kg of alloxan monohydrate in normal saline. After 1 h the animals were provided feed *ad libitum.*The blood glucose level was checked before alloxanisation and 24h after alloxanisation as above.Animals were considered diabetic when blood glucose level was raised beyond 200 mg/100 ml of blood.This condition was observed at the end of 72 h after alloxanisation.The animals were segregated into five groups of six rats each.Group I served as solvent control and received only vehicle (2 ml/Kg)through oral route.Group II received Metformine (100 Mg/Kg), Group III, IV and V received the test drugs at doses of 100 Mg/Kg in a similar manner. Blood glucose level of each rat was measured at 1, 2, 4 and 6^{th} hour after the administration of the drug.

3.3 Screening for antidiabetic activity:

The Screening for antidiabetic activity was conducted as per the method described by Dash et al. The test samples were suspended in Tween 20 in distilled water.Metformine (100mg/kg) was used as reference control during the study.All the test samples were administered through oral route.

Table-3:Anti-diabetic activity of some synthetic metal complexes with metformine, in single dose treated alloxan induced hyperglycemic rats by oral routes.

Groups & Treatment	Blood Glucose Levels (mg/dI)					
	0h	1h	2h	4h	6h	%age decrease At the end of 6hrs
I.Solvent Control (Tween+ Water)	323.46±3.01	332.5±5.23	348.5±3.85*	356.16±4.23*	352.33±8.06*	-------
II. Metformine (100mg/kg)	332.66±6.63	225.16±4.42*	176.16±4.72*	114.33±6.31*	105.83±6.72*	68.18
III.Ni-Metformine (100 mg/kg)	347.76±4.15	247.16±3.66*	223.83±6.21*	210.66±7.43*	161.33±7.66*	53.60
IV.Co-Metformine (100 mg/kg)	269.73±5.18	254.33±6.19*	121.83±7.41*	92.83±6.26*	75.83±9.39*	72.11
V.Cu-Metformine (100 mg/kg)	206.32±4.67	132.47±3.87*	121.63±6.59*	107.93±5.28*	86.66±8.81*	57.99*

Values are expressed in MEAN ± S.E.M of six animals. * P< 0.00

4. Results and Discussion:

- Metal complexes and the standard drug metformin shows decrease of blood glucose lebel to a significant extent. (P<0.001) at different interval of time till the end of 6h in single dose, treated alloxan induced hyper glycemic in rats.
- However at the end of 6h of study the test compound, % decrease of blood glucose is calculated as **68.18, 53.6, 72.1, 57.99** in respect of Met, Ni, Co and Cu.
- The mtformin complex with Co has max potency to reduce the blood glucose in hyper glycemic animals which may be due to the presence of Co.
- The enhanced effect envisaged to be due to the structural impacts of the complexes, however, more investigation is required to establish structure-function correlation.

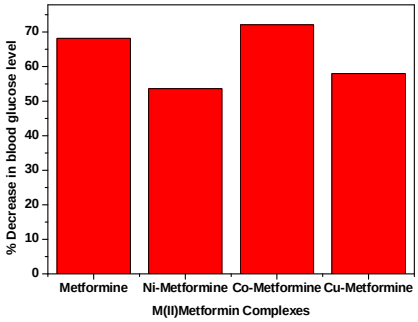

Fig 3: % Decrease in blood glucose level at the end of 6 h.

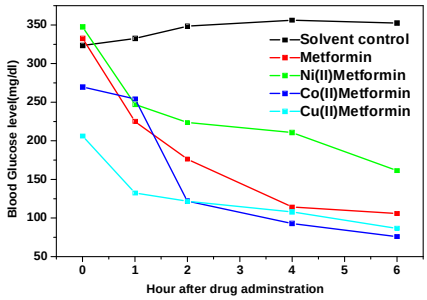

Fig-4: Decrease of blood glucose level after drug administration.

5. Acknowledgement:

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