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Role of chromium complexes in pharmaceutical industries

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Abstract : Chromium has an atomic weight of 51.996. The element may occur in compounds in di-, tri-, or hexavalent forms. Hexavalent chromium is the highest oxidation state of elemental chromium. Trivalent chromium is the most stable oxidation state for chromium, and it is this form that is found in common nutritional supplements, generally as the picolinate. Chromium supplementation has been studied for a variety of indications, especially diabetes and weight loss, but clinical studies have shown inconsistent results. To date, no chromium-containing biomolecules have been definitively described, and no clinical manifestation of trivalent chromium deficiency in humans has been established. The argument for chromium supplementation relies on evidence from case reports of resolution of diabetic symptoms refractory to insulin via chromium added to total parenteral nutrition, and experiments in which animals deficient in chromium exhibited impaired glucose metabolism. The chromium hydrochloride complex as a diabetic drug model was synthesized by the chemical reaction between chromium (III) chloride hexahydrateand metforminHCl (Mfn.HCl) in methanol solvent (III) metformin.

Keywords : Metformin hydrochloride, Chromium(III) complex, Anti-diabetic activity, Spectroscopic

INTRODUCTION

General uses-Chromium supplementation has been studied for a variety of indications, especially diabetes and weight loss, but clinical studies have shown inconsistent results. The role of supplemental chromium remains controversial.

The $[Cr(Mfn\text{-}HCl)_2(Cl)_2].Cl.6H_2O$ complex was characterized using micro analytical measurements, molar conductance, spectroscopic (infrared, and UV-vis.), effective magnetic moment, and thermal analyses. The infrared spectroscopic data in the comparison between free Mfn.HCl ligand and its chromium (III) complex proved that metformin hydrochloride react with chromium (III) ions as a bidentate ligand through its two amino groups. The anti-diabetic activities of the Mfn. HCl drug, chromium salt and Cr (III)-2Mfn.HCl complex were discussed on the male rats. The chromium (III) metformin HCl complex was recorded successful efficiency in the decreasing blood glucose level and HbA1C against diabetic rats. The Cr(III)-2Mfn.HCl complex has succeeded to great extent as antidaibetic drug with enhanced the antioxidant defense system as well as act as pronounced efficient hypoglycaemic agent compared to metformin HCl free drug.

Metformin hydrochloride (Mfn.HCl) structure was referred in Figure 1. Diabetes is a metabolic syndrome which was characterized by hyperglycemia and glycosuria resulting from the defect in the secretion or the action of insulin, or both of them[1,2]. Some metal complexes or organo-metallic compounds have been used in medicine for centuries. Supplement contains trivalent chromium was needed for a person with type 2 diabetes mellitus, according to its important role in glucose metabolism[3].

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The Cr (III) metal ion interacts with the insulin and its receptors on the first step in the metabolism of glucose entry into the cell, and facilitates the interaction of insulin with its receptor on the cell surface[4,5]. Chromium increases insulin binding to cells, insulin receptor number as well as activates insulin receptor kinase leading to increase sensitivity of insulin receptor. Additional studies were urgently needed to elucidate the mechanism of the action of chromium and its role in the prevention and control of diabetes[6]. Metformin, the most common prescribed oral medication in type 2 diabetes, lowers HbA1c around 1.5%, rarely causes hypoglycemia (compared with insulin or sulfonylureas), has relatively few contraindications, its adverse effects are generally tolerable, did not cause weight gain, was cheap, and was highly acceptable among patients[7]. Metformin exerts it was main antihyperglycemic effects through activation of AMP-activated protein kinase, resulting in reduced hepaticgluconeogenesis[8]. In addition, moderate improvements in lipid profile and weight reduction have been reported with metformin use[8]. Herein, this paper reports the synthesis, characterization and chromium (III) metformin complex as a prospective antidiabetic candidate.

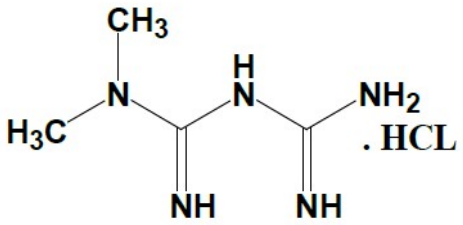

Figure 1: Structure of metformin hydrochloride ligand.

The of metformin hydrochloride drug ligand (2 mmol, 0.332 g) was dissolved in 25 mL methanol then mixed with 25 ml of methanolic solution of (1 mmol, 0.267 g) CrCl3.6H2O. A mixture of molar ratio of 1:2 was heated at ~80°C under reflux for about 3 hours. The mixture was left overnight at room temperature until precipitated. The precipitate obtained was filtered off and washed by diethyl ether then left over anhydrous calcium chloride. The yield of the solid leaf green colour powder product was about ~ 85%. The formula weight of chromium(III) complex is $C_8H_{36}C_{l5}CrN_{10}O_6$, molecular weight is 597.74 g mol^{-1}, and the microanalytical data of theoretical and experimental are as follows: theoretical=%C, 16.06; %H, 6.0 Effect on lipid profile.

Induction of hyperglycaemia: Hyperglycemia was induced by a single i.p. injection of STZ (50 mg/kg)[9]. Briefly, rats were weighed and injected with STZ dissolved in a citrate buffer (0.1 M, pH 4.5). After 72 h blood samples were withdrawn from the retroorbital venous plexus under light ether anesthesia and the plasma was separated by centrifugation for the determination of glucose level. The treatment was carried out for 30 days after 72 h from STZ injection. Only rats with plasma glucose levels more than 230 mg/dl were selected and considered as hyperglycemic animals that have been subjected to further experimentation. At 7 days post-induction of hyperglycemia, blood glucose was assayed by the glucose oxidase method, using a glucometer. The animals were carefully monitored every day and weighed every week during the experiment.

Collection of blood and organs: Blood samples of the fasted rats were collected from the medial retro-orbital venous plexus immediately with capillary tubes (Micro Haematocrit Capillaries, Mucaps)[10]. About 9 mL of blood collected in two tubes from each animal, one with EDTA for obtaining plasma, the second was allowed to clot for 30 min. Then, the blood in two tubes was centrifuged at 3,000 rpm for 15 min to separate serum and plasma for different biochemical analyses.

Effect on cholesterol: Table 1 demonstrates that diabetic untreated rats (STZ) afforded a significant increase in cholesterol level as compared to normal control group while treatment of diabetic rats with Metformin/ Cr^{+3} elicited non-significant changes in cholesterol level when compared with normal control group while other diabetic group treated with Metformin afforded significant elevation in cholesterol when compared with normal control group while both groups treated with either Metformin or Metformin/Cr^{+3} showed significant decrease in cholesterol level when compared with diabetic untreated group but the effect was more intense in diabetic group treated with Metformin/Cr^{+3}. The non-significant increase in cholesterol level was reported in group treated with $CrCl_3.H_2O$ treated group as compared to normal control group.

Table 1

Groups	Cholesterol (mg/dl)	Triglycerides (mg/dl)	HDL-c (g/dl)	LDLc (g/dl)	VLDLc (g/dl)
1st	73.22±5.78^{d}	90.23±4.23^{d}	38.52±2.88^{a}	28.63±9.95^{d}	18.04±2.96^{c}
2nd	269.32±11.03^{a}	220.75±10.66^{a}	5.45±2.45^{e}	58.63±7.09^{a}	44.15±3.41^{a}
3rd	97.36±6.54^{b}	119.48±4.23^{b}	24.44±1.32^{d}	39.52±2.49^{b}	23.89±2.85^{b}
4th	74.25±1.72^{d}	94.15±5.44c^{d}	32.36±3.98^{b}	29.75±4.60^{cd}	18.83±1.95^{c}
5th	76.25±3.20c^{d}	93.20±2.10c^{d}	31.25±1.20^{c}	28.50±3.54^{d}	18.64±1.20^{c}

Effect on insulin level: Concerning the effect of Metformin and their Cr^{+3} complexes on insulin level, the results revealed that administration of Metformin/ Cr^{+3} complexes afforded non-significant increase in insulin level as compared to normal control group while of STZ only to rats elicited significant decrease in insulin level when compared to normal control group. The other diabetic treated group with Metformin elicited significant decrease in insulin level by 60 % as compared to normal control group as shown in **table 2**. There is no significant change reported in group treated with chromium salt treated group. The Cr(III) interact with the insulin and its receptors on the first step in the metabolism of glucose entry into the cell, and facilitates the interaction of insulin with its receptor on the cell surface[5] and thus our results come in harmony with these findings as the combination of Metformin with Cr^{+3} increased the level of insulin in diabetic rats and the best results was shown in diabetic group treated with Metformin/Cr^{+3} as they showed the high value of insulin level by 1.76 % as compared to normal control group and by 65.11% increment as compared to diabetic untreated group and this go side by side in confirming our results that reported the success of Cr^{+3} complexes with Metformin in reducing blood glucose level and increasing insulin level and thus alleviating the side effects of diabetes mellitus and improving characterization of Metformin/ Cr^{+3} .So we consider the first author to clarify this improving effect of Metformin/Cr^{+3} on diabetes mellitus reducing complications. Chromium increases insulin binding to cells, insulin receptor number as well as activates insulin receptor kinase leading to increase sensitivity of insulin receptor[6].

Table 2

Groups	Insulin (µU/ml) in pancreatic homogenates	Serum C-peptide (pmol/mL)
1st	17.52±1.05a^{b}	3.87±1.01^{ab}
2nd	6.22±0.53^{e}	1.12±1.03^{d}
3rd	12.43±1.51^{d}	2.44±1.25^{c}
4th	15.55±1.87^{c}	3.85±1.34^{b}
5th	16.99±0.96b^{c}	3.45±1.10^{b}

CONCLUSION

The chemical interaction between chromium (III) chloride hexahydrate and metformin HCl (Mfn.HCl) produce diabetic mimetic model of chromium (III) metformin hydrochloride. The infrared spectroscopic results were proven that metformin hydrochloride reacted with chromium (III) ions as a bidentate ligand through its two amino groups. The chromium (III) Metformin complex has succeeded in decreasing blood glucose parameters in diabetic rats and proving its antidiabetic performance and thus proving the efficiency of metformin and Chromium (III) complex in elevating antioxidant capacities.

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