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Polarograpy of Zn (II)-Tolbutamide complex and its Pharmacological Study

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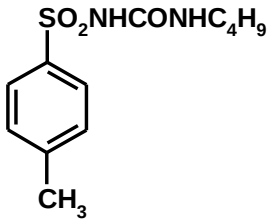
ABSTRACT

The formation of complexes of tolbutamide and Zn(II) was studied in aqueous media at pH 3.4±0.1 by polarography and spectroscopy. The polarogram indicated formation of complexes between tolbutamide and Zn(II). Tolbutamide produces a well-defined direct current polarogram and differential pulse polarogram in 1M KCl (supporting electrolyte) at pH 3.4±0.1. The stoichiometry of the Zn(II)-tolbutamide complex is 1:1. Antidiabetic studies on the drug and its metal complex have been performed in albino mice. Revealing the complex to be more potent in antidiabetic activity compared to the parent drug.

Introduction

Anti-diabetic drugs treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, and pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral antihyperglycemic agents. Sulfonylureas were discovered by the chemist Marcel Janbon and co-workers,[1] who were studying sulfonamide antibiotics and discovered that the compound sulfonylurea induced hypoglycemia in animals.(2) Research has shown the Maitake mushroom (*Grifola frondosa*) has a hypoglycemic effect, and may be beneficial for the management of diabetes.[3-7] The reason Maitake lowers blood sugar is due to the fact the mushroom naturally acts as an alpha glucosidase inhibitor. Other mushrooms like Reishi,[8,9] *Agaricus blazei*,[10-13] *Agrocybe cylindracea*[14] and *Cordyceps*[15-19] have been reported to lower blood sugar levels to a certain extent, although the mechanism is currently unknown Walnut leaf can significantly reduce fasting blood glucose levels in rats with alloxan-induced diabetes, and rats thus treates show some evidence of regeneration of the beta cells.[20] Garlic also significantly reduces fasting blood glucose levels in rats with alloxan-induced diabetes.[21] Tolbutamide $C_{12}H_{18}N_2O_3S$, is a first generation potassium channel blocker, sulfonylurea oral hypoglycemic drug [22]. It is a white crystalline substance, used to augment insulin secretion in the treatment of diabetes mellitus [23, 24].This drug may be used in the management of type II diabetes if diet alone is not effective. Tolbutamide stimulates the secretion of insulin by the pancreas [25]. Since the pancreas must synthesize insulin in order for this drug to work, it is not effective in the management of type Ist diabetes. It is not routinely used due to a higher incidence of adverse effects compared to newer second generation sulfonylureas [26], such as glyburide.



Tolbutamide

Experimental

All the chemical used were of Sigma Aldrich/BDH/CDH grade. Double distilled water was used to prepare all the solutions. Stock solution of 1M KCl and .01M Tolbutamide was prepared in double distilled water and ethanol (3:2 v/v).

Experimental sets were prepared by keeping overall metal ion and supporting electrolyte (Potassium Chloride) concentrations fixed at 1.0mM and 1.0M respectively. The pH value of experimental sets was adjusted to 3.4 ±0.1, using dil. HCl and sodium Hydroxide solution. The authentic sample solution of tolbutamide was of Sigma Aldrich laboratories chemical grade. Experimental set for the polarographic analysis of tolbutamide was prepared by taking (0.01M)1ml of sample solution and 10ml (1M) of KCl as supporting electrolyte in a polarographic cell and the total volume was made is 50ml with distilled water. The pH of the test solution was adjusted to 3.4±0.1.

Table-Formation Constant of Tolbutamide complexes

Complex	Stoichiometry	Formation Constant log β_1
Zn-(II)- Tolbutamide	1:1	3.7

Pharmacological Experiments

The pharmacological data in the table shows that the initial blood sugar level is 220 mg/dl (after alloxan treatment) which on administration of the tolbutamide drug and its complex show a decrease with time.

The table shows that Zn(II)-tolbutamide complex is most effective of the complexes under study in bringing down the blood glucose level from 220 mg/dl to 82 mg/dl. Though, the

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complexes of tolbutamide under study are seen to be antidiabetic agents but Zn(II)-tolbutamide complex has been seen to be less effective in bringing down the glucose level as compared to the tolbutamide.

Polarogram of Zn(II)- Tolbutamide

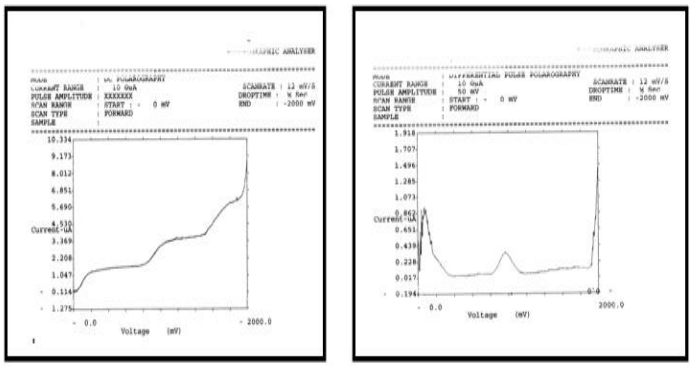

Fig Direct current Polarogram and Differential pulse polarogram of Zn(II)- tolbutamide complex in KCl (0.2M) at pH 3.4±0.1.

Plot of $E_{1/2}$ vs log Cx

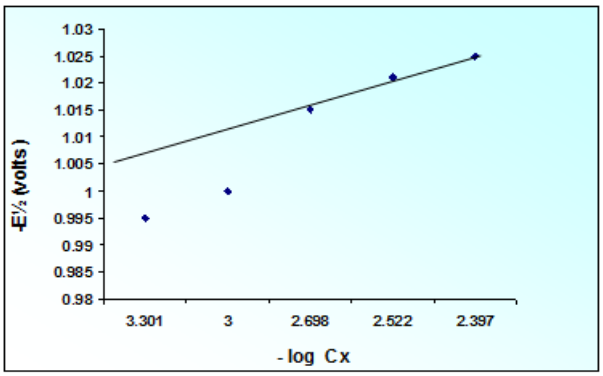

Fig. - Zn(II)- Tolbutamide Complex system

Results and Discussion

Tolbutamide and its complexes gave well-defined cathodic reduction wave at pH = 3.4±0.02 in 0.2M KCl. The plots of i_d vs $\sqrt{h_{corr}}$ yielded straight lines in each case, passing through the origin confirming the diffusion controlled nature of the reduction process.

Effect of ligand concentration:-

On increasing the ligand concentration in each set and subjecting these experimental sets to polarography. It was observed that the half wave potential shifted to more electronegative value. The plot of change in half wave potential with logarithm of change in ligand concentration yielded a straight line, suggesting the formation of single complex specie in case of Zn(II)-Tolbutamide system.

IR spectral analysis of Fe(II)-Tolbutamide Complex

On comparison of the IR spectra of tolbutamide and its complex with titled metal. It was observe that the bands at 3260 cm^{-1} to 3260 cm^{-1} which were observed in the spectrum of the drug have either completely disappeared or have shifted to a lower frequency side in case of Zn(II) complex beside two new bands have appeared at 3510 cm^{-1} and 3360 cm^{-1} group in the spectrum of Zn(II)-tolbutamide complex indicating the involvement of –NH nitrogen in the complex formation, which is also confirmed by the shifting of band due to amide group at 1660cm^{-1} in the spectrum of pure drug to 1700cm^{-1} in the spectra of Zn(II) complex respectively.

The analytical data of tolbutamide complexes under study and the results of the polarographic study suggest metal to tolbutamide ratio of 1:1. Thus a tentative structure to the metal: Ligand complex may be given as under.

Amount of Tolbutamide and its complex (Zn(II)-tolbutamide), which were given orally to albino rats = 0.036gm/100 gm

Conclusion

The data show stoichiometric ratio of 1:1 for the Zn(II) Tolbutamide complex. The polarographic method is used for qualitative and quantitative analysis of tolbutamide and is recommended for quality control in the drug industry. The increased potency of the complex may allow use as a potent antidiabetic drug.

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Table- Polarographic data on Zn(II)–Tolbutamide complex system Zn(II)=1.0 mM, 0.2 M KCl supporting electrolyte pH= 3.4±0.1,

Concentration of ligand	log Cx	$E_{1/2}$
0.0000	-	-0.99
0.0005	-3.301	-0.995
0.0010	-3.000	-1.0
0.0020	-2.698	-1.015
0.0030	-2.522	-1.021
0.0040	-2.397	-1.025

Table- Blood Glucose levels of diabetic albino rats after administration of Tolbutamide and its Zn(II) complexes

S. No.	Time interval (hrs.)	Initial blood glucose level (mg/dl)	Parent drug blood glucose level (mg/dl)	Zn(II)-Tolbutamide Complex with blood glucose level (mg/dl)
1.	0	220	220	220
2.	2	-	210	201
3.	4	-	190	174
4.	6	-	140	122
5.	8	-	136	104
6.	10	-	101	90
7.	12	-	96	84
8.	14	-	-	82

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