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Spectrophotometric Study of Stability Constants and Thermodynamic Parameters of Metformin-Mn(II) complex at Different Temperatures

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Abstract

Metformin is an oral antidiabetic drug in the biguanide class. It is the first-line drug of choice for the treatment of type 2 diabetes, in particular, in overweight and obese people and those with normal kidney function.Metformin has functional groups that enable it to act as a chelating agent. Stability constants and thermodynamic parameters of metformin-Mn complex have been determined by Job's method of continuous variation at different temperatures. At temperatures of 25^{o}C and 40^{o}C, the Job's curves displayed a maximum at a mole fraction χ_{Mn} = 0.78 and 0.79 respectively, indicating the formation of complex with I:4 metal to ligand ratio.The values of the stability constants at 25^{o}C and 40^{o}C were 4.35 x 10^3 and 5.04 x 10^3 respectively. Gibbs free energy, standard enthalpy change and standard entropy change at 25^{o}C and 40^{o}C were -2.07 x 10^4 kJ/mol, -2.22 x 10^4 kJ/mol, -52.57 kJ, -52.57kJ, 69.82 kJ/K and 71.03 kJ/K respectively. These values suggested that the formation of metformin-Mn complex was Spontaneous.

Keywords: Stability constant, metformin, complex, manganese.

1. Introduction

The global stability constant of complexes and stoichiometry metal:ligand ratio are frequently estimated spectrophotometrically using a wide selection of traditional methods such as continouus variation method[1] and mole ratio method[2]. Metformin, is an oral antidiabetic medication . It is one of the best drug of choice for the treatment of type 2 diabetes, for patient who are overweight and obese with normal kidney function [3 - 5]. Metformin reduces glucose production in the liver [6]. Report suggests metformin may prevent cancerious complications and cardiovascular diseases associated with diabetes [7 - 9]. Metformin promotes weight loss and helps in the reduction of LDL cholesterol and triglyceride[7,8]. It is one of the World Health Organization Model List of Essential Medicines for the treatment of diabetics [10]. In the United States alone, over 48 million prescriptions were reported to have taken metformin in 2010 [11]. It is believe to be the most widely prescribed antidiabetic drug in the world [11]

Manganese is a mineral naturally occurring in our bodies in very small amounts. Manganese is an actual component of manganese super oxide dismutase enzyme[12]. It is a powerful antioxidant that seeks out the free radicals in the human body and neutralizes these damaging particles, thereby preventing many of the potential dangers they cause[12]. Some of the health benefits of manganese include a benefit to healthy bone structure, bone metabolism, and helping to create essential enzymes for building bones[12]. It also acts as a co-enzyme to assist metabolic activity in the human body[12]. Apart from these, there are other health benefits of manganese including the formation of connective tissues, absorption of calcium, proper functioning of the thyroid gland and sex hormones, regulation of blood sugar level, and metabolism of fats and carbohydrates [12].

We hereby report spectrophotometric study of stability constants and thermodynamic parameters of metformin-Mn(II) complex at different temperatures.

2. Materials and Methods

2.1 Spectrophotometric measurements were performed on a UV-1700 Shimadu beam spectrophotometer (Department of Chemistry, Michael Okpara University of Agriculture Umudike), using matched 10mm quartz cells.Metformin was purchased from Apotox NZ pharmaceuticals, Nigeria. Manganese(II) chloride ($MnCl_2.4H_2O$) and all other chemicals were of analytical grade. They were purchased from (Riedel –Denaen Ag Setlzer Hannover Company Germany). Double distilled water was used throughout this study.

2.2 Preparation of 2 x 10^{-1}M $MnCl_2.4H_2O$

$MnCl_2.4H_2O$ (39.582g, M Wt = 197.91gmol^{-1}) was dissolved in freshly distilled water in a beaker and made up to the mark in a 1000ml volumetric flask.

2.3 Preparation of 2 X 10^{-1}M Metformin

Metformin (25.583g, 129.16gmol^{-1}) was dissolved in freshly distilled water and made up to the mark in a 1000 ml volumetric flask.

2.4 Procedure for Job's Continuous Variation Method [1]

Manganese (II) chloride tetrahydrate solution (2 x 10^{-1}M) (1,2,3,4,5,6,7,8,9ml) were pipetted and transferred into 50ml volumetric flasks and an aliquot (9,8,7,6,5,4,3,2,1 ml) of 2 x 10^{-1}M metformin was added, respectively in such a way that the mole fraction of the solution remains constant. Colour of the solution was changed from milky colour to white. Wavelength of maximum absorbance was noted against a blank, which appeared at 500nm. All the measurement were performed at 500nm at 25°C and 40°C respectively. The pH was maintained at 4.01using buffer solution. By apply continuous variation method, also called Job's method[1], the metal to ligand ratio and stability constant of the complex were determined using equation 1 and 2 [13]. Gibbs free energy, change in enthalpy and entropy were calculated using equations 3, 4 and 5 respectively.

$$X_{Mn} = \frac{X_{Mn}}{1-X_{Mn}} \quad (1)$$

$$K_{St} = \frac{\left[\frac{A_2}{A_1}\right]}{\left[1-\frac{A_2}{A_1}\right]x[C_{met}-C_{Mn}\,x\,A_2/A_1]} \quad (2)$$

Where A_1 is the absorbance at break point, A_2 is the actual absorbance, C_{Mn} is the concentration of manganese while C_{mt} is the concentration of metformin.

$$\Delta G = -RTInK_{St} \quad (3)$$

$$In\left(\frac{K_2}{K_1}\right) = \frac{-\Delta H^{\emptyset}}{R}\left(\frac{1}{T_2}-\frac{1}{T_1}\right) \quad (4)$$

Where K_2 is the stability constant at absolute temperature T_2, K_1 is the stability constant at absolute temperature T_1, $H^{\emptyset}$ is the standard enthalpy change of the reaction and R is the gas constant.

$$\Delta G = \Delta H - T\Delta S \quad (5)$$

3. Results and Discussion

3.1 The structure and prospective view of metformin are shown in Figures 1 and 2. The absorption spectra of metformin-Mn complex and manganese(II) chloride tetrahydrate is presented in Figure 3. Job's continuous variation curve at 25°C and 40°C are presented in Figures 4 and 5 respectively. Calculated values of stability constants and thermodynamic parameters are shown in Table 1.

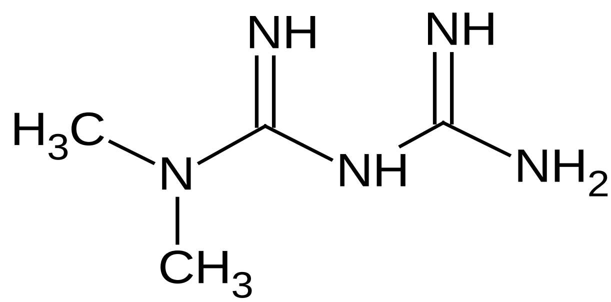

Figure 1: Structure of metformin

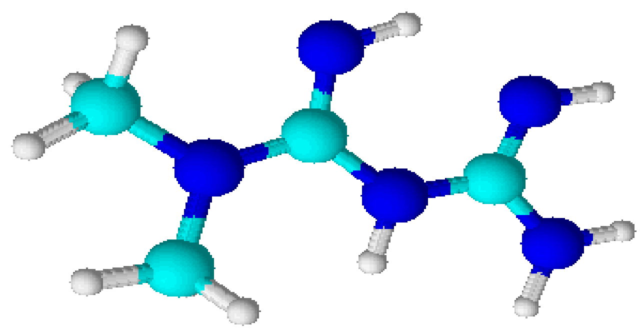

Figure 2: Prospective view of metformin

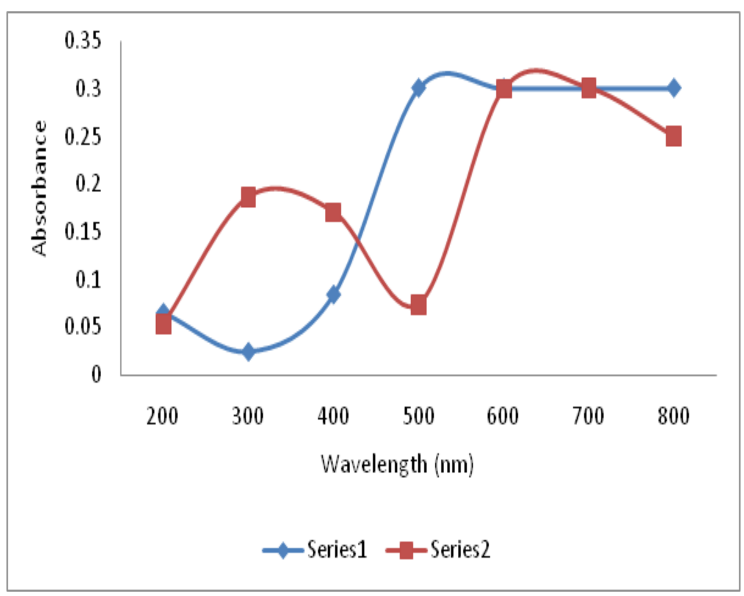

Figure 3: Absorption spectra of metformin-Mn complex (Series 1). Manganese(II)chloride tetrahydrate (Series 2).

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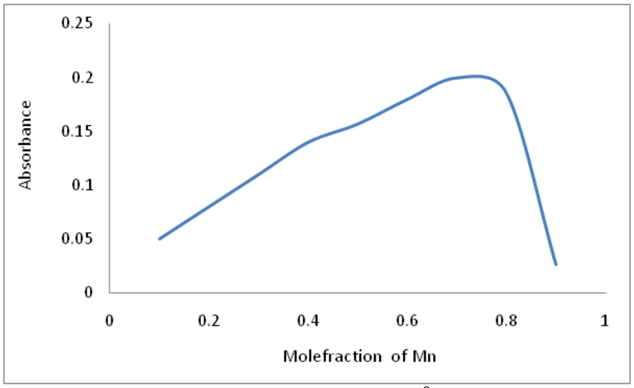

Figure 4: Job's curve at 25^0C

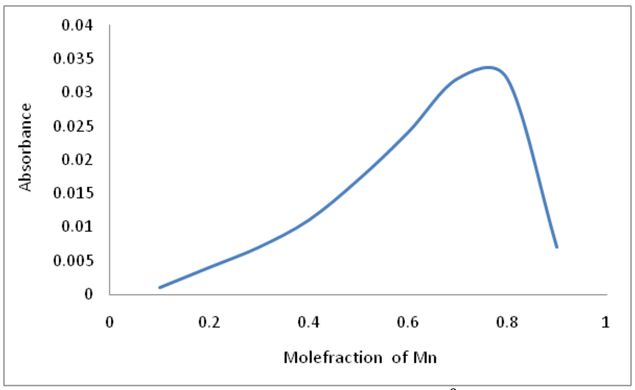

Figure 5: Job's curve at 40^0C

Table 1: Calculated values of stabilty constant and thermodynamic parameters

Temp (K)	pH	M:L atio	K_{St}	ΔG (kJ/mol)	ΔH^{θ} (kJ)	ΔS^{θ} (kJ /K)
298	4.01	1:4	4.35×10^3	-2.07×10^4	-52.57	69.82
313	4.01	1:4	5.04×10^3	-2.22×10^4	-52.57	71.03

M = manganese, L = medtformin

3.2 Properties of the complex

The reaction of metformin with manganese(II)chloride tetrahydrate was investigated at two different temperatures i.e 25^oC and 40^oC. The absorption spectra were recorded over wavelength range of 400-800 nm. It was found that metformin with manganese(II) chloride tetrahydrate formed a white, water soluble complex. The complex gave an absorption maxium at 500nm (Figure 3, Series 1) and was used as λmax for the analytical measurements. Under the same conditions, pure metformin does not absorb significantly over the investigated wavelength range. However manganese(II) chloride tetrahydrate itself absorbs maximally at wavelength of 600 nm (Figure 3, Series 2). In solution, manganese was present as $[Mn(H_2O)]^{2+}$ and showed λmax at 600nm. Water behaves as a weak field ligand so manganese aquo complex acts as a liable complex, which can be easily replaced by metformin, to form a stable complex. (λmax = 500nm).

3.3 The composition of complex and stability constant.

The stochioimetric ratio of metformin to Mn(II) in the complex was determined by Jobs method of equimolar solutions [1]. The curve in Figure 4 and 5 displayed a maximum at a mole fraction, χ_{Mn} = 0.78 – 0.79, which indicates the formation of complex, having 1 : 4 metal to ligand ratio.Calculated values of stability constant, Gibb's free energy, enthalpy change and entropy change have been tabulated in Table 1. Thermodynaic parameters showed that the complex was favorably formed, since $\Delta H < 0$, $\Delta S > 0$ and $\Delta G < 0$.

4. Conclusions

Metformin an antidiabetic drug, formed a reasonably stable complex with Mn^{2+}. The stability constant of Mn(II) -metformin have been determined spectrophotometriclly using continuous variation method. The positive values of the stability constant showed that the complex was favorably formed. The thermodynamic parameters suggested that the complex was formed spontaneously. Owing to a high formation constant , metformin intake can remove Mn(II) ions from the body and this may disturb the formation of enzymes, skeletal deformation in human body and weight loss. Manganese deprivation profoundly impairs the intestinal absorption of iron and thus can cause skeletal deformation.

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