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Research Article

Chemistry for New drug discovery

Comparative Study of Complexation of Midodrine Hydrochloride and Noradrenaline with Ag (I) Metal Ion – A Spectroscopic Method

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Abstract: The aim of this work was to study the stability constants of Midodrine and Noradrenaline with metal ion Ag (I) using the UV /Visible spectrophotometric technique in an aqueous solution. The drug-metal complexes were used to restrict the growth of pathogens and parasites which are injurious to humans. In medicinal inorganic chemistry, transition metal have major role. The binding site of the drug molecule interact with transition metal that exhibit various oxidation states and this activity of transition metals led to the recent development of a new drugs which are based on metals and are considered to be potential candidates for pharmacological and therapeutic applications. In this article we compare metal ligand complex formation of Midodrine Hydrochloride and Noradrenaline with transition metal ion Ag (I). The formed complexes were absorbed maximally at 300nm and 280 nm. The different experimental parameters affecting the development of the colour were carefully analyzed and optimized. The stoichiometry of Midodrine-Ag (I) & Noradrenaline-Ag (I) complexes consists of metal/ligand in 1:1 ratio. The stability constants of the complex were calculated to be 5.72 & 4.34 by Job's continuous method. The order of stability constant (β_n) was found to be Midrodrine-Ag (I) > Noradrenaline-Ag (I). The stability constant data showed the ligand (drugs) are used as antidote or chelating agent for medication. The high concentrations of metal in complexation are toxic for human body. This works focuses on research and development of a new synthetic drug - metal complexes. In the molecular structure of Midodrine and Noradrenaline, nitrogen oxygen atom are chelating to transition metal Ag (I) and used as metallodrug. This analysis encourages further research in this field for future applications. This method can be used for routine analysis of Midodrine hydrochloride formulation and to check the stability of bulk samples. It is important to note that the presence of metal ions in complex biosynthesis may have a significant impact on the therapeutic effects of these biological compounds.

Keywords: Complexation, Spectrophotometric Analysis, Midodrine hydrochloride, Noradrenaline, stability constant.

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1. INTRODUCTION

As drugs have various functional groups which can bind to receptors or enzymes or metal ions present in the body, they can conform to many types of complexes (Figure: 1) and can enhance the activity of drugs. The metal complexes of drugs play an important role in drug action and metabolism[1]. Midodrine (MID) hydrochloride is a vasopressor and a prodrug which is preferably used for the treatment of Symptomatic orthostatic hypotension[2]. Its active metabolite desglymidodrine is an alpha 1-adrenoceptor agonist and exerts its actions via activation of the alpha-adrenergic receptors of the arteriolar and venous vasculature, producing an increase in vascular tone and elevation of blood pressure[3]. Midodrine is 2-amino-*N*-[2-(2, 5-dimethoxyphenyl) hydroxyethyl] acetamide;hydrochloride chemical formula $C_{12}H_{19}ClN_2O_4$.[4]

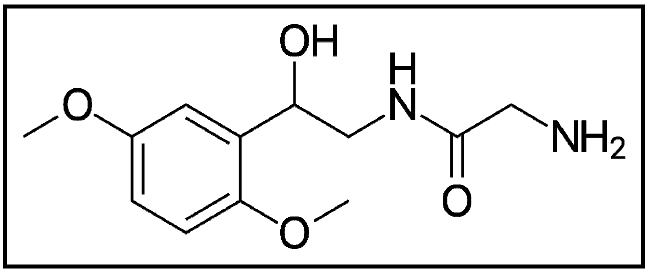

Fig 1 Structure of Midodrine Hydrochloride

Epinephrin Noradrenaline[(2*R*)-2-(3,4-dihydroxyphenyl)-2-hydroxyethyl]azanium , also known as adrenaline(Fig-2).In particular, epinephrine acts on nearly all body tissues and increases heart rate and the force of heart contractions, facilitating blood flow to the muscles and brain. Epinephrine relaxes smooth muscle and helps the conversion of glycogen into glucose in the liver increasing the blood sugar level it also causes acceleration in breathing and as medicine. It is used in treatments for cardiac arrest, asthma, and glaucoma[5]. The objective of this work to analysis complexation of Midodrine & Noradrenaline with Ag (I) metal ion by using UV Visible Spectroscopic method and compare the stability constant of both drugs.

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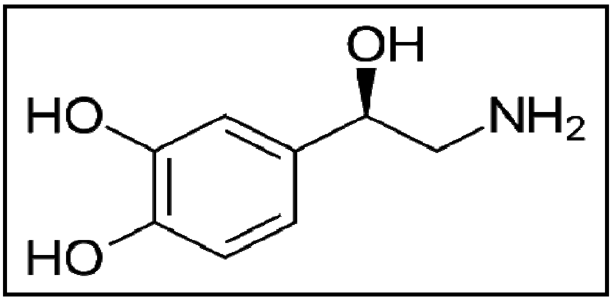

Fig 2 Structure of Norepinephrine

2. MATERIALS AND METHODS

2.1 *Apparatus*

A Systronic UV/Vis double beam spectrophotometer with 1 cm quartz cells was used to measure the absorbance[6]. The pH measurements were made with systronic pH meter model 371 all measurements were performed at room temperature (35 ±0.01°C)[7].

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2.2 *Reagents*

Noradrenaline and Midodrine were obtained from sigma as hydrochloride form and their stock solution (1×10^{-2} M) was prepared by dissolving the accurately weighed amount in glacial acetic acid and the volume was completed to the mark with deionized water. Metal stock solution (0.01 M) was prepared by dissolving appropriate amounts of silver nitrate with deionized water. The phosphate buffer solution are used for varying pH value.

2.3 *Experiment*

A series of solutions containing up to 4.0 ml of buffer solution, 0.5 ml (0.01 M) of the metal ions and 3.5 ml (1 x 10-2 M) of drugs were mixed in 10 ml measuring flask and then diluted up to the mark with water. The mixture was allowed to stand for 10 min[8]. The absorbance was measured at the maximum wavelength (λ_{max}) 300 nm & 280 nm against a blank solution prepared in the same manner but not containing metal ions. The calibration graph was prepared by using the same procedure (at least seven concentration points) and were linear passing through the origin[9]. Stoichiometry of Midodrine and noradrenaline complexes formed in the solution was determined spectrophotometric ally applying the continuous variation[10]. The obtained results revealed the formation of 1:1 (M: L) Midodrine and Noradrenaline complexes with Ag (I) metal ions. The logarithmic constants (log βn) and the free energy changes (ΔG) of the formed complexes was calculated from the data of continuous variation method by applying equations 1 and 2[11].

$$\beta n = A/A_m / 1- [A/A_m]^{n+1} C_1^{\,n} N^2 \quad .... \quad (1)$$
$$\Delta G = -2.303\ RT \log \beta n \quad .... \quad (2)$$

where βn is the stability constant of the metal chelate, A is the absorbance at ligand concentration CL. Am is the absorbance at full color developed, n is the order of the complex formed, T is the absolute temperature and R is the gas constant.

3. RESULTS AND DISCUSSION

In this research work, the biological and pharmaceutical evolution of the Midodrine and Noradrenaline complex with Ag (I) metal ion and stability constant of the complex in different composition were determined by spectroscopic method[12]. The UV Spectral Absorbance of the ligand on complexation with the metal Ag (I), new bands appeared at wavelength 299. Researchers had a significant interest in the utilization of metal complexes as drugs to treat several human diseases [13].Several experimental values were reported for the associated pKa due to the presence of phenolic sites in Noradrenaline and Midodrine. Using the average values, the molar fractions of the acid− base species of Noradrenaline and Midodrine have been estimated. According to the gathered data, it can be concluded that both Adrenaline and Noradrenaline are capable of chelating metal ions, under physiological conditions, yields several complexes[14]. The metal ligand intraction depend on concentration of ligand and pH of the solution. The magnitude of log $_{\beta n}$ values depend on the densities of both ligand and coordination number of metal ions[15].The presence of metal ions in complex biological systems may have a significant impact on the therapeutic effects of these biological compounds[16]. The simple analysis of the stability constants of complexes with the same stoichiometry may not be sufficient alone to make accurate comparisons and speculations about the ability of a ligand[17]. The stability constant of a complex in the solution is usually determined by the knowledge of measurement of equilibrium constants (K) for complex forming reactions. The knowledge of stability constant will be helpful to rationalize understanding of the behaviors of metal chelate in the solution[18]. The stability constant value for complexation of Midodrine and Noradrenaline with Ag (I) metal ion by spectrophotometric method have been presented in (Table: I)

Table I:Spectrophotometric analytical characteristic of Midodrine& Noradrenaline complexes with Ag (I) ion.

Drug name	Metal ion	λ max	M/L Ratio	βn	- ΔG (KJ mol^{-1})
Midodrine	Ag (I)	300 nm	1:1	5.72	4.47
Noradrenaline	Ag (I)	280 nm	1:1	4.34	3.75

Value of β_n is stability constant and – ΔG is negative value of free gibb's energy .that is Midodrine> Noradrenaline, 5.72 > 4.34 when compare.

Midodrine and Noradrenaline complexes exhibits maximum absorption in the UV-Visible region at 300 nm & 280 nm respectively in presence of phosphate buffer. The complexes of this antihyportensive drug with the metal ions indicate the formation of 1:1 complexes. The stability constant for Midodrine Ag (I) and Noradrenaline Ag(I) have been found to be in order Midodrine> Noradrenaline (Figure 3). The negative value of ΔG indicates that complex formation is spontaneous.

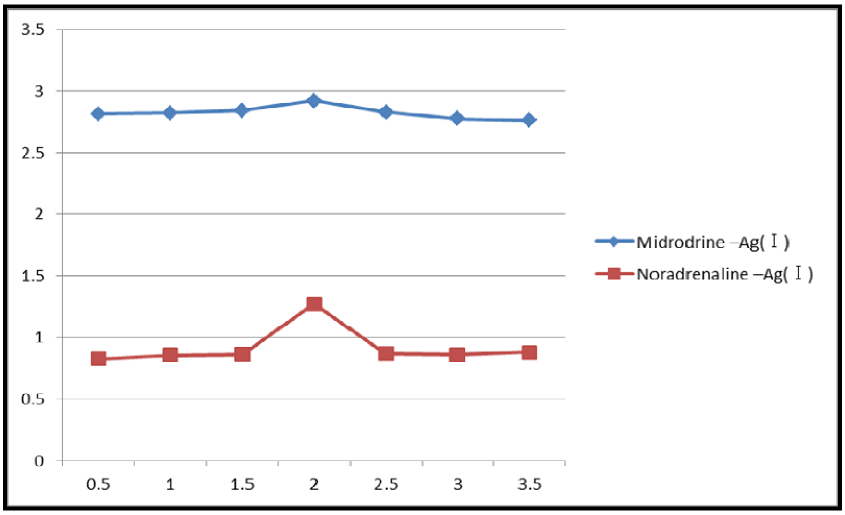

Fig 3 Absorbance vs. Concentration plot for Midodrine -Ag (I) and Noradrenaline-Ag (I) complexes

4. CONCLUSION

The present research work has demonstrated the feasibility of the use of UV-Vis spectroscopy and complexation reaction for determination of Midodrine & Noradrenaline. The determination process is based on the ability of Midodrine & Noradrenaline to form stable 1:1 (M: L) complexes with Ag (I) metal ions. On comparing the stability constant, Midodrine is more stable than Noradrenaline that is 5.72 > 4.34. This U.V. Spectrophotometric method is quite simple, accurate and sensitive. Presence of both drugs can be determined in pharmaceutical preparation and also in biological samples by complexation with metal ions by spectroscopic method. Trace metal ions can be determined by using both drugs separately as a complexing agent.

5. ACKNOWLEDGEMENT

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6. AUTHOR CONTRIBUTION STATEMENT

Dr. Namita Bhardwaj Conceptualized and the supervisedthis study and Miss Jaishri Kaushik performed the experiments and gathered the data for the manuscript. Both authors discussed the final version of the manuscript

7. CONFLICT OF INTEREST

Conflict of interest declare none

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