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ORIGINAL ARTICLE

Spectrophotometric study of stability constants of cimetidine–Ni(II) complex at different temperatures

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Abstract Cimetidine, a histamine H_2-receptor, has a structure which enables it to act as a chelating agent. The formation of nickel(II) complex with cimetidine has been studied spectrophotometrically at an absorption maximum of 622 nm at different temperatures. The data show that nickel(II) and cimetidine combine in the molar ratio of 1:2. The stability constants of the complex were calculated to be $1.40–2.4 \times 10^8$ by continuous variation method and $1.24–2.4 \times 10^8$ by mole ratio method at 25 and 40 °C, respectively. The immediately formed complex shows stability with respect to time and temperature.

1. Introduction

The entire surface of the mammal's stomach is lined by mucus-secreting cells and 80% of which is comprised of gastric glands. These glands form gastric acid by secreting HCl, pepsinogen, intrinsic factor and mucus. Hormones like acetylcholine, gastrin and histamine control gastric acid secretion. Specific receptors present on these secreting cells also activate HCl-secretion. Histamine stimulates the parietal cells to release HCl. Minor amounts of histamine are continuously formed by the gastric mucosa with little production of HCl. Secretions of histamine on parietal cells are H_2-receptors and it is possible to reduce HCl-production by blocking these receptors. The most commonly used H_2-blocker drugs in human and animals are cimetidine, ranitidine, famotidine and nizatadine (Myers, 2006; Tirmizi et al., 2009, 2010).

Metal ions play a vital role in all living systems and any malfunctioning of these ions can initiate a number of physiological abnormalities and symptoms of clinical disorders (Wattoo, 2001). Transition metal ions are responsible for

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proper functioning of different enzymes. Researchers have become increasingly interested in the coordination chemistry of nickel complexes as models for the active sites in nickel-containing enzymes. This is largely due to the discovery of nickel at the centers of many important enzymes. Six nickel enzymes are discovered so for i.e. NiFe hydrogenases, methyl coenzyme M reductase, carbon monoxide dehydrogenase, acetyl coenzyme A synthase and more recently nickel superoxide dismutase (NiSOD). Nickel centers with reversible Ni(II)/Ni(I) and Ni(III)/Ni(II) couples and low Ni(III)/Ni(II) potentials are crucial to the activity of these nickel enzymes. Additionally, there are several proteins required for the delivery and assembly of the nickel ions into the active sites of some of these proteins (Prushan, 2001).

The drug under this study, cimetidine (2-cyano-1-methyl-3-(2-[(5-methyl-1H-imidazol-4-yl)methylthio]ethyl)guanidine), is a histamine H_2-receptor antagonist and is used in the treatment of patients with gastric and duodenal ulcers and other hypersecretory conditions (Hussain and Habib, 2007). Its chelating ability could result due to the presence of two electron-donating nitrogen and sulfur atoms separated by two carbon atoms (Penston and Wormsley, 1986; Naveh et al., 1987). The nitrogen and sulfur atoms of cimetidine can thus form thermodynamically stable saturated five-membered rings by interacting with transition metals (Amigo et al., 1987; Martinez et al., 1991; Crisponi et al., 1995; Onoa et al., 2002). Abadia et al. (1986) and Baran and Proniewicz (1999) reported first cimetidine–Ni(II) complexes. However, to the best of authors knowledge, stability constants of cimetidine–Ni(II) complex at different temperatures have yet not appeared in the literature. These stability constants are useful to study the effects of cimetidine on trace elements and mineral metabolism. It is possible that changes in trace element and mineral concentration induced by cimetidine might be responsible for drug side effects (Velinov et al., 2001; Silverman, 2004). In the present study, spectrophotometric methods were used for the determination of interaction of nickel(II) with cimetidine in acidic medium and stability constants were determined at 25 and 40 °C, respectively. Structure of cimetidine and possible metal chelation is given in Fig. 1.

2. Experimental

2.1. Apparatus

Spectrophotometric measurements were performed on a UV-1700 Shimadzu double beam spectrophotometer (Japan) using matched 10 mm quartz cells. A Horiba F.8 pH meter (Spain), calibrated with standard buffer solutions of pH 4 and 10, was used for pH measurements.

2.2. Reagents

Cimetidine is marketed under the trade name Tagamet®. The pure sample was gifted by Wilson Pharmaceuticals, Pakistan. Nickel chloride hexahydrate and all other chemicals used were of analytical grade purity purchased from Merck Germany. $NiCl_2{\cdot}6H_2O$ was taken in an accurate amount and was not further standardized. Double-distilled water was used throughout this study.

2.3. Preparation of 2×10^{-1} M $NiCl_2{\cdot}6H_2O$

$NiCl_2{\cdot}6H_2O$ (4.76 g, 20 m mol, M. Wt. = 237.7 $gmol^{-1}$) was dissolved in freshly distilled and dry ethanol in a beaker and was made up to the mark in a 100 mL volumetric flask.

2.4. Preparation of 2×10^{-1} M cimetidine

Cimetidine (5.046 g, 20 m mol, M. Wt. = 252.34 g mol^{-1}) was dissolved in freshly distilled and dry ethanol in a beaker and was made up to the mark in a 100 mL volumetric flask.

2.5. Procedure for continuous variation method

Nickel(II) (2×10^{-1} M) chloride hexahydrate solution (0, 1, 2, …, 6 mL) was pippeted out and transferred into seven 50 mL volumetric flasks and an aliquot (6, 5, …, 0 mL) of 2×10^{-1} M cimetidine was added, respectively in such a way that the mole fraction of solution remained constant. Colour of the solution was changed from light green to light blue. Wavelength of maximum absorbance was noted against a blank, which appeared at 622 nm. All the measurements were made at 622 nm at 25 and 40 °C, respectively.

2.6. Procedure for mole ratio method

From 2×10^{-1} M nickel(II) chloride hexahydrate solution, 2 mL was pippeted out and transferred into each of the seven 50 mL volumetric flasks and an aliquot (1, 2, …, 7 mL) of 2×10^{-1} M cimetidine was added to each, respectively. Wavelength of maximum absorbance was noted against blank reagent (nickel(II)chloride hexahydrate), which appeared at 622 nm. All the measurements were made at 622 nm at 25 and 40 °C, respectively.

3. Results and discussion

3.1. The properties of complex

The reaction of cimetidine with nickel(II) chloride hexahydrate was investigated at two different temperatures i.e. 25 and

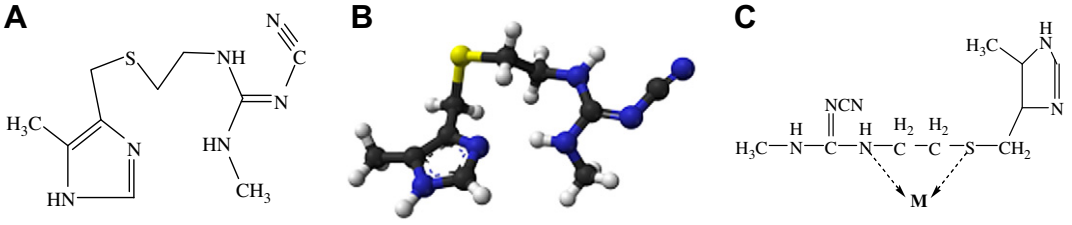

Figure 1 Structure of (A) cimetidine, (B) model drawing and (C) metal chelation with cimetidine.

40 °C. The absorption spectra were recorded over the wavelength range of 400–800 nm. It was found that cimetidine with nickel(II) chloride hexahydrate formed a light blue, water soluble complex. The complex gave an absorption maximum at 622 nm (series 2 Fig. 2), and was used as λ_{max} for the analytical measurements. Under the same conditions, pure cimetidine does not absorb significantly over the investigated wavelength range. However nickel(II) chloride hexahydrate itself absorbs at 722 nm, which is maximum absorbance λ_{max} (series 1 Fig. 2).

In solution, nickel was present as $[Ni(H_2O)_6]^{2+}$ and showed λ_{max} at 722 nm. Water behaves as a weak field ligand so nickel-aquo complex acts as a labile complex, which can be easily replaced by cimetidine, to form a stable complex of stoichiometry ML_2 (λ_{max} = 622 nm). Full colour development was observed immediately and the absorbance remained unchanged. Metal ion binding is not able to change some conformational features of cimetidine, which could be a biologically important factor (Silverman, 2004; Sarwar, 2006).

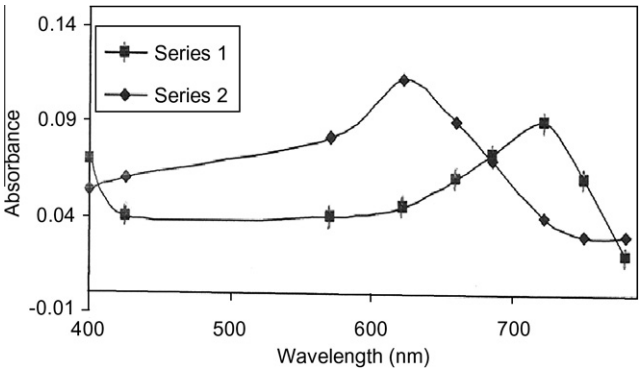

Figure 2 Absorption spectra of nickel(II) chloride hexahydrate (series 1); and complex with cimetidine (series 2). [$C_{(cimetidine)}$ = 2×10^{-1} M, $C_{[Ni(H2O)6]Cl2}$ = 2×10^{-1} M].

3.2. The composition of complex and stability constant

The stochiometric ratio of cimetidine to Ni(II) in the complex was determined by Job's method of equimolar solutions (Sarwar, 2006). Nickel(II) chloride hexahydrate standard solutions 2×10^{-1} M were pippetted into seven volumetric flasks (0, 1, 2, 3, …, 6 mL) and an aliquot of 2×10^{-1} M cimetidine (6, 5, 4, …, 0 mL) was added, respectively keeping the mole ratio constant. All the measurements were made at 622 nm at two different temperatures i.e. 25 and 40 °C (Table 1). The curve in Fig. 3 displayed a maximum at a mole fraction X_{metal} = 0.33–0.37, which indicates the formation of complex having 1:2 metal to ligand ratio.

By applying continuous variation method, also called Job's method, the metal to ligand ratio and the stability constant of the complex have been determined. It requires the series of solutions of varying concentration of two constituents where their sum is kept constant. Difference between the measured absorbance and absorbance is calculated for mixed constituents on the assumption of no reaction between them, is plotted against mole fraction. The resulting concentration shows a maximum at the mole fraction corresponding to their complex. It is necessary to know the exact concentration of the complex formed i.e. the exact concentration of the metal ions combined with ligand and the exact concentration of ligand combined with metal ions to form a complex. Corresponding equation

Table 1 Experimental data of nickel(II)–cimetidine complex by continuous variation method.

Sr. No.	Metal concentration	Ligand concentration	X_{Ni}	Absorbance at 622 nm	
				25 °C	40 °C
1	0.0	0.24 M = 12×10^{-4} mole	0.0	0.001	0.001
2	0.04 M = 2×10^{-4} mole	0.20 M = 10×10^{-4} mole	0.17	0.046	0.046
3	0.08 M = 4×10^{-4} mole	0.16 M = 8×10^{-4} mole	0.33	**0.078**	**0.077**
4	0.12 M = 6×10^{-4} mole	0.12 M = 6×10^{-4} mole	0.50	0.064	0.066
5	0.16 M = 8×10^{-4} mole	0.08 M = 4×10^{-4} mole	0.66	0.050	0.049
6	0.20 M = 10×10^{-4} mole	0.04 M = 2×10^{-4} mole	0.83	0.034	0.034
7	0.24 M = 12×10^{-4} mole	0.0	1.0	0.016	0.018

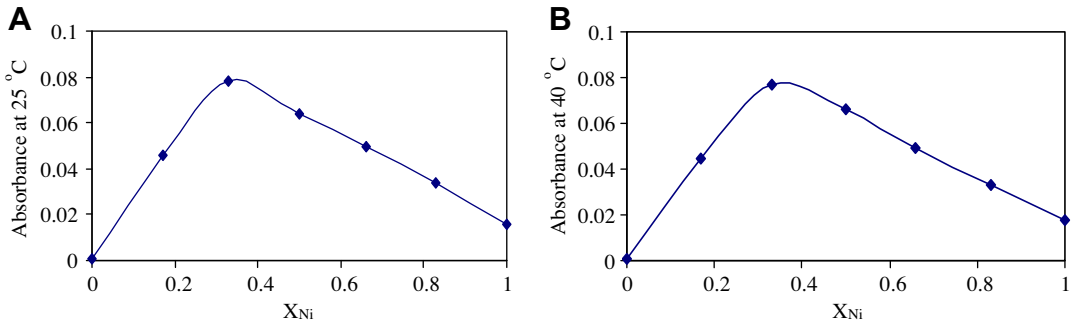

Figure 3 Job's curves for stability constants of equimolar solutions at (A) 25 °C and (B) 40 °C at 622 nm. Note that temperature elevations up to 40 °C shows no change in Job's curves.

(Tirmizi et al., 2009, 2010), used in this study for Job's method is as following;

$$K_{\text{Cim}} = \frac{[ML]}{[M] \times [L]} \tag{1}$$

$$K_{\text{Cim}} = \frac{[A_2/A_1]}{[1 - A_2/A_1] \times [C_{\text{Cim}} - C_{\text{Ni}} \times A_2/A_1]} \tag{2}$$

where, A_1 = absorbance at break point, A_2 = actual absorbance, C_{Ni} = concentration of nickel and C_{Cim} = concentration of cimetidine.

In Fig. 3, the extrapolated value A_{ext} at the point of cross section, on the continuous variation plots corresponds to the total absorbance of the complex, if the complex formation has been completed. Experimental values of absorbance at different temperatures are given in Table 1. Actually complex is dissociative in nature and absorbance reading is, therefore, somewhat lower. From continuous variation curves, A, A_{ext} and C_{Cim} were obtained at different temperatures.

Mole ratio method, another method for determining the stoichiometry of the complex spectrophotometrically, is especially applicable to determine stoichiometry of a weak complex. As the complex has metal to ligand ratio that equals 1:2 so the suggested general equation is;

$$M^{n+}_{\text{Ni}} + 2L_{\text{Cim}} \rightleftharpoons [ML_2] \tag{3}$$

$$\text{Ni}^{2+} + 2\text{Cimetidine} \rightleftharpoons [\text{Ni–Cim}_2]\ \text{Complex} \tag{4}$$

By using the mole ratio method, at constant Ni(II) concentration (4×10^{-4} moles = 0.08 M) and varying cimetidine concentrations (2×10^{-4} moles = 0.04 M to 14×10^{-4} moles = 0.28 M), at λ_{max} = 622 nm and at two different temperatures i.e. 25 and 40 °C (Table 2), a sharp band was observed at 1:2 mole ratio of Ni(II) to cimetidine (see also Fig. 4).

The molar absorption coefficient of the complex can be calculated by using the following equation;

$$A = \varepsilon_{\lambda} bc \tag{5}$$

$$\varepsilon_{\lambda} = A/bc \tag{6}$$

A is absorbance at λ_{max}, c is concentration of the metal complex and b is pathlength (I cm). ε_{λ} is dependent upon wavelength and is called molar absorption coefficient and has units of L mol^{-1} cm^{-1}. The use of this term specifically requires the concentration to be expressed in units of molarity and sample path length in cm. ε_{λ} value is quite low which confirms d–d transitions. The corresponding equation (Tirmizi et al., 2009, 2010), for mole ratio method is as follows:

$$K_{\text{Cim}} = \frac{[A/\varepsilon b]}{[C_{\text{Ni}} - A/\varepsilon_{\lambda} b] \times [C_{\text{Cim}} - A/\varepsilon b]} \tag{7}$$

where; $\varepsilon_{\lambda} \times b$ = molar absorptivity constant, and A = absorbance at peak point.

By applying Mollard method, firstly at 2.0×10^{-1} M nickel(II) concentration and excess cimetidine (14×10^{-4} moles = 0.28 M), the absorbance obtained at 25 °C was 0.090 nm, secondly taking nickel(II) in excess, $X_{0.83}$ (10×10^{-4} moles = 0.20 M) and 2×10^{-4} moles = 0.04 M cimetidine, the absorbance at 25 °C was 0.034 nm. The results obtained by this method showed the 1:2 mole ratio of Ni(II)–cimetidine in the complex.

By applying Job's and mole ratio methods (Table 3), on the basis of data obtained, the stability constant has been

Table 2 Experimental data of nickel(II)–cimetidine complex by mole ratio method.

Sr. No.	Metal concentration	Ligand concentration	Absorbance at 622 nm	
			25 °C	40 °C
1	0.08 M = 4×10^{-4} mole	0.04 M = 2×10^{-4} mole	0.020	0.022
2	0.08 M = 4×10^{-4} mole	0.08 M = 4×10^{-4} mole	0.041	0.042
3	0.08 M = 4×10^{-4} mole	0.12 M = 6×10^{-4} mole	0.060	0.061
4	0.08 M = 4×10^{-4} mole	0.16 M = 8×10^{-4} mole	**0.081**	**0.084**
5	0.08 M = 4×10^{-4} mole	0.20 M = 10×10^{-4} mole	0.085	0.088
6	0.08 M = 4×10^{-4} mole	0.24 M = 12×10^{-4} mole	0.089	0.089
7	0.08 M = 4×10^{-4} mole	0.28 M = 14×10^{-4} mole	0.090	0.091

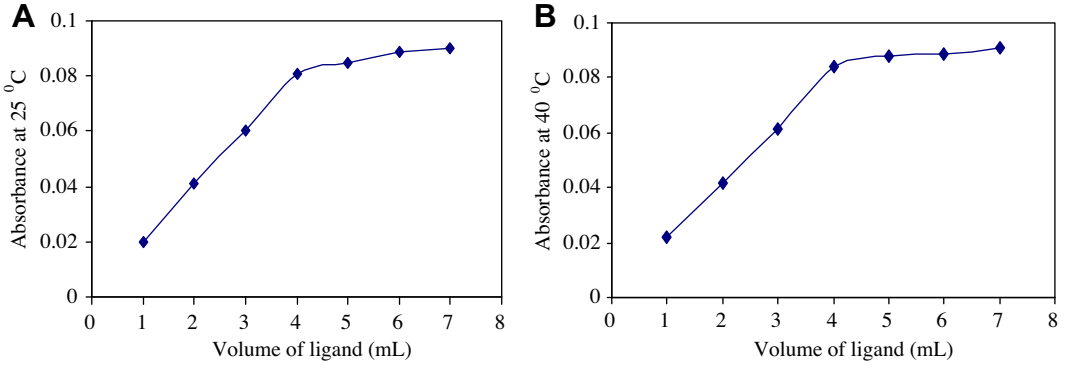

Figure 4 Mole ratio method curves for stability constants (A) 25 °C and (B) 40 °C at 622 nm. Note that temperature elevations up to 50 °C shows no change in curves for mole ratio method.

Table 3 Metal–ligand formation constants calculated from continuous variation method and mole ratio method at 25 and 40 °C.

Sr. No.	Methods	Metal:ligand	Formation constant (K) at temp (°C)			
			25 °C	Log K	40 °C	Log K
1	Continuous variation method	1:2	1.40×10^8	8.15	2.4×10^8	8.30
2	Mole ratio method	1:2	1.24×10^8	8.10	2.4×10^8	8.30

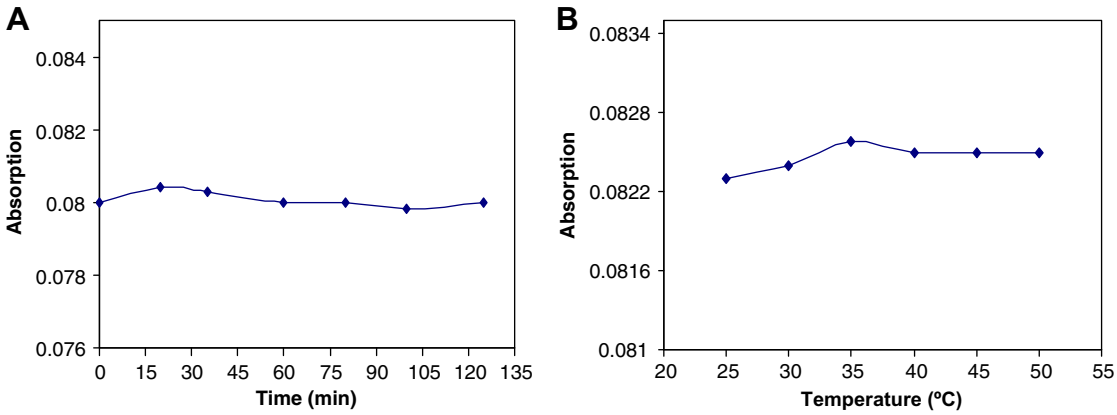

Figure 5 Stability of nickel(II)–cimetidine complex with respect to (A) time and (B) temperature.

determined and the mean value of K_{Cim} obtained by two different methods are in fair agreement.

3.3. The stability of complex with respect to time and temperature

Stability of nickel(II)–cimetidine complex with respect to time and temperature is given in Fig. 5. The colour of the complex appears immediately after mixing the reactants at any particular temperature and with the passage of time, no change in the concentration of the complex or colour intensity was observed, which shows that there is no effect of time on the complex concentration.

Similarly, temperature variation does not show any significant change in colour intensity of the complex. Stability constant measurements also show that there is no effect of temperature on the stability constant. There is evidence that a stable complex is immediately formed by mixing the two reagents together at room temperature and on increasing the temperature no change in colour, intensity and wavelength of maximum absorption was observed.

Stability constant is a Kinetic Factor. It can be correlated with ΔG (free energy), ΔH (enthalpy), ΔS (entropy), which are the thermodynamic factors. They are inter-convertible as shown here;

$$K_{\text{Stability}} = e^{-E_{\text{activation}}}/RT \tag{8}$$

$$\ln K_{\text{Stability}} = \frac{-E_{\text{activation}}}{RT} \tag{9}$$

$$E_{\text{activation}} = -RT \ln K_{\text{Stability}} \tag{10}$$

In the present work, we have concentrated only on determining the stability constants of metal complexes with cimetidine. The composition of the metal complex with H_2-receptor and its stability constant can also be determined at different pH values and in different solvents. Keeping in view objectives of the present study, we kept in mind the pH and solvent of the stomach. The pH of stomach is 2.5 (HCl is 1.0×10^{-2} M) and solvent is H_2O, which is ≈55.5 M and this was the limitation of our present work.

4. Conclusion

Cimetidine, an anti ulcer drug, forms a reasonably stable complex with Ni^{2+}. Job's method of analysis corresponds well with the analogous values obtained using mole ratio method of analysis. Owing to a high formation constant at body temperature, cimetidine intake can remove nickel from the body and this may disturb the functions of enzymes and can cause anaemia and weight loss. Nickel deprivation profoundly impairs the intestinal absorption of iron and thus can cause anaemia.

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