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Voltammetric and Spectroscopic Studies of Memantine Hydrochloride and its Transition Metal Complexes

A. Natekar[a,b] and R. Dey[b,]*

[a]*Department of Chemistry, Dnyanprassarak Mandal's College and Research Centre, Assagao-Bardez, Goa-403507, India*

[b]*Department of Chemistry, BITS Pilani, K.K. Birla Goa Campus, Zuarinagar, Goa-403726, India*

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In the present work, an electroanalytical technique (cyclic voltammetry) has been used to understand the electrochemical behavior of memantine hydrochloride and evaluate the overall response of the drug. The solution variables, such as the concentration of drug, and instrumental variables, such as scan rate, have been studied. It has been reported that functional groups in a parent drug could bind to transition metal ions; this led to facilitation of the drug delivery. In the present study, four transition metal complexes of Memantine hydrochloride including Fe, Cu, Ni, and Co complexes have been prepared. Characterization of transition metal complexes is carried out using IR and Atomic Absorption Spectroscopy. The redox properties are investigated using cyclic voltammetry.

Keywords: Memantine hydrochloride, Cyclic voltammetry, Transition metal complexes, Spectral characterization

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is growing worldwide [1]. Alzheimer's disease is a type of dementia that primarily affects the elderly population over 65 years of age [2]. In AD, abnormal changes in the brain get worse over time, and eventually affect many aspects of the brain function [3]. It causes unusual behavior, personality changes, severe memory loss, and a decline in cognitive function in the brain [4]. The drugs used for the treatment of Alzheimer's disease are Tacrine, Rivastigmine, Galantamine, Donepezil, and Memantine.

Memantine hydrochloride, 1-amino-3,5-dimethyl-adamantane hydrochloride (Fig. 1), which was discovered in 1968 by Eli Lilly [5], is a novel therapeutic agent used as Alzheimer's disease medication. Memantine hydrochloride

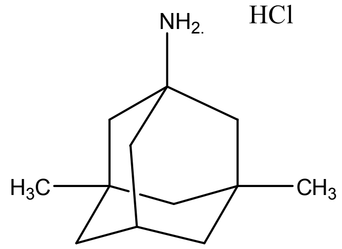

Fig. 1. Structure of memantine hydrochloride.

has putative neuro-protective properties; it blocks the calcium channels activated by N-methyl-D-aspartate (NMDA) receptor stimulation [6]. It is a FDA-approved non-acetyl cholinesterase blocker that is used to treat moderate to severe AD [7]. It is also used to treat various illnesses such as glaucoma, Parkinson's disease (PD), stroke, amyotrophic lateral sclerosis (ALS), drug dependency, and chronic pain [8]. It is a tricyclic amine that is chemically and pharmacologically related to the antiviral drug amantadine [9]. It is usually taken orally as hydrochloride salt [10].

*Corresponding author. E-mail: ranjandey@goa.bits-pilani.ac.in

Various methods such as Liquid Chromatography (LC) [9], Gas Chromatography (GC) [10], Spectrophotometry [11-13], Spectro Fluorimetry [14], and High Performance Liquid Lhromatography (HPLC) [15-20] methods have been reported for determination of Memantine hydrochloride.

Few drugs in form of transition metal complexes showed better healing properties than the parent drug [21-25]. Metals have unique characteristics such as redox activity, variable coordination modes, variable oxidation states, and reactivity towards organic substrates [22]. Metals are susceptible to donate their electrons to form positively charged ions, which are soluble in biological fluids [23]. Different biological functions are carried out in the brain with transition elements such as Fe(III), Cu(II), and Zn(II), indicating their participation in redox reactions. The presence of transition metal ions in amyloid-beta aggregation and oxidative stresses is major pathogenesis for AD. The deactivation of such transition metal ions and the binding of the metal chelators in the brain are viable replacements to treat AD patients [24]. Transition metal complexes are used as anti-diabetic, anti-inflammatory, anti-infective, and anti-cancer compounds [26]. These metal complexes are investigated using a sensitive and relatively fast technique of cyclic voltammetry [27].

To the best of our knowledge, there is no in-depth investigation on the synthesis and electrochemical properties of metal complexes of memantine hydrochloride. The synthesized metal-drug complexes have been characterized using cyclic voltammetry (CV), as an electroanalytical tool, coupled with spectroscopic techniques such as IR (Infrared) and AAS (Atomic Absorption Spectroscopy).

EXPERIMENTAL

In the present work, all the procured chemicals were of analytical grade. Memantine hydrochloride (active pharmaceutical ingredient) was obtained from Unichem Laboratories Ltd. Goa, India as a gift sample. The percentage purity of the drug was found to be 95% (w/w). The stock solution of memantine hydrochloride was prepared and further diluted to obtain 0.001 M to 0.0001 M solution using standard procedures [28]. Phosphate buffer (pH 7.2) was also prepared in double-distilled water and used as a supporting electrolyte. 10 ml solutions of memantine hydrochloride were added to the voltammetric cell with 10 ml Phosphate buffer (pH 7.2). Successive cyclic sweeps were taken until the voltammogram was stable. Then the cell was kept undisturbed for a few seconds and the voltammogram was recorded between -1.5 V to 1 V. Synthesis of Memantine hydrochloride metal complexes was carried out following the procedure given in the literature [27,28].

Cyclic Voltammetric (CV) Analysis

The redox behavior of the drug and its transition metal complexes was studied with Iviumstat (Ivium Technologies) using Phosphate buffer of pH 7.2 as a supporting electrolyte. The three-electrode system incorporates an Ag/AgCl electrode as a reference electrode, platinum wire as an auxiliary electrode, and a glassy carbon electrode as a working electrode. In order to enhance the resolution of the peaks, a mirror finish was obtained by polishing a glassy carbon electrode with a smooth polishing cloth after each cycle [27].

Spectroscopic Characterization

Infrared spectroscopy is a powerful tool for chemical identification. IR spectra of the complexes were recorded on IR Spectrophotometer (Shimadzu, IR Affinity 1), in the region 400-4000 cm^{-1}. Atomic Absorption Spectrophotometer was used for elemental analysis and characterization. The percentage of metal in each of the metal complexes was confirmed using AAS (Shimadzu, AA-7000). All the solutions for the current work were prepared using an analytical balance (Mettler Toledo, AB135-S/FACT) with a precision of ±0.01 mg.

RESULTS AND DISCUSSION

The Memantine hydrochloride complexes were prepared using four different transition metal complexes namely Cobalt, Nickel, Copper, and Iron. All the complexes were stable at room temperature, non-hygroscopic, and completely soluble in water. Prepared complexes were characterized for further investigations using CV, IR and AAS.

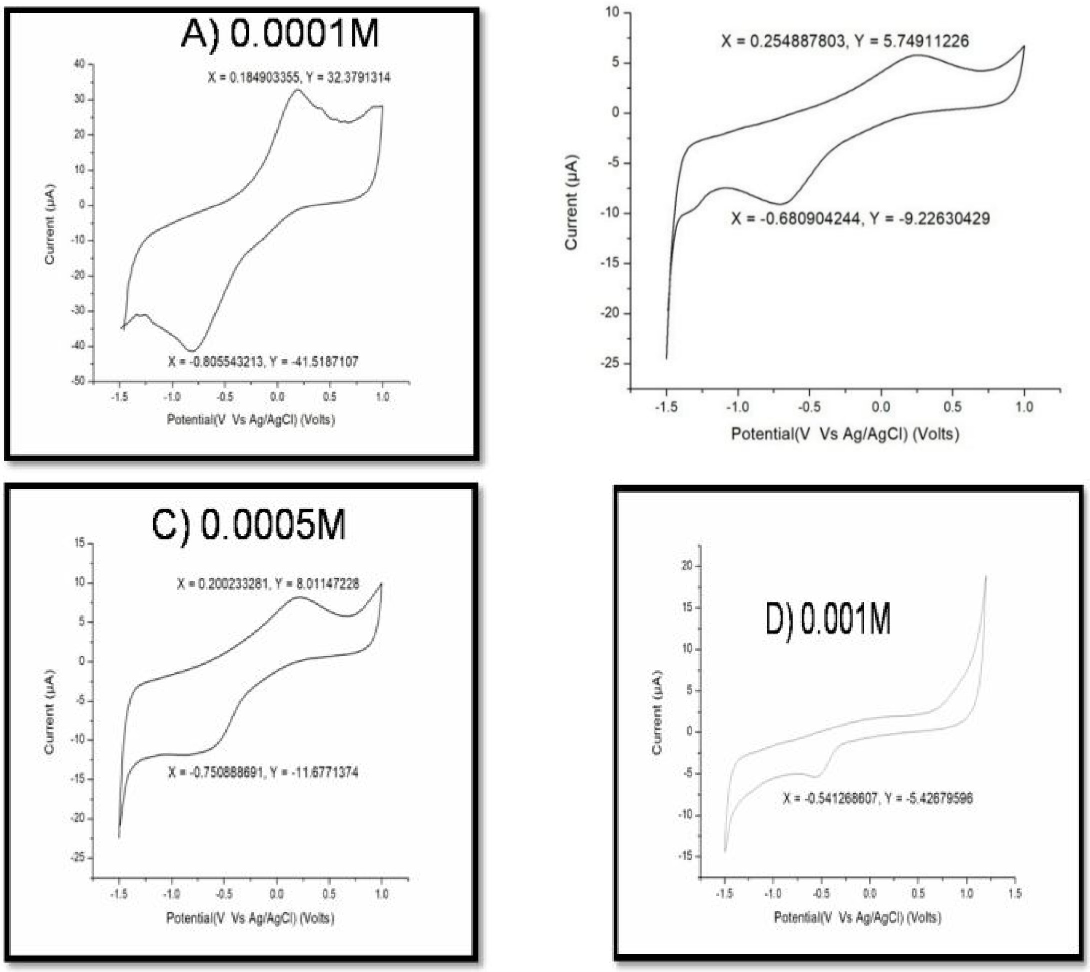

Fig. 2. Cyclic voltammograms for the solution of memantine hydrochloride having strengths (A) 0.0001 M, (B) 0.00025 M, (C) 0.0005 M and (D) 0.001 M respectively.

Cyclic Voltammetric Studies

Figure 2 shows that both oxidation and reduction peaks were observed at 0.0001 M, 0.00025 and 0.0005 M concentration of the memantine HCl, whereas the reduction peak was more noticeable compared to the oxidation peak. The later oxidation was not much prominent as it might have been broader for 0.001 M. This shows that the reduction phenomenon may be predominant at the higher concentration compared to the lower concentrations. Amino group presented in memantine HCl is responsible for the oxidation and reduction peaks in the CV studies.

The scan rate was kept at 25 mV s^{-1} that showed greater sensitivity. Cyclic voltammetry was carried out with and without phosphate buffer. It was observed that when a buffer solution was introduced, better results with well-defined peaks were obtained. Hence, it was used throughout further studies [29]. The current compliance was ±5 A.

From Fig. 3, a voltammogram of Fe API complex exhibits the reduction peak at E_{pc} = -0.25 V, and a comparable oxidation peak at E_{pa} = +0.5 V. The peak separation is 0.75 V, which increases with the scan rate. Increased value of ΔEp indicates the formation of the quasi-reversibility for Fe(III)/Fe(II) couple. Similarly, voltammograms were recorded for Co-API, Cu-API, and Ni-API complexes. The reduction peak at E_{pc} = -0.125 V, the corresponding oxidation peak at E_{pa} = +0.35 V, and the

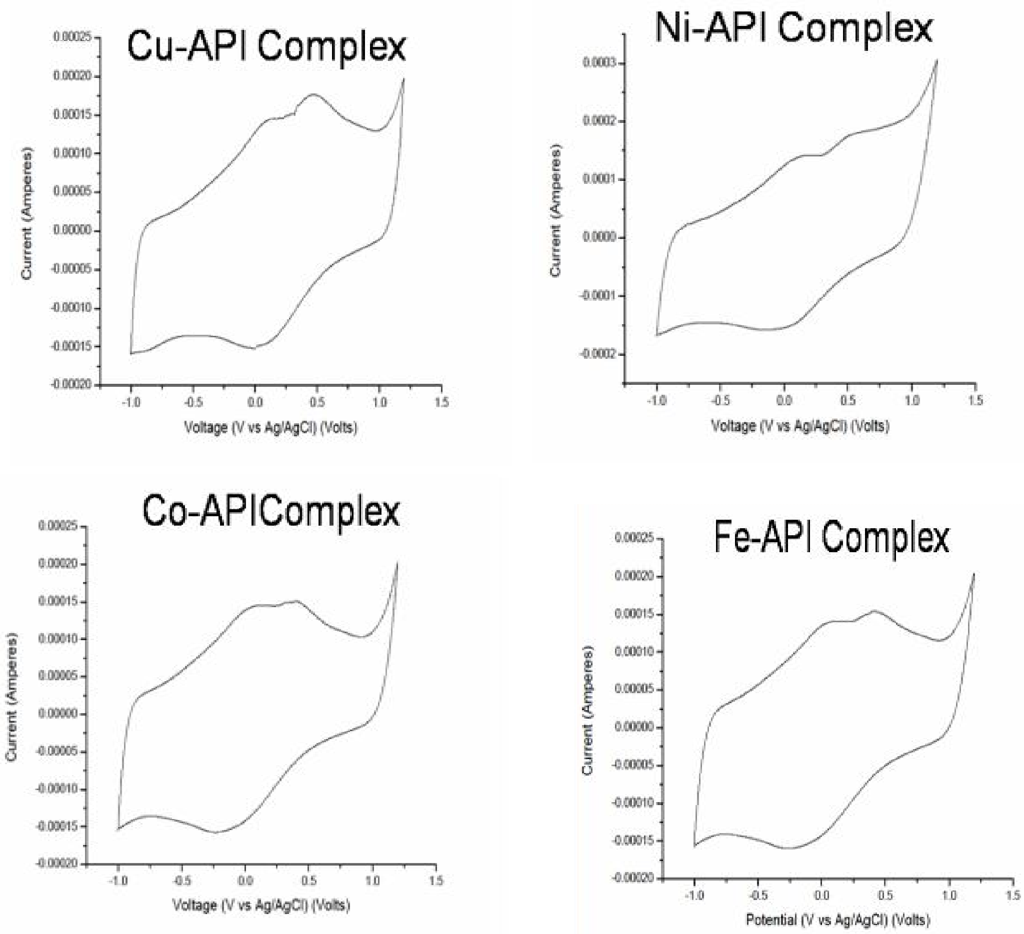

Fig. 3. Cyclic voltammograms of metal complexes.

peak separation at 0.475 V were observed for Co(III)/Co(II) couple. Reduction peak at E_{pc}= -0.15 V and oxidation peak at E_{pa} = +0.55 V with peak separation of 0.7 V were seen for Cu(II)/Cu(I) couple. Also, reduction peak at E_{pc} = -0.05 V and oxidation peak at E_{pa} = +0.45 V with peak separation of 0.5 V for Ni(II)/Ni(I) couple. These results show evidence of quasi-reversible for all the four metal complexes under the present investigation [30,31].

Comparison of Figs. 2 and 3 shows that there are two oxidation peaks for all the drug-metal combinations voltammograms (Fig. 3). The single peak at +0.20 V that is a common peak in all the sub-figures of Fig. 2 is related to the drug (memantine HCl). The nitrogen in the amino group binded to the metal resulted in another additional peak in Fig. 3, due to the presence of the related metal (Fe, Ni, Co or Cr). For the reduction counterpart, the broad band may be due to the proximity of the two closely spaced reduction peaks, which may be fused together.

It was observed that all transition metal memantine hydrochloride complexes showed both oxidation and reduction peaks. The characteristics of forward and backward peak potentials interpret the degree of reversibility. The proportion of cathodic to anodic peak heights was less than one. Hence, the peak current increases with an increase in square root of the scan rates [21-27].

IR Spectroscopic Studies

The IR spectra of the functional group attached to the metal atom provided valuable information. From Fig. 4, the N-H stretching (asymmetric) band of the amino group expected for memantine hydrochloride is in the region 3500-3350 cm^{-1}. For pure memantine hydrochloride, it

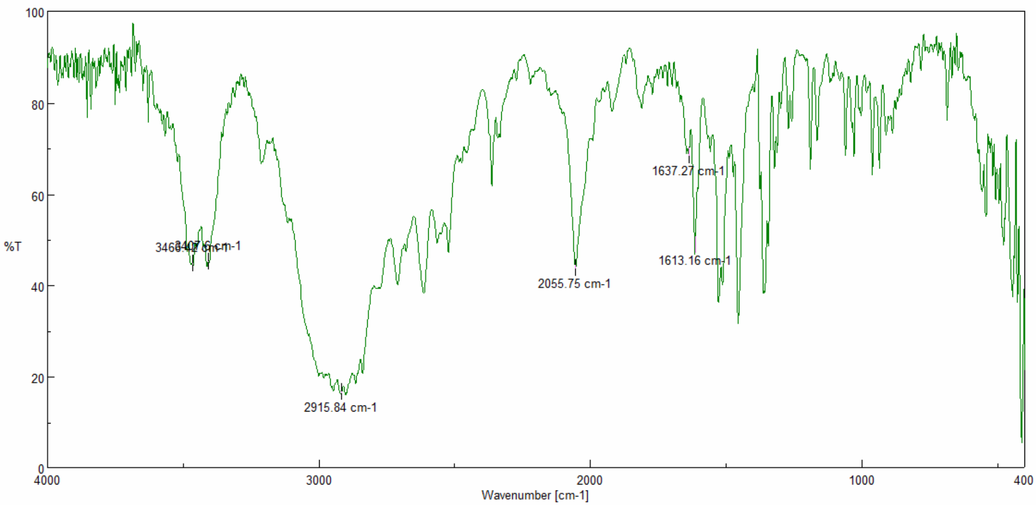

Fig. 4. IR spectra of Memantine hydrochloride.

appeared at 3468 cm^{-1}. The N-H stretching bands appeared at 3207.62 cm^{-1} and 3174.83 cm^{-1} for Fe complex (Fig. 5) and Cu-Complex (Fig. 6), respectively. Both Ni-complex (Fig. 7) and Co-complex (Fig. 8) appeared at 3466.09 cm^{-1}. Similarly, N-H stretching (symmetric) band appeared at 3400 cm^{-1} for memantine hydrochloride, at 3409 cm^{-1} for Fe complex, at 3398 cm^{-1} for Cu-complex, at 3404 cm^{-1} for Co-complex, and at 3398 cm^{-1} for Ni-complex. N-H (bending) for memantine hydrochloride appeared at 1600 cm^{-1}. For Fe-complex N-H (bending) was observed at 1524 cm^{-1}, for Cu-complex at 1540 cm^{-1}, for Ni-complex at 1534 cm^{-1}, and for Co-complex at 1525 cm^{-1}. C-H stretching for memantine hydrochloride was at 2915.84 cm^{-1}; for Fe-complex C-H stretching was observed at 2925 cm^{-1}, for Cu-complex at 2922 cm^{-1}, for Ni-complex at 2925 cm^{-1}, and for Co-complex at 2921 cm^{-1}. Similarly, C-N (stretching) band appeared at 1200 cm^{-1} for memantine hydrochloride and for Fe complex it appeared at 1057 cm^{-1}, for Cu-complex at 1062 cm^{-1}, for Ni-complex at 1057 cm^{-1}, and for Co-complex at 1063 cm^{-1}.

The significant asymmetric and symmetric stretching peaks exhibited the conformation in which the nitrogen of amine group attached to the metal [28-32]. It also showed the characteristic peaks of N-H bending, C-N (stretching) and C-H (alkanes) for all the complexes.

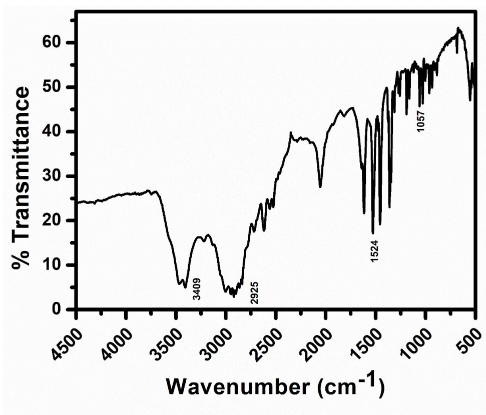

Fig. 5. IR spectra of Memantine-Fe complex.

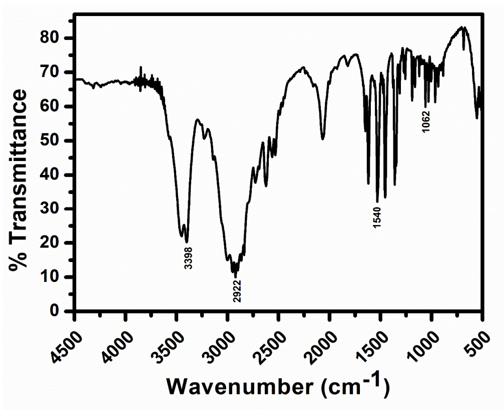

Fig. 6. IR spectra of Memantine-Cu complex.

Atomic Absorption Spectroscopic (AAS) Studies

AAS is a relatively simple high throughput, cost

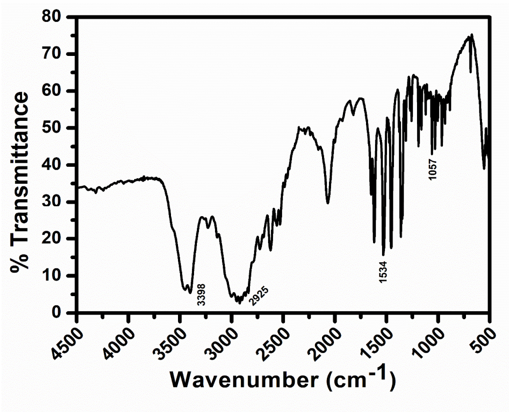

Fig. 7. IR spectra of Memantine-Ni complex.

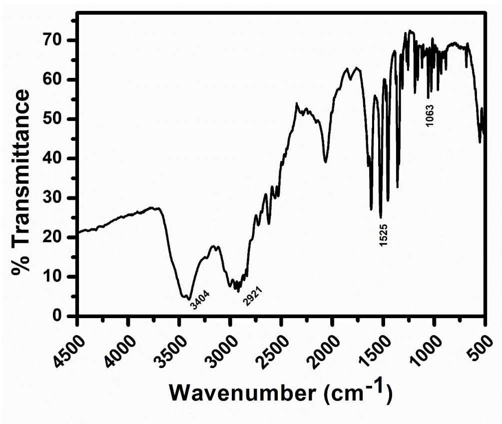

Fig. 8. IR spectra of Memantine-Co complex.

effective and an accurate technique to analyze compounds in solution. It has various applications in F&B, pharma and clinical industries. It is also used for metallurgical applications to find the amount of precious metals presented in rocks. It employs the principle wherein the free atoms in the ground state absorb the light at a particular wavelength; this very specific absorption is a characteristic of the studied metal. When the electron returns to the ground state, the emitted energy in the form of light has a wavelength characteristic, providing information about the presence of a particular metal/element.

The absorbance is directly proportional to the concentration of the analyte absorbed under the existing set of conditions. AAS was used to determine the presence of the metal in the drug and its approximate amount. The flame used for the analysis was an acetylene-air mixture.

The metal atoms were analyzed at particular wavelength using the lamp for the corresponding metals in the study. The particular wavelengths were: Co at 240.7 nm, Cu at 324.8 nm, Fe at 248.3 nm and Ni at 232.0 nm. Absorbance values were at 0.9726 for memantine Fe-complex, at 0.1128 for memantine-Cu complex, at 0.7890 for memantine-Ni complex, and at 0.6562 for the memantine-Co complex. A number of reference standard solutions of particular metal with different concentrations of diluted stock solutions of a specific metal complex were prepared, and concentrations of metal in each of these diluted solutions of metal complexes were measured at the specific wavelength for each metal complex using background correction method. Percentages of metal in each of the metal complexes were calculated using this equation as shown in Table 1.

The concentration of original sample = Concentration of dilute sample × dilution factor

Table 1. Atomic Absorption Spectroscopic Studies: The Concentration of Metal in a Diluted Sample (mg ml^{-1}) and Concentration of Metal in the Metal Complexes (%)

Metal complex	Dilution factor	Concentration of metal in a diluted sample (mg ml^{-1})	Concentration of metal in original sample (ppm)	Concentration of metal in original sample (%)
Memantine-Fe complex	16778.52	2.2192	37234.899	3.72
Memantine-Cu complex	24826.216	2.7503	68279.543	6.83
Memantine-Ni complex	24437.927	2.0627	50408.112	5.04
Memantine-Co complex	24777.006	1.431	35470.761	3.55

From Table 1, it is observed that the concentration of metal in the original sample for memantine Fe-complex is 3.72%, for memantine-Cu complex is 6.83%, for memantine-Ni complex is 5.04%, and for memantine-Co complex is 3.55% [33]. The concentration of metal observed in AAS shows that it bonds to the original sample to form the transition metal-memantine complexes.

CONCLUSIONS

In this study, the variation in the peak current with a change in concentration of the drug and scan rate resulted in the oxidation and reduction signal of memantine hydrochloride. Four metal complexes of memantine hydrochloride with iron, copper, nickel, and cobalt have been synthesized. The IR spectral data provided strong evidence for the formation of the metal complexes. Furthermore, AAS analysis determined the percentage of metal in each of the complexes, confirming the bonding of metal ions to the API. The cyclic voltammogram showed both positive and negative potential peaks. Complexes exhibited a quasi-reversible one-electron transfer character.

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