

Coordination Behavior of Cefpodoxime Proxetil toward Transition Metal Ions: A Potentiometric Approach

Abhijit V. Bachute^{1,*} and Bhagwansing S. Dobhal²

¹ Department of Chemistry, Sambhajirao Kendre College, Jalkot, Dist- Latur-413532, Maharashtra, India

² Department of Chemistry, B. R. Barwale College, Jalna-431203, Maharashtra, India.

Corresponding Author: abhijitbachute327@gmail.com

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Abstract

In the present study, coordination behavior of cefpodoxime proxetil towards the biologically important transition metal ions was studied by potentiometric titration technique in aqueous medium. Binary complexes of Cu(II), Ni(II), Co(II), Zn(II), Fe(II) and Cd(II) with cefpodoxime proxetil have been studied at constant ionic strength and temperature. The Irving–Rossotti method was used to calculate the stability constants of proton–ligand and metal–ligand from the data obtained by potentiometric titration. The results showed the formation of stable 1:1 metal–ligand complexes in solution. The differences in the stability constants with different metal ions were explained in terms of ionic radius, electronic configuration and ligand field stabilization effects. Among the transition metal ions studied, the binary metal complex of Cu(II)–cefpodoxime proxetil is the most superior and stable. The Cu(II) system showed the highest displacement of the metal–ligand curve below the ligand curve indicating stronger interaction, greater proton release upon coordination and higher stability of the generated complex. The study reveals the efficient chelating ability of cefpodoxime proxetil by its donor atoms and gives valuable insight into the coordination chemistry, solution equilibria and biological relevance of transition metal complexes of pharmaceutical ligands.

Introduction:

In the last years, transition metal complexes have gained a lot of interest because of their important applications in medicinal chemistry, pharmaceutical sciences and biological systems. Many biochemical processes such as oxygen transport, electron transfer, enzymatic catalysis and metabolic regulation [1-5](Chandrangsu et al., 2017; Kaczmarek et al., 2018; Musib et al., 2023; Su et al., 2024), are definitely dependent on metal ions. The interaction of biologically active ligands with transition metal ions is of special interest because the

formation of metal complexes can change the physicochemical and pharmacological properties of therapeutic compounds [6-8](Krishna et al., 2024). Metal – drug interaction studies give valuable information about the coordination behavior, stability, bioavailability and therapeutic activity of the pharmaceutical ligands (Nouman et al., 2024; Zeevaart et al., 1999).

Cefpodoxime proxetil is a widely used semi synthetic third generation cephalosporin

antibiotic for the treatment of bacterial infections. The molecule has many possible donor sites such as amino, carbonyl, ester and carboxylate group which can coordinate with metal ions. The presence of these functional groups allows cefpodoxime proxetil to act as an effective chelating ligand and to form stable complexes with transition metal ions (Ali et al., 2024; Saathoff et al., 1992). The biological efficiency, solubility and antimicrobial activity of the drug can be influenced by the formation of metal complexes (Mishra et al., 2019; Olanrewaju et al., 2025). Hence, the study on the coordination behavior of cefpodoxime proxetil towards biologically important metal ions is significant in understanding metal–drug interactions and their pharmaceutical implications.

Among different analytical techniques, potentiometric titration is one of the most reliable and widely used methods for the study of proton–ligand and metal–ligand equilibria in solution (Ghasemi et al., 2015). The technique enables the determination of stability constants and it provides important information concerning the stoichiometry and stability of coordination complexes formed in aqueous medium. The stability of metal complexes is affected by several factors like ionic

radius, charge density, electronic configuration, and ligand field stabilization energy (Singh et al., 2019).

The present investigation deals with the coordination behaviour of cefpodoxime proxetil with transition metal ions like Cu(II), Ni(II), Co(II), Zn(II), Fe(II) and Cd(II) in aqueous medium at constant ionic strength and temperature by using potentiometric method. The stability constants of proton-ligand and metal-ligand were determined to investigate the complexation tendencies and solution equilibria of the metal complexes obtained. Furthermore, identifying these thermodynamic parameters facilitates a deeper understanding of the ligand's affinity for metallic centers, which is critical for evaluating the potential modulation of drug bioavailability in physiological environments (Islam, 2020; Islam & Akter, 2019).

Materials and Methods:

Analytical reagent grade cefpodoxime proxetil was used as ligand without any further purification. The complexation studies were carried out with metal salts of Cu(II), Ni(II), Co(II), Zn(II) and Fe(II). All the chemicals and reagents used in the present investigation were of AR grade and double distilled water was used throughout the experimental work. A standard sodium

hydroxide solution was prepared and standardized before use. A dilute hydrochloric acid solution was used for pH adjustments during the titration process. For potentiometric measurements, an ELICO Model L-120 pH Meter with combined glass electrode was used. The pH meter was calibrated using standard buffer solutions of pH 4.1, 7.0 and 9.2 before each set of measurements to ensure accuracy and reproducibility. The ionic strength of the medium was kept constant during the experiment with sodium nitrate solution. All the potentiometric titrations were carried out under controlled experimental conditions and at constant temperature, with continuous stirring. The microburette used for titration was calibrated by the standard method of Vogel for accurate measurement of volumes. The titration curves were generated by recording the pH of the solution at specific intervals following the sequential addition of the titrant to the ligand and metal–ligand mixtures.

Result and Discussion:

The proton–ligand stability constants (pK) were initially calculated through the analysis of titration curves, reflecting the ionization behavior of the carboxylic and amino groups within the cefpodoxime proxetil structure (Hussain et al., 2016).

These values were subsequently utilized to compute the stepwise metal–ligand stability constants, providing a quantitative measure of the chelating affinity for the selected transition metal ions (Alrashdi et al., 2018). These computational results, refined through specialized software such as MINIQUAD 75, provide a comprehensive profile of the species distribution across varying pH levels, mirroring the potential chemical forms of the drug within physiological fluids (Balakrishna, 2024).

The potentiometric titration curves shown in the **Figure 1** are related to the formation of binary complex between Cu (II) ions and cefpodoxime proxetil in aqueous medium at a metal-to-ligand ratio of 1:1 (Hosny, 1999). The experimental conditions were as follows: total volume (V_0) = 50 mL, temperature = 27 °C, ionic strength (μ) = 0.007, ligand concentration (T_l) = 0.0004 M, metal ion concentration (T_m) = 0.0004 M, and sodium hydroxide concentration (N) = 0.2000 N. Three different curves were obtained for acid only (A), acid with ligand (A+L) and acid with ligand and Cu(II) ions (A+L+Cu). (Balakrishnan & Santappa, 1974)

The blue curve (A) is the titration of the solution of the mineral acid. Initially, the pH is low, due to the high concentration of hydrogen ions in the medium. When

sodium hydroxide is added, the pH rises gradually, and close to the equivalence point a sharp rise in pH occurs due to neutralization. The red curve (A + L) corresponds to the acid solution containing cefpodoxime proxetil. The curve is slightly displaced from the acid curve since the ligand loses a proton while titrating. The presence of amino, carbonyl, carboxylate and ester groups in cefpodoxime proxetil affects the ionization and buffering effect and the titration profile. (Fernandes et al., 1997)

The green curve (A + L + Cu) corresponds to the system containing both cefpodoxime proxetil and Cu(II) ions. The curve remains well below the ligand curve during the titration indicating the formation of stable copper-ligand complexes. The rise of pH during coordination is suppressed due to the release of hydrogen ions and confirms the strong interaction between Cu(II) ions and cefpodoxime proxetil. Potentiometric data reveal the formation of a stable 1:1 copper complex. This reflects the efficient chelation ability of cefpodoxime proxetil toward Cu(II) ions.

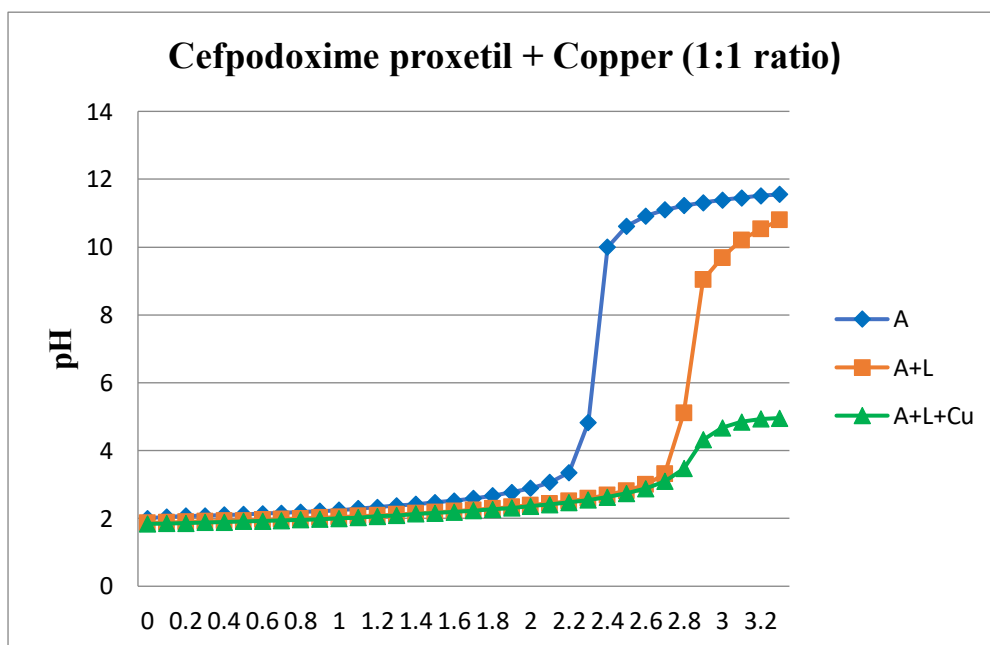


Figure 1: Potentiometric graphical representation for copper (II) complex with cefpodoxime proxetil

The **figure 2** represents the potentiometric titration curves representing the binary complex formation of Co(II) ions and cefpodoxime proxetil in aqueous medium

at 1:1 metal to ligand ratio. Three curves were obtained for acid alone (A), acid with ligand (A + L) and acid with ligand and Co(II) ions (A + L + Co). The variation in

pH with gradual addition of sodium hydroxide provides useful information regarding the dissociation of protons and formation of metal-ligand complexes.

The blue curve (A) is the titration of the mineral acid solution. The pH is initially low because of the high concentration of H^+ ions in solution. When sodium hydroxide is added slowly, neutralization takes place and there is a steep increase in pH close to the equivalence point. The red curve (A+L) is for the acidic solution containing cefpodoxime proxetil. This curve is slightly shifted from the acid curve because during the titration the ligand is losing protons. The presence of functional groups such as amino, carboxylate, carbonyl and ester groups in the ligand contribute towards ionization and exert a

buffering effect and thus change the titration profile.

The green curve (A + L + Co) is below the ligand curve during the whole titration indicating the formation of stable cobalt–ligand complexes. The increase in pH is suppressed by the release of hydrogen ions during complexation and confirms strong interaction of Co(II) ions with cefpodoxime proxetil. Potentiometric data reveal the formation of a stable 1:1 cobalt complex which points to the efficient chelating behaviour of cefpodoxime proxetil towards Co(II) ions. These observations suggest that the relative stability of these complexes is dictated by the coordination of the metal center to the ligand's specific donor sites, similar to behaviors documented in related cephalosporin metal-complexation studies (Umekar et al., 2021).

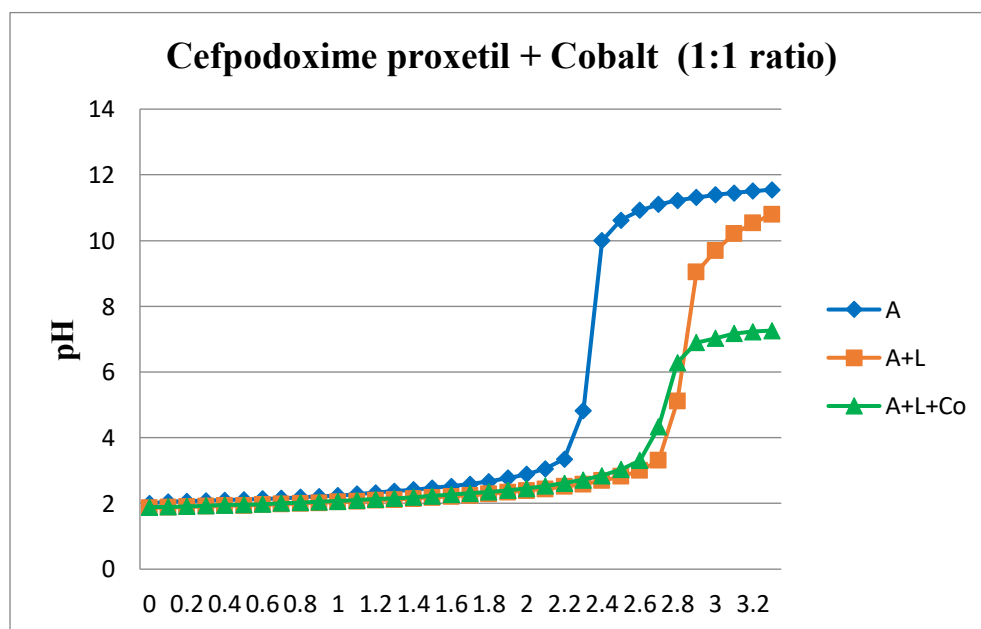


Figure 2: Potentiometric graphical representation for cobalt (II) complex with cefpodoxime proxetil

The potentiometric titration curves shown in the **figure 3** represent the binary complex formation between Fe(II) ions and cefpodoxime proxetil in aqueous medium at a metal-to-ligand ratio of 1:1. Three curves corresponding to acid alone (A), acid with ligand (A + L), and acid with ligand plus Fe (II) ions (A + L + Fe) were obtained. The change of pH during slow addition of sodium hydroxide gives valuable information about proton dissociation and formation of metal-ligand complexes.

The blue curve (A) is the titration of the mineral acid solution. At first the pH is low because there are lots of H⁺ ions in solution. As sodium hydroxide is slowly added, neutralization occurs and there is a sharp rise in pH near the equivalence point. The red curve (A + L) represents the acid

solution with cefpodoxime proxetil. The curve of this is slightly displaced from the acid curve, since during titration the ligand dissociates a proton. The functional groups such as amino, carboxylate, carbonyl and ester groups in the ligand aid in ionization and have buffering effect that alters the titration profile.

The green curve (A + L + Fe) remains much lower than the ligand curve throughout the titration process, indicating the formation of stable iron–ligand complexes. The coordination releases hydrogen ions, inhibits the increase in pH and indicates the strong interaction between Fe(II) ions and cefpodoxime proxetil. The potentiometric data indicate the formation of a stable 1:1 iron complex, demonstrating the efficient chelating ability of cefpodoxime proxetil towards Fe(II) ions.

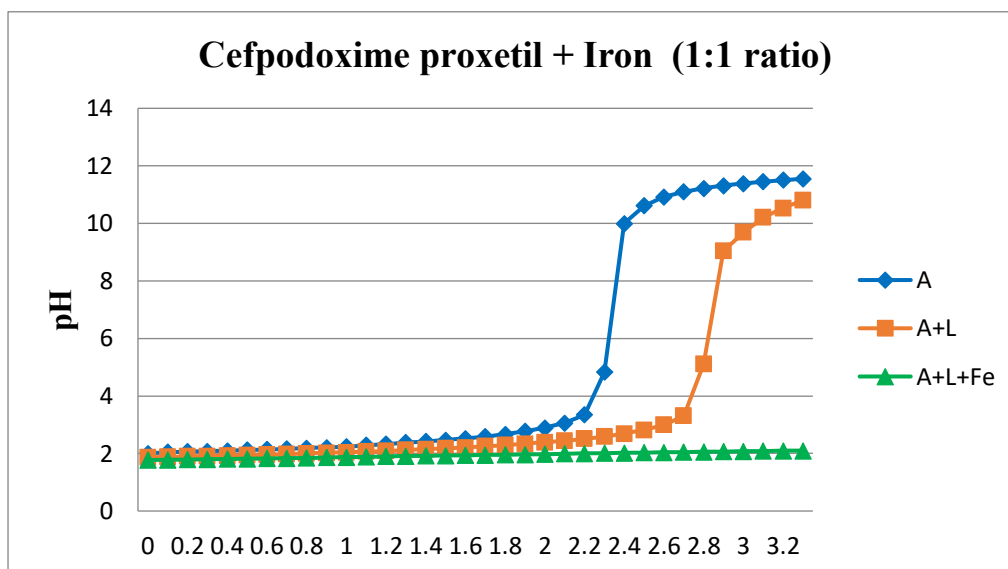


Figure 3: Potentiometric graphical representation for iron (II) complex with cefpodoxime proxetil

The **figure 4** shows the potentiometric titration curves revealing the binary complex formation of Ni (II) ions with cefpodoxime proxetil in aqueous medium at a metal to ligand ratio of 1:1. Three different curves were obtained, corresponding to acid alone (A), acid with ligand (A + L) and acid with ligand plus Ni(II) ions (A + L + Ni). The variation of pH on gradual addition of sodium hydroxide gives important information about the proton dissociation and the formation of metal–ligand complexes.

The blue curve (A) corresponds to the titration of the mineral acid solution. In the beginning the pH is low because of the high concentration of the hydrogen ions in the medium. Sodium hydroxide is added gradually and the sharp rise in pH occurs

near the equivalence point where neutralization occurs. The red curve (A + L) is for the acid solution with cefpodoxime proxetil. The acid curve is shifted slightly from this curve because of the ligand proton dissociation during titration. As cefpodoxime proxetil contains functional groups such as amino, carboxylate, carbonyl and ester group, these groups get ionized and hence there is a buffering effect which changes the titration profile.

In the titration, the green curve (A + L + Ni) is below the ligand curve, indicating the presence of stable nickel-ligand complexes. The pH increase was suppressed by the release of hydrogen ions during the coordination which is a proof for the strong interaction between Ni (II) ions with cefpodoxime proxetil. The potentiometric

data show the formation of a stable 1:1 nickel complex, indicating the effective

chelating ability of the cefpodoxime proxetil towards Ni(II) ions.

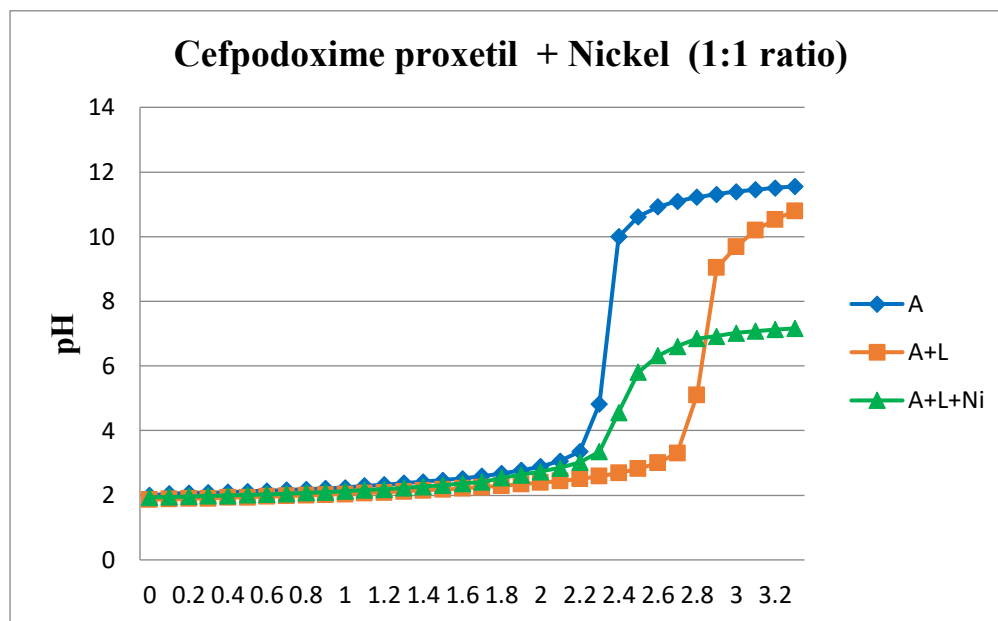


Figure 4: Potentiometric graphical representation for nickel (II) complex with cefpodoxime proxetil

The potentiometric titration curves for the binary complex formation between Zn(II) ions and cefpodoxime proxetil in aqueous medium are presented in the **figure 5** at metal to ligand ratio of 1:1. Three different curves were obtained, for acid alone (A), acid with ligand (A + L) and acid with ligand + Zn(II) ions (A + L + Zn). The pH change during the gradual addition of sodium hydroxide is a useful indicator of proton dissociation and the formation of metal-ligand complexes.

The blue curve (A) shows the titration of the mineral acid solution. At first the pH is low because the solution contains a high concentration of hydrogen ions. The

neutralization takes place during the slow addition of the sodium hydroxide. Near the equivalence point a sudden rise in pH is observed. The red curve (A + L) is for the acid solution with cefpodoxime proxetil. The acid curve is shifted slightly from this curve because of the ligand proton dissociation during titration. Ionization and buffering action of functional groups such as amino, carboxylate, carbonyl and ester are present in cefpodoxime proxetil which would change the titration profile.

The green curve (A + L + Zn) is lower than the ligand curve during the entire titration process, which indicates the formation of stable zinc–ligand complexes. The release

of hydrogen ion during coordination depresses the increase of pH and confirms the strong interaction between Zn(II) ions and cefpodoxime proxetil. The potentiometric data indicate the formation of stable 1:1 zinc complex with a good chelating ability of cefpodoxime proxetil towards Zn(II) ions. These findings corroborate that the stoichiometry of

cefpodoxime complexes is consistent with the 1:1 metal-to-ligand ratio observed in alternative chelation studies of this drug (Kamalesh, 2014). Furthermore, the stability of these interactions underscores the structural flexibility of cefpodoxime, which facilitates the coordination of various transition metals through its diverse functional sites (Ali et al., 2017).

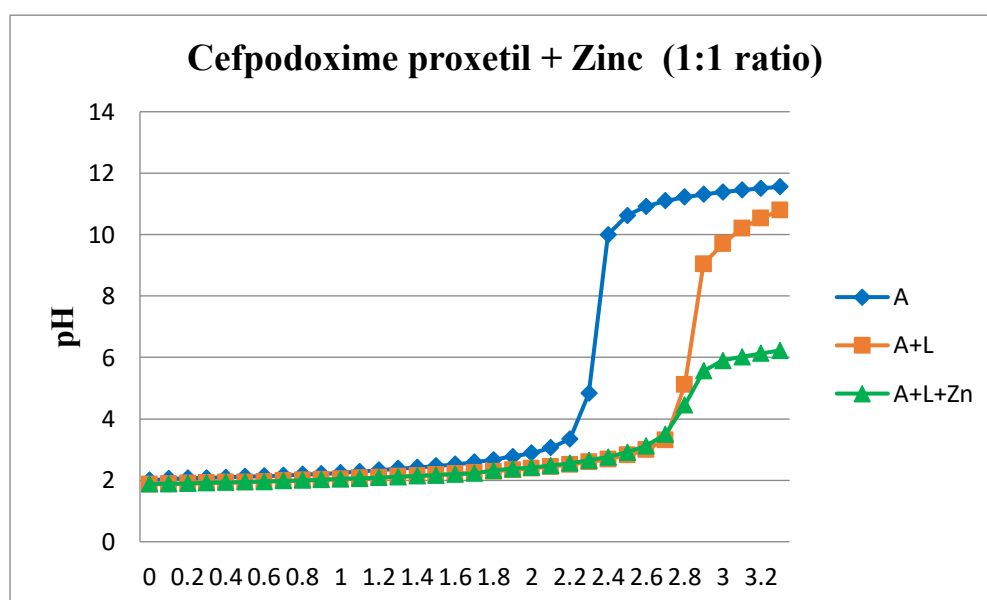


Figure 5: Potentiometric graphical representation for zinc (II) complex with cefpodoxime proxetil

The binary complex formation of Cd(II) ions with cefpodoxime proxetil in aqueous medium with metal to ligand ratio 1:1 is demonstrated by the potentiometric titration curves given in the **figure 6**. Three curves were obtained: acid alone (A), acid

+ ligand (A + L), and acid + ligand + Cd(II) ions (A + L + Cd). The pH change during the slow addition of sodium hydroxide gives useful information on the proton dissociation and metal-ligand complex formation.

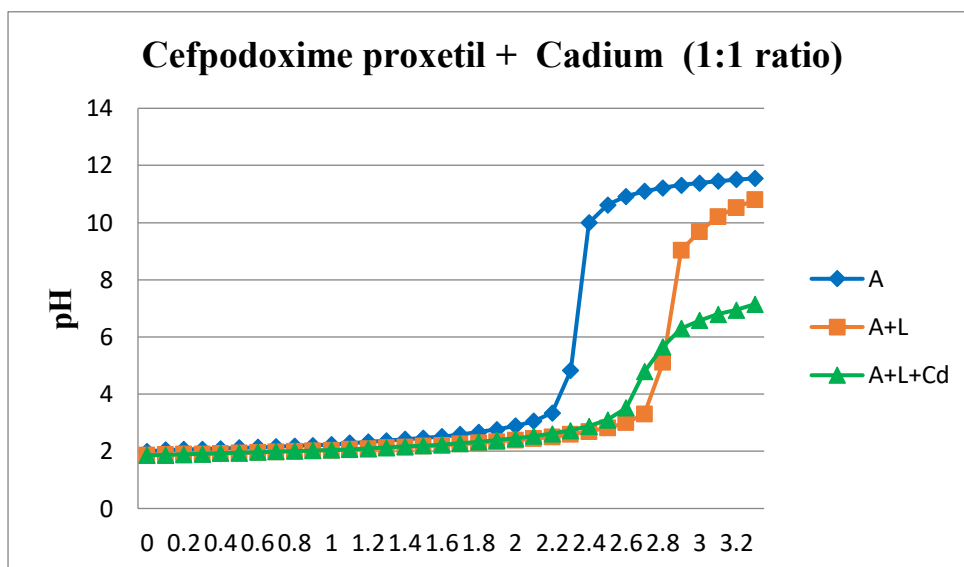


Figure 6: Potentiometric graphical representation for cadmium (II) complex with cefpodoxime proxetil

The titration of a mineral acid solution is shown by the blue curve (A). The initial value of pH is low because of the high concentration of hydrogen ions in the medium. Sodium hydroxide is added gradually. Near the equivalence point, there is a rapid increase in pH as neutralization takes place. The red curve (A + L) represents the acid solution with cefpodoxime proxetil. The acid curve is shifted slightly from this curve because of the ligand proton dissociation during titration. The functional groups responsible for ionization and buffering effect in cefpodoxime proxetil are amino, carboxylate, carbonyl and ester groups which changes the titration profile.

The green curve (A + L + Cd) is always under the ligand curve during the titration

process, which suggests the presence of stable cadmium-ligand complexes. The coordination releases the hydrogen ions that prevent the pH from increasing confirming the strong interaction of Cd(II) ions with cefpodoxime proxetil. The potentiometric data suggest the formation of a stable 1:1 cadmium complex, which demonstrates the good chelating ability of cefpodoxime proxetil towards Cd(II) ions and gives insight into the coordination chemistry and solution equilibria of cadmium–drug complexes.

Potentiometric titration studies were performed to explore the binary complex formation of cefpodoxime proxetil with transition metal ions such as Cu(II), Co(II), Fe(II), Ni(II), Zn(II) and Cd(II) in aqueous medium at 1:1 metal to ligand ratio. The

titration curves of acid alone (A), acid with ligand (A+L) and acid with ligand plus metal ions (A+L+M) showed significant changes in pH on incremental addition of sodium hydroxide, confirming the dissociation of protons and the formation of metal–ligand complexes. In all the systems the ligand curves were slightly shifted from the acid curves as a consequence of the dissociation of the proton of cefpodoxime proxetil. Ionization and buffering action during titration was aided by functional groups such as amino, carboxylate, carbonyl and ester groups. (Patil & Mhaske, 2001)

The metal-ligand curves were consistently lower than the ligand curves indicating release of hydrogen ions during coordination and formation of stable metal complexes. The high gap between ligand and metal-ligand curves confirmed the strong interaction of cefpodoxime proxetil with investigated metal ions. (Yamauchi & Odani, 1981) The potentiometric measurements indicated the formation of stable 1:1 complexes in all the systems studied. The observed stability behavior was explained in terms of the coordination tendency, ionic radius and ligand field stabilization effects of the metal ions. These results show the efficient chelating ability of cefpodoxime proxetil towards transition

metal ions. These findings emphasize the importance of identifying specific binding sites, as the electronic structure and spatial arrangement of these antibiotic-metal complexes are critical for determining their potential pharmacological efficacy (Ramotowska et al., 2019). Specifically, the involvement of the 7-position side chain and the basicity of the beta-lactam ring appear to be decisive factors influencing the stability and stoichiometry of these metallic species (Gaber et al., 2003). In this context, the computed stability constants provide a quantitative baseline for evaluating how these coordination behaviors correlate with previous observations of cephalosporin derivatives in comparable aqueous environments (Алексеев et al., 2006; Алексеев & Sokolova, 2016).

Conclusion:

The present potentiometric study demonstrated the formation of binary complexes of cefpodoxime proxetil with transition metal ions Cu(II), Co(II), Fe(II), Ni(II), Zn(II) and Cd(II) in aqueous medium. Potentiometric titration curves clearly indicate dissociation of the ligand proton and subsequent formation of the metal–ligand complex with a significant displacement of the metal–ligand curves below the ligand curves. The decrease of pH observed upon coordination indicated

the release of hydrogen ions and formation of stable complexes in solution.

The study found cefpodoxime proxetil to be an effective chelating ligand through donor groups such as amino, carboxylate, carbonyl and ester functionalities. Stable 1:1 metal–ligand complexes were obtained for all the metal ions studied. The stability of the complexes was affected by ionic radius, electronic configuration, tendency of coordination and ligand field stabilization effects of metal ions. Of the studied systems, Cu(II) and Fe(II) complexes exhibited relatively stronger interactions with cefpodoxime proxetil. The study gives an overall insight into the coordination chemistry, solution equilibria and metal-binding of cefpodoxime proxetil with biologically important transition metal ions. These results underscore the potential of cefpodoxime proxetil as a candidate for metal-based therapeutic applications, consistent with the observed trends in similar cephalosporin derivatives where complexation can enhance biological activity.

Conflict of Interest:

The authors declare that they have no conflict of interest.

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