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Complexation Of Zn^{2+}, Mn^{2+}, Co^{2+}, Fe^{2+} Cations With Cefuroxime (Cephalosporin) And Amoxicillin Antibiotics

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Abstract: The intricate interplay between antibiotics and transition metal ions play an important role in drug distribution and efficacy. This study explores the interaction between two commonly used antibiotics, cefuroxime and amoxicillin, with transition metal ions. The complexes formed between these antibiotics and Zn (II), Mn (II), Co (II), and Fe (II) ions were synthesized and characterized using using High-Performance Liquid Chromatography (HPLC), UV-Vis spectrometry, and Fourier-Transform Infrared spectroscopy (FTIR). FTIR spectra confirmed the formation of metal-antibiotic complexes. HPLC results revealed changes in retention time for complexes compared to individual antibiotics, while UV-Vis spectra also showed peak shift for these complexes. This study provides insights into the behavior of drugs in presence of transition metal ions for understaning drug distribution of these antibiotics.

Keywords: Cefuroxime; Amoxicillin; Metal complex; Drug Discovery.

1. Introduction

Antibiotic resistance is caused by the daily and often overuse of antibiotics by people [1–3]. The World Health Organization's Antimicrobial Monitoring System has recognized this pattern of antibiotic resistance as a severe public health threat [4–6]. It is crucial to develop new approaches to enhance the field of drug design. Among them, an effective way is to enhance antibacterial activity by conjugating the existing drugs with metal ions [7–11]. Transition metals ability to coordinate and complex formation with antibiotics brings the desired increase in the antibacterial effect and minimizes the growth of the bacteria [12,13]. In pharmacology and other fields, a huge prospect can be achieved by synthesizing antibiotic-metal complexes using zinc, manganese, cobalt, iron ions. It particularly focuses the action of these medications, which may augment the positive outcomes of treatment and reduce the incidence of side effects. Additionally, It is important to mention that metal complexation slows the rate of oxidation of the antibiotics suggesting an improved application for the substance in terms of stability and in relation to delivery of the drugs [14–16].

Moreover, the complexation of various metal ions with antibiotics demonstrates potential to develop targeted fortifications that will deliver the antibiotics with great efficiency and minimal harm to the human body. These combinations may have potential advantages, which include improved antibacterial activity, better penetration of the drug as well as improved selectivity for the pathogen [17,18]. The purpose of the work is to provide insights in how these metal ions interact with antibiotics to enhance drug design of these drugs.

With respect to the bio-function activity, Amoxicillin which is a bacteriolytic β-lactam antibiotic and Cefuroxime which is a second-generation cephalosporin antibiotic, both possess bacteriolytic properties which are attributed to their β-lactum ring [19,20]. Though there some studies on antibiotocs-ligand synthesis, but there are very limited studies on second generation cephalosporine antibiotics with transition metal ions. In the present study synthesis of complexes of zinc (II), manganese (II), cobalt (II), iron (II) complexes with cefuroxime and amoxicillin were performed. Spectroscopic and chromatographic studies involving UV-visible, FTIR spectroscopy and HPLC have been carried out to elucidate drug design.

2. Experimental

2.1. Materials and Methods

In this work all chemicals and solvents utilized were of analytical reagent grade. Both cefuroxime axetil and amoxicillin trihydrate used in this study were procured from Renata Pharmaceuticals Ltd. The metal salts from which the metal ions were isolated were $ZnSO_4$_$7H_2O$, $MnSO_4$, FeSO4, and $Co(NO_3)_2$. The buffer solution was prepared using both disodium hydrogen phosphate (Na_2HPO_4) and sodium dihydrogen phosphate (NaH_2PO_4). All the experiments used deionized water. Initially, methanol was mixed with a 1:1 mmol solution of the drug and metal salts.

After an hour of agitation, the mixture was let to stand overnight. The complexes were then washed, followed by drying at room temperature, and filtered off. The compounds that were produced as a result were insoluble in ethanol, and benzene. A

960M000g FTIR Spectrophotometer from the ATI Mattson Infinity Series, USA was utilized to collect the infrared spectra of the materials. To measure the spectra of the materials under research, a wavenumber range of 4000 – 400 cm-1 was adopted. Scan resolution of 4 cm and scan rate of 32 cm/min were used which enabled the investigation of antibiotic-metal complexes. Measurements of the drugs' absorption properties and their 1:1 mixing with metal in solution at various pH (3.4, 6.8, 7.4, 8.4) were carried out for comparison using the UV-Vis Spectroscopy method.

Each time, the concentration of the components was kept very low, and a UV-visible spectrometer (Model EMC-11D-V, Germany) was used to carry out the measurements. The buffers were used to dilute the sample's stock solutions to the required concentrations, and spectra were collected at 0.2-second intervals between 200 and 700 nm. Pressure resistance of 50 MPa was attained by using the Shimadzu Japan HPLC model LC-2050c for the high-pressure liquid chromatography examination. Excel was used to represent the data.

3. Results and discussions

3.1. UV-Vis Spectroscopy

The electronic spectra of Zn (II), Co (II), Mn (II), and Fe (II) complexes in buffer solution (pH=7) was observed in the UV region with a peak absorption at 278 nm for Cefuroxime and again 229 and 272 nm for amoxicillin trihydrate. The amide n -π* transition in the b-lactam ring and the π-π* aromatic ring excitation, respectively, could possibly be correlated to the λ max at these bands [7,21–23]. For cefuroxime axetil complex with the metal ions showed absorption peak shoulder at 268-200 nm indicating π-π* transition and at less absorption shoulder in 340 nm to more than 500 nm region (vis range) and for Amoxicillin –metal complexes showed spectra at low intensity range of 567-670 nm (vis range) due to n -π* intra-ligand transition demonstrated in figure 1.

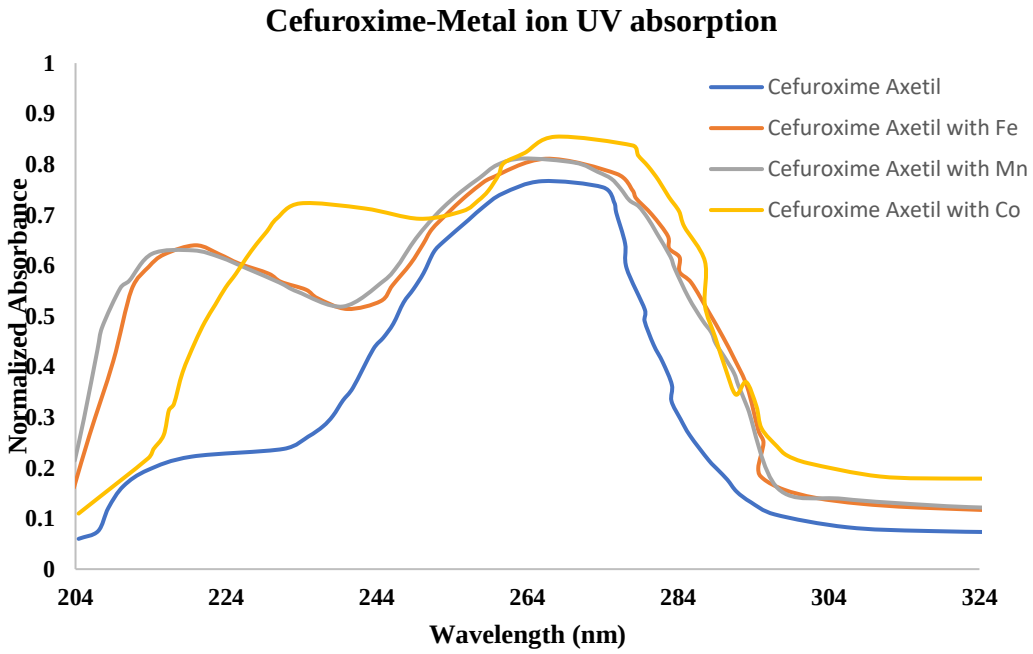

Figure 1: UV Spectra illustrated Cefuroxime Axetil in absence and presence of transition metal ions.

Some complexes showed d-d electronic transition band and the energy levels n, π, π* are perturbed. In the case of Zn (II)-antibiotic complexation, no such absorption peak was obtained as there was no d-d transition. Amoxicillin-metal complexes only had UV-Vis spectrometric analysis.

3.2. FTIR Spectroscopy

Successful complexation of cefuroxime and metal ions was ensured by the comparision of the characteristic infrared spectral bands of cefuroxime in both states. Before complexation there was no band in 1770-1800 cm^{-1} region demonstrated in figure 2. A significant band appeared in 1782 cm^{-1} which was obtained from the β-lactum ring's carbonyl group's stretching vibrations. This characteristic band was found almost at the same wave number in all complexes. Cefuroxime in free state showed a band at 1593cm^{-1} which was from the amide group's stretching vibrations.

Then the band disappeared into metal complexes. This suggested that the carbonyl oxygen from β-lactum ring did not participate in the bonding though coordination of metals occurred through amide carbonyl group. Antisymmetric and symmetric vibration bands appeared at 1545 cm^{-1} and 1389 cm^{-1} respectively for carboxylate group. Antisymmetric COO band shifted toward higher wave numbers and symmetric COO shifted toward lower wavenumbers suggesting interaction between the carboxyl group of cefuroxime and metal ions [24,25].

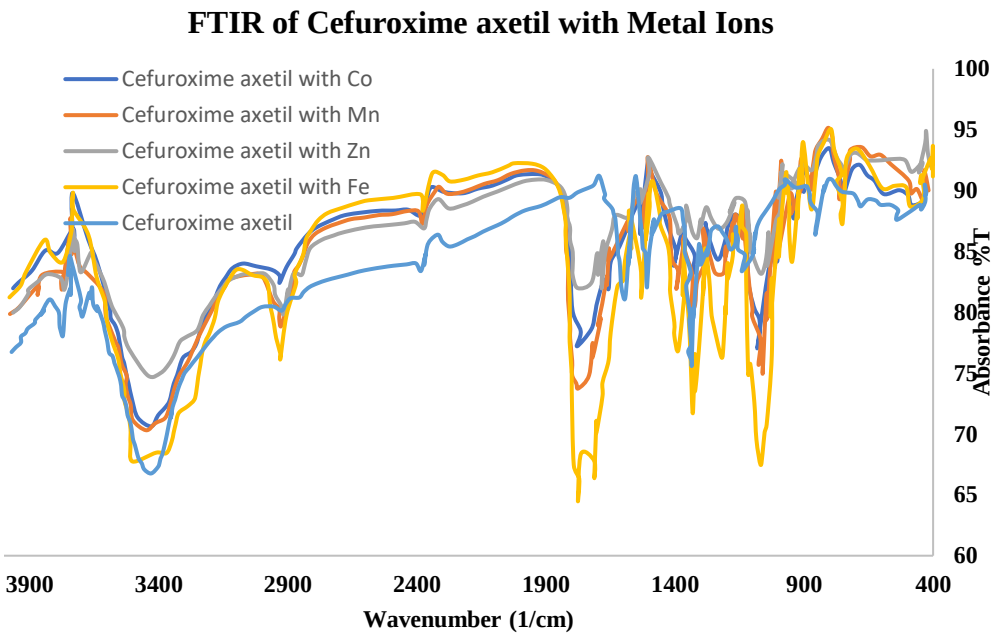

Figure 2: FTIR spectra represented interaction of metal ions with antibiotics as Fe-Cefuroxime, Zn-Cefuroxime , Mn-Cefuroxime, and Co-Cefuroxime complex .

3.3. High Performance Liquid Chromatographic (HPLC) analysis

Comparing the chromatogram of pure Cefuroxime Axetil and that of the mixture of Cefuroxime Axetil and zinc sulfate it was found that the retention time and the peak height of each other were not very closer to each other. The retention time of single drug Cefuroxime was 2.864 minutes and from the chromatogram of complex with zinc sulfate two different peaks has been detected. The retention time of one peak was 1.849 minutes with area 147607 and the other peak was found with the retention time 1.849 minutes with area 3309 demonstrated in figure 3 (A,B). These differences in the chromatogram indicated successful interaction.

Antibiotic complex with metal ions, especially zinc, is important for a variety of biological and medicinal purposes. In this instance, the complex displayed two peaks, one at 2.876 and the other at 1.849 minutes which is a new peak, whereas the pure antibiotic displays a peak at 2.86 minutes. Zinc ions are capable of interacting with Cefuroxime and form complexes that alter its composition and the functions. Low peak recovery in Cefuroxime-zinc complex may be attributed to the ability of Cefuroxime to chelate with zinc ions, altering the shape of a compound's peak and retension time.

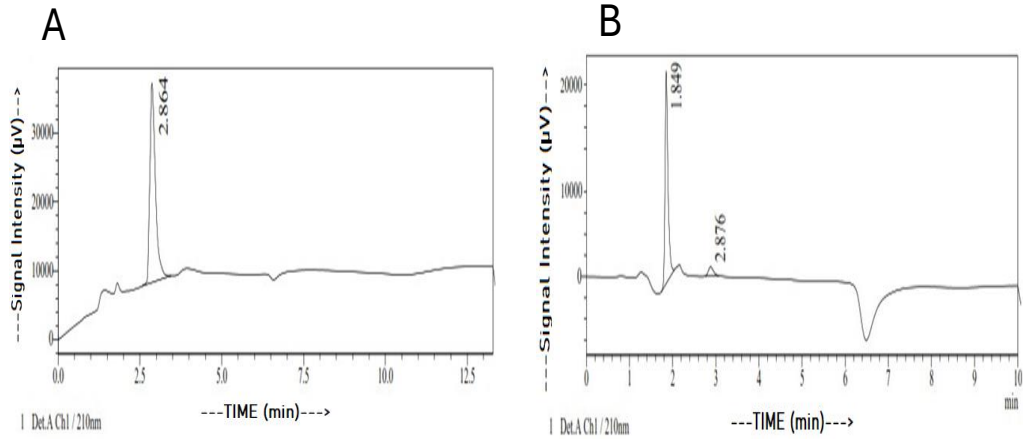

Figure 3: HPLC chromatogram of pure Cefuroxime Axetil (A), and complex of Cefuroxime Axetil-Zinc sulfate (B).

There was a definite interaction between Cefuroxime Axetil and the metal ions. Cefuroxime became more soluble and bonded with the solvent methanol. The solvent used was methanol-water (50:50). Details on antibiotics with and without metal ion modification are provided in Table 1. Thus, there was less interaction between the complex and stationary phase. So, retention time is found to be less for the complex.

Table 1: HPLC chromatogram of complex of samples with and without Metal ion modification

SN	Sample Type	Peak#	Ret. Time	Area	Height	Area%	Height%
1	Cefuroxime Axetil and Zinc sulfate [a]	1	1.849	147607	24984	97.81%	98.35%
2	Cefuroxime Axetil and Zinc sulfate [a]	2	2.876	3309	419	2.19%	1.65%
	Total		4.725	150916	25403	100%	100%
1	Cefuroxime Axetil [b]	1	2.864	342785	28970	100%	100%
	Total		2.864	342785	28970	100%	100%

[a] with modification Complex [b] without modification Complex

4. Ligand Binding

The synthesis, characterization, and analytical data of cefuroxime's complexes indicate that the antibiotic, second generation of cephalosporin, may form complexes with transition metal ions such as Zn^{2+}, Mn^{2+}, Co^{2+}, and Fe^{2+}.

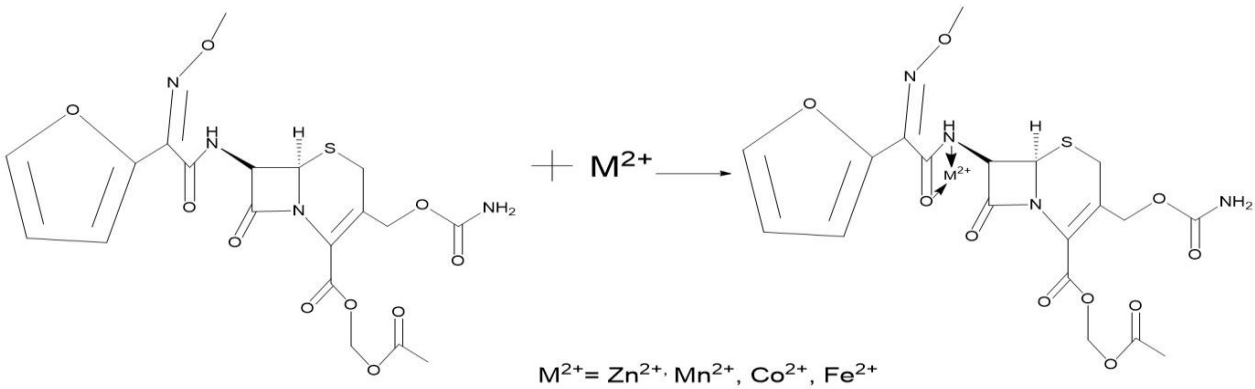

Figure 4: Coordination of cefuroxime axetil with zinc, manganese, cobalt, iron

Cefuroxime functions as a multidentate ligand in these compounds due to their several chelation routes, which include coordination through the lone pair of electrons from nitrogen of the NH_2 group, and the carboxylate. Figure 4 indicates the potential ligand binding of cefuroxime Axetil with the experimental metal ions through coordination bonding.

5. Conclusion

The main objectives of this study were to synthesize and characterize the obtained metal complexes with amoxicillin and cefuroxime. The complexes were subsequently studied by UV-Vis spectrophotometry, FTIR spectroscopy, and HPLC analysis, with metal cefuroxime being a predominant focus. It showed that the metal antibiotic complexes revealed modification in solubility and showed ability to alter their electrochemical behavior that can avert antibiotic oxidation. The solubility and stability of antibiotics can be enhanced by complexation with these metal ions, potentially increasing its bioavailability and shelf life.

CRediT authorship contribution statement

Malay Kumar Das: Formal analysis, Investigation, Software, Writing – original draft, Writing – review & editing.
Keya Das: Formal analysis, Software, Writing – original draft, Writing – review & editing.
Ashequl Alam Rana: project administration, supervision, Writing – review & editing.
Md. Ashaduzzaman: project administration, supervision, Writing – review & editing

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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