Nickel(II)-Complex of Ceftibuten Dihydrate: Synthesis, Characterization and Thermal Study

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ABSTRACT: Ceftibuten dihydrate is a semisynthetic, orally administered, third generation cephalosporin antibiotic which is effective against most of the pathogens causing infections in the respiratory tract. Complexation of ceftibuten dehydrate (Ligand, L) was performed with hydrated Ni(II) salt (Metal, M) in the ratio of 2:1 (L:M) in aqueous medium at 90 ^{o}C. The metal complex was then characterized by spectral techniques and thermal analyses. The FT-IR spectral data of metal complex suggested the monodentate bonding of metal ion to carboxylate group. Spectral evidence also supported the formation of five-membered ring *via* coordination of metal ion to β-lactam nitrogen and carboxylate group of parent drug. Thermal behavior of ligand and complex were studied. Thus, thermo-analytical (DSC and TGA) results also supported the formation of new metal complex, indicating the successful interaction of metal ion to ligand.

Key words: Ceftibuten, Ni(II)- complex, Interaction, Thermal analyses.

INTRODUCTION

Drug research is an important field of medicinal chemistry. It includes new drug synthesis with therapeutic importance[1-3], isolation of bioactive compounds from different parts of medicinal plants *via* solvent extraction[4,5] and metal complexation of drug with improved bioactivity.[6-8] Drug-drug interaction[9,10] is also an emerging field of drug research. Moreover, in advance study, computer aided design has been implemented to discover new drug.[11]

Presently metal complexation of drug is an important area of research in pharmaceutical chemistry. In this study, complexation of ceftibuten dihydrate has been performed using Ni(II) salt as metal source. Ceftibuten dihydrate is chemically (+)-(6R,7R)-7-[(Z)-2-(2-amino-4-thiazoyl)-4-carboxycrotonamido]-8-oxo-5-thia-1-azabicyclo(4,2,0)oct-2-ene-2-carboxylic acid, dihydrate with molecular formula $C_{15}H_{14}N_4O_6S_2{\cdot}2H_2O$ and molecular weight 446.45.[12] It is a class of β-lactam, orally administered third generation cephalosporin antibiotic, effective against the most of the pathogens causing infections in the respiratory tract.[13] Ceftibuten dihydrate belongs to bactericidal antibiotic that kills bacteria through binding of essential target protein of bacterial cell wall and thus inhibits replication.[14]

Literature survey showed that metal complexes of nitrogen containing ligands possess a variety of range of biological properties such as antibacterial, antifungal, antitumor and antiviral activities.[15-17] Actually the lipophilicity of parent ligand is increased through the complexation with metal ions and thus boost up the penetration capability of the ligand into the lipid membrane of bacteria. As a result, new cell wall formation is greatly hampered. Without a cell wall, a bacterial cell is defenseless to outside water and molecular pressures, which causes the cell to die quickly.[18,19] Thus, the antimicrobial activity of ligands can be improved through chelation.[20] Even some inactive ligands may acquire pharmacological properties upon chelation.[21] From the literature survey, it is also revealed that pharmacologically

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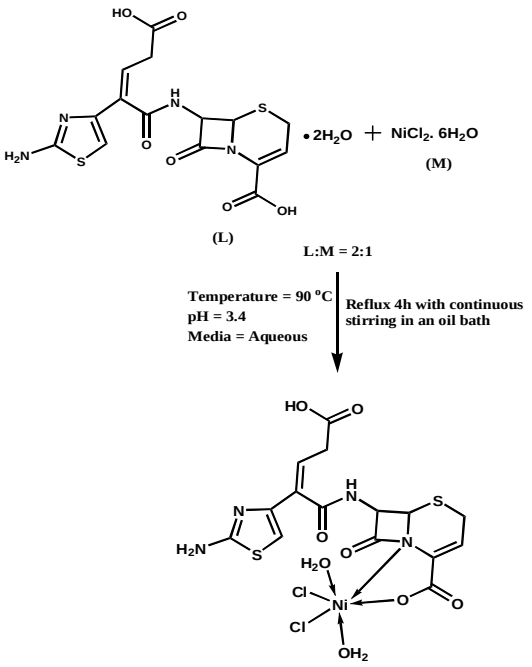
important metals like copper, nickel, magnesium, cobalt, chromium and zinc are widely used for complexation and thus, playing a vital role in the development of treatment of various life threatening infectious diseases.[22] In searching of more potent chemotherapeutic agent, researchers have also introduced mixed ligand complexes.[23] Recently, an article on Cu(II)-complex of ceftibuten dihydrate has been reported from our group.[24] In that work, Cu(II) salt was used as metal source. In current study, Ni(II) complex of ceftibuten dihydrate was synthesized as stated by the methods reported in previous article. After that the newly synthesized metal complex was characterized by using spectral techniques like FT-IR and thermal analyses like DSC and TGA.

MATERIALS AND METHODS

Instrumentation. Development of new drug-metal complex was verified by several analytical techniques like melting point determination, FT-IR spectra, DSC and TGA. Melting point of pure drug and its Ni(II)-complex were recorded by working with digital melting point apparatus (WRS-1B). FT-IR spectrophotometer (Model: 8400s, Shimadzu, Japan) was used to acquire FT-IR spectra. The spectra were taken as KBr discs in the region of 4000-400 cm^{-1}. DSC studies were performed in aluminum sealed pan at the temperature range of 20-700^oC by using DSC instrument (Model: DSC 131 EVO, Setaram Instrumentation, France). N_2 gas flow rate and temperature rising rate were kept at 20 ml/min and 10^oC/min, respectively to record the thermograms. TGA studies were carried out for both ligand and chelate using TGA 50H (Shimadzu, Japan). The thermograms were recorded at the region of 25-800 ^oC in aluminum pan, maintaining at 10 ^oC/min and 10 mL/min heat and N_2 gas flow rate, respectively.

Materials. The drug was collected from Incepta Pharmaceutical Ltd., Dhaka, Bangladesh as a gift. The potency of the drug was about 99%. Nickel(II) chloride ($NiCl_2.6H_2O$) was used as metal source to make coordinate complex. The solvents and other chemicals were procured from the local suppliers.

Synthetic procedure for complexation with Ni (II) salt. To verify the synthetic route as reported earlier[24], the Ni(II)-complex of ceftibuten dihydrate was prepared by maintaining same pH, solvent and temperature of reaction according to scheme-1. The ratio of ligand and metal in the complex formation was maintained at 2:1. A colored precipitated was obtained after complexation, which was also purified following same procedure as like Cu(II)-complex of ceftibuten dihydrate.[24] The complex was found to be air and moisture stable, dissolved in aqueous medium at 90^oC and organic solvent DMSO, not dissolved in common organic solvents like methanol, ethanol, acetonitrile, acetone and diethyl ether. Yield was obtained as 75% and recorded m.p. was 305^oC (decomposed).



Scheme 1. Synthetic scheme for complexation of ceftibuten dihydrate with $NiCl_2.6H_2O$.

RESULTS AND DISCUSSION

Thermal analysis. Both TGA and DSC analyses of pure drug, ceftibuten dihydrate and its metal complexes were studied to explore thermal stability as well as to establish melting point.[25,26] The TGA and DSC data are summarized in Table 1.

Table 1. Thermo analytical results of parent drug and its metal complexes.

Compound	Temperature of TGA (°C)	Weight loss (%) Found	DSC Temp. (°C)
Ceftibuten dihydrate (Parent drug)	20-176	9.8	98 endothermic
	176-396	55.8	
	396-630	91.8	242.7 exothermic
	630-800	93.6	
Ni(II) complex (Present work)	20-171	10.8	89.3 endothermic
	171-394	41.3	
	394-609	79.9	219.7, 308 endothermic
	609-800	83.3	
Cu(II) complex (Reported)[12]	25-175	8.32	86.7 endothermic
	175-311	34.7	
	311-507	75	269.2 endothermic
	507-800	83	

Thermogravimetric analysis (TGA). The structure of metal antibiotic complex can be proposed by using TGA.[27] Pure drug and its metal complexes showed multistage degradation profiles where mass changes were observed at 25°C and continued up to 800°C with increasing temperature. The resulting TGA curves of pure drug and its Ni(II) chelate are shown in Figure 1. Hydrated metal salts are usually used for coordination of drugs. In case of hydrated complex, water loss always takes place relatively at higher temperature (above 150°C) than uncoordinated complex.[28] Kumar *et al.* showed similar degradation pattern in TGA curve of Fe(II) and Ni(II) complex of penicillin G and ciprofloxacin.[29] Tahia *et al.* also showed a different degradation pattern of metallodrug, from its parent drug, levofloxacin.[17] In present study, a weight loss of 9.77% was found in TGA of pure drug at 176.21°C, corresponding to loss of water molecules. After that 55.78% weight loss was found at 396°C, 91.33% at 630°C and finally 93.64% weight loss was observed at 800°C. The drug-metal complex also showed multistage degradation pattern, starting with release of water molecules. The degradation pattern of metal complexes is completely different from parent drug, suggesting the successful interaction of drug and metal ion. In case of Ni(II)-complex of parent drug, weight loss was found as 10.78%, 41.29%, 79.93% and finally 83.34% at 171°C, 394°C, 609°C and 800°C, respectively. It is noted that the complex possessed better thermal stability compared to parent drug, and a residual mass was obtained even after heating to 800°C. Ali *et al.* reported similar multistage degradation pattern in case of metal(II) complexation of flucanozole, starting with initial loss of water molecule followed by removal of ligand moiety.[25]

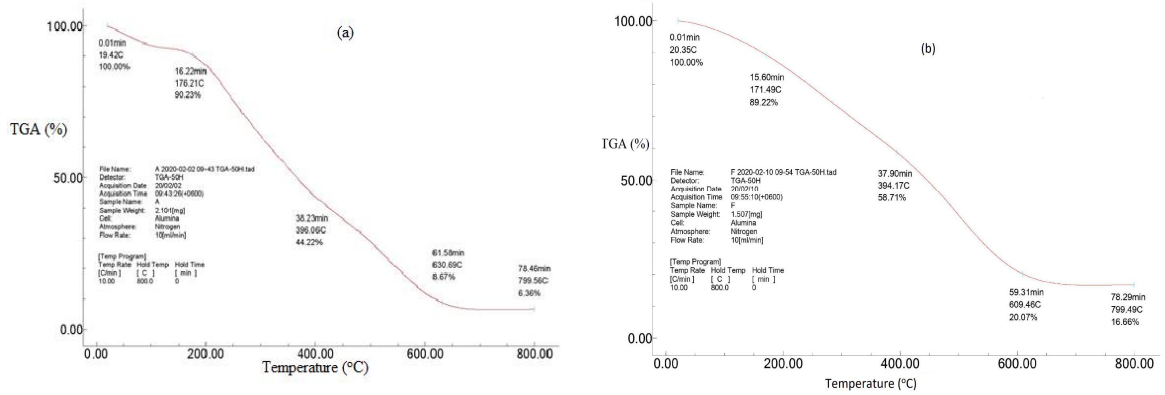


Figure 1. TGA thermograms of ceftibuten dihydrate (parent drug) (**a**), ceftibuten-Ni(II) complex (**b**).

Differential scanning calorimetry (DSC). The DSC curves recorded for parent drug and its complexes are shown in Figure 2. The DSC result of pure drug showed an endothermic peak at 98°C associated with dehydration of water molecules, and an exothermic peak at 242.7°C which corresponded to its melting point. The calorimetric curve of Ni(II)-complex of parent drug showed three endothermic

peaks. An endothermic peak at 89.35°C is associated with removal of water molecules. Another peak (endothermic) obtained at 219.76°C might be due to sample mass loss or sample phase transition. One more peak (endothermic) found at 308.35°C, considered as melting temperature of the complex. The absence of melting peak (242.7°C) of pure drug in the calorimetric curve of the complexes indicated that the drug metal interaction occurred which resulted in new and definite compound without the interference of starting materials. Similar findings in the DSC curve were obtained in the metal(II) complexation of fluconazole[25], Schiff base ligand derived from hydrazine benzoxazine[30], and 14, 15 and 16-membered macrocyclic ligands.[31] In case of Ni(II) complexation of Schiff base ligand derived from hydrazine benzoxazine, the authors found an endothermic peak at 108.62°C in DSC curve, corresponding to loss of hydrated water molecule. Another two peaks at 177.13°C for phase transition and at 322°C corresponding to melting were also reported.

FT-IR analysis. Formation of a new coordination complex as well as the binding site of ligand to metal ion were elucidated by analyzing FT-IR spectra. Any shifts in frequency or appearance of new peaks indicated the formation of new compound, different from starting material. The main vibrational frequencies of parent drug and its metal chelates are summarized in Table 2.

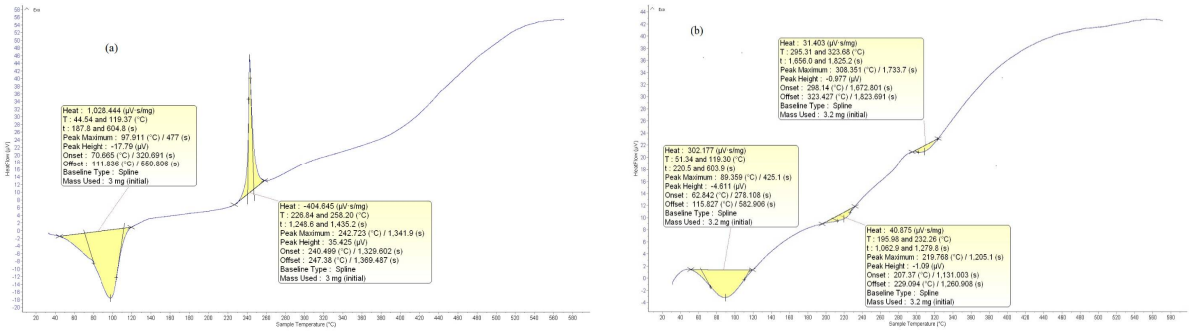


Figure 2. DSC thermograms of ceftibuten dihydrate (parent drug) (**a**), ceftibuten-Ni(II) complex (**b**).

Table 2. Characteristic FT-IR frequencies (cm^{-1}) for parent drug and its metal complexes.

Compound	ν(CO) lactam	ν(3°N) lactam	ν(COO) asymmetric	ν(COO) symmetric	$\Delta\nu$	ν(M-N)*
Ceftibuten dihydrate (Parent drug)	1770	1361	1651	1415	236	-
Ni(II)-complex (Present work)	1759	1103	1624	1398	222	478
Cu(II)-complex[24]	1755	1114	1629	1402	227	476

*M-N indicates the Metal–Nitrogen coordination bonding.

It was reported the formation of coordination complexes of different ligands by examining FT-IR spectra.[31,32] Figure 3 shows that in the FT-IR spectra of parent drug (free ligand) as well as its Ni(II)-chelate, significant changes in the frequency of absorbed radiation, characteristic of different functional groups of free ligand were observed due to interaction with metal ion. Analyzing IR data of ceftibuten dihydrate (Figure 3a), it was found that lactam (C=O) and carboxyl (C=O) bands appear at 1770 and 1651 cm^{-1}, respectively. Like Cu(II)-complex[24] of ceftibuten dihydrate, significant changes in the frequency of lactam (C=O) was not observed in Ni(II)-complex of pure drug as well. It means that the carbonyl group of lactam ring was not involved in the formation of coordination complexes

of ceftibuten dihydrate. The non-participation of lactam (C=O) in the formation of coordination complexes was observed in case of cefixime with copper ion complex[33] and penicillin G with iron(III) ion complex.[29] Sultana *et al.* also reported the non-involvement of lactam (C=O) in case of different metal complexes of cephradine.[34,35] In Ni(II)-complex, another two significant peaks appearing at 1624 and 1398 cm^{-1} are due to ν_{asym}COO- and ν_{sym}COO- stretching bands, respectively (Figure 3b). In this study, the separation value, $\Delta\nu > 200$ cm^{-1} ($\Delta\nu = \nu_{asym} - \nu_{sym}$) confirms monodentate fixing of metal ion with carboxylate group present in parent drug.[29,36]

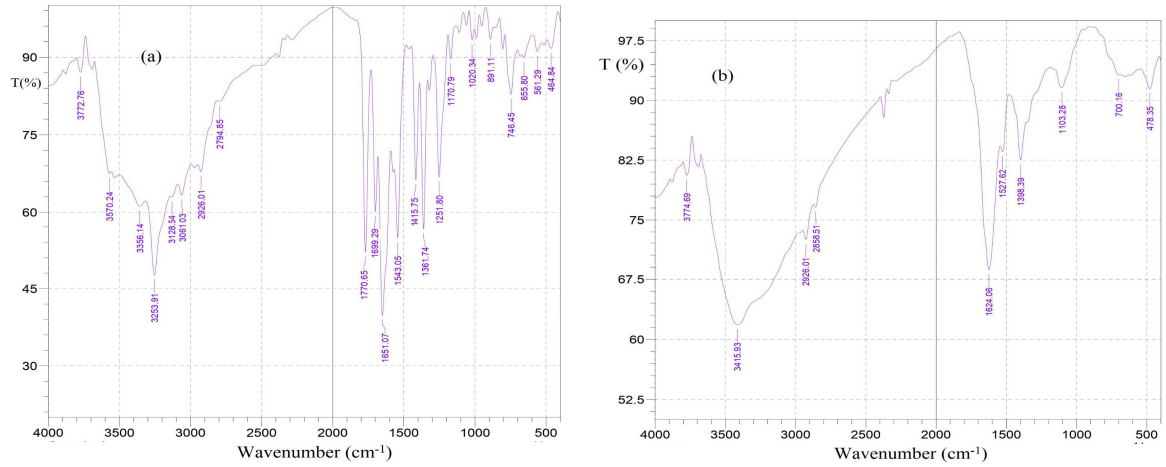


Figure 3. FT-IR spectra of ceftibuten dihydrate (parent drug) (**a**), ceftibuten-Ni(II) complex (**b**).

The frequency of 3^{o}N atom present in β-lactam ring of parent drug is shifted (1361→ 1103 cm^{-1}) in the complex, due to involvement of 3^{o}N atom in chelation.[24,34,35] There was a new peak found at 478 cm^{-1} in the FT-IR spectrum of the complex [Figure 3(b)] which was due to ν (Ni-N).[32] El Tabl *et al.* reported a peak at 480 cm^{-1} for Ni-N bond in Ni(II)-complexes of L-amino acids, used as foliar fertilizers. The M-N stretching vibration appearing at 478 cm^{-1} supports the formation of coordination complex through N atom in β-lactam ring. The FT-IR spectrum of the coordinated complex showed a broad band in the region of 3100~3600 cm^{-1} giving evidence of coordinated water present in the metal complex.[37] The presence of coordinated water was also identified in the cadmium (II) complex of tolfenamic acid by Salekin *et al.*[38] A peak at about 3313 cm^{-1} confirmed the presence of coordinated water in cadmium (II) complex of tolfenamic acid. In present study, the thermoanalytical results of metal complex also supported the presence of coordinated water in the complex. Therefore, both spectroscopic and thermal results stated the evidence for the formation of new Ni(II)-complex of ceftibuten dihydrate. Spectral studies indicated the coordination of Ni(II) ion through β-lactam nitrogen and carboxylate oxygen of drug molecule forming a five-membered ring (Scheme-1). In above mentioned complexes it was suggested monodentate coordination of metal ions to carboxylate group, according to the report[36] published previously as $\Delta\nu > 200$ cm^{-1} ($\Delta\nu = \nu_{asym\ COO^-} - \nu_{sym\ COO^-}$) which was supportive evidence of the scheme.

CONCLUSION

Ceftibuten-Ni(II) complex was synthesized from drug metal interaction of ceftibuten dehydrate with $NiCl_2$ in aqueous medium at 90^{o}C and then characterized. Both spectral and thermoanalytical results confirmed the new metal complex formation. The FT-IR spectrum of metal complex showed significant changes in the frequency of absorbed radiation, characteristic of different functional groups of free ligand, suggesting the formation of complex.

The DSC and TGA results also supported the formation of the complex.

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