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Original Article

Studying of Complexes of Zn(II) and Co(II) with Acyclovir (2-amino-9-((2-hydroxyethoxy)methyl)-1,9-dihydro-6H-purine-6-OH)

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Abstract *- In this paper, the optimal conditions for the synthesis of complex compounds of zinc (II) and cobalt (II) metals [$(C_8H_{10}N_5O_3)_2Zn$] and [$(C_8H_{10}N_5O_3)_2Co$] with aciclovir, one of the drugs used against viruses, were determined. In this case, 0.1 M $ZnSO_4$ and 0.1 M $CoSO_4$ solutions and 0.2 M, 0.4 M and 0.6 molar ethanol solutions of aciclovir were used. During synthesis, the temperature was 50-60 ^0C, and the mixing duration was two hours. In addition, all reactions were carried out at pH=5. Physico-chemical properties of obtained complex compounds were analyzed by methods such as IR-spectra, DTA and TGA, and Scanning Electron Microscope.*

Keywords *- Acyclovir, Zinc sulfate, Cobalt sulfate, Ethanol, Scanning Electron Microscope, IR-spectra***.**

1. Introduction

As an extension of our efforts to develop various antibacterial and anticancer agents, we are now looking at the contributions that antiviral agents can make. Acyclovir is an antiviral drug which acts against the Herpes viruses, including herpes simplex 1 and 2 (cold sores and genital herpes), varicellazoster(shingles and chicken pox) and the Epstein-Barr virus (mononucleosis) [1,2].

Our approach is to utilize known successful drugs and incorporate them into polymers where the other "co-monomer" can also act to enhance the biological activity. Acyclovir and its metal Complexes are widely used to inhibit several herpes viruses[3,4]. The preparation and use of Acyclovir compounds with several metals are given below[5]. The oxidation of acyclovir by diperiodatocuprate(III) in aqueous alkaline media at a constant ionic strength of 0.01 mol·dm−3 was studied spectrophotometrically at 25 °C. The reaction between acyclovir and DPC in alkaline media exhibits 1:4 stoichiometry (acyclovir: diperiodatocuprate(III))[6].

Nanoparticles of carboxymethyl cellulose acetate butyrate complexed with the poorly soluble antiviral drug acyclovir (ACV) were produced by precipitation, and the formulation process and properties of nanoparticles were investigated. Two different particle synthesis methods were explored—a conventional precipitation method and rapid precipitation in a multi-inlet vortex mixer. The particles were processed by rotavap followed by freeze-drying[7, 8]. Three diazoles namely 5-methyl-1,3,4-oxadiazole -2(3H)-thione, 5-methyl-1,3,4-thiadiazol-2(3H)-thione and 4-amino-5-methyl-2H-1,2,4-triazole-3-thiol were synthesized from acetic acid or ethyl acetate and this compound was tested in vitro against Gram-positive and Gram-negative bacteria, the results showed that Hg2+ complexes of oxadiazole and thiadiazole derivatives showed significant antibacterial effects on vancomycin[9]. Next work studied two types new copper(II) complexes with the antiviral drug acyclovir(H2L) have been synthesized: the mononuclear complex [Cu(H2L)Cl2]·1.5H2O and the binuclear one [Cu2(H2L)3(H2O)2Cl·5(H2O) [10].

Acyclovir (acycloguanosine, 9-carboxy methoxy methyl guanine is the most commonly used guanine analog antiviral drug. It is primarily used for the treatment of herpes simplex as well as herpes zoster (shingles) infections[11,12]. The metal-coordinating properties of aciclovir are currently of great interest[5-8] from a mechanistic point of view, with metal ions (Zn2+) or (Mg2+, Mn2+ and Co2+) containing some DNA polymerases activated. In addition, metal complexes of aciclovir can show antiviral activity, different from the free ligand [13].

1.1. The Purpose of Research

Synthesis of new complex compounds based on Zn^{2+} and Co^{2+} with aciclovir, one of the physiologically active substances, consists of studying the composition, structure and physicochemical composition of the obtained complex compounds.

1.2. Research Methods

In this research work, the results of the analysis obtained using the IK spectrophotometer and MIRA-2 LMU SEM scanning electron microscope were used to study the complex compounds synthesized on the basis of Zn^{2+} and Co^{2+} with acyclovir. In addition, the analysis results obtained from the derivativeogram of the differential heat analysis were used.

2. Experimental Part

2.1. Synthesis of Zn(II) Complex with Acyclovir

$ZnSO_4$*$5H_2O$, acyclovir, 96% ethanol and distilled water were used as solvents for the synthesis of Zn(II) complex compounds. The synthesis process was carried out in an open laboratory. Compounds were synthesized by taking 10 ml of 0.1 molar aqueous solutions of $ZnSO_4$ and adding 0.2M, 0.4M, and 0.6 molar acyclovir solution in ethanol to the boiler for 2 hours and 10 minutes. H_2SO_4 was used in order to ensure pH=5 of ZnSO4 solutions.

To get rid of sulfuric acid, an equivalent amount of 0.01 M solution of $Ba(NO_3)_2$ was used.The entire synthesis process was carried out in the temperature range of 50-60 ^{0}C. The solutions of the isolated complex were colorless. The solution was filtered in order to get rid of BaSO4 precipitation from the obtained colorless solutions. To reduce the water and ethanol in the solution, the solution was evaporated in a water bath.When the solvents were sufficiently reduced, acetone was added to separate the complex compound from the remaining solution. As a result, crystals formed at the bottom of the container.

2.2. Synthesis of Co(II) Complex with Acyclovir

In the synthesis of complex compounds of Co(II), $CoSO_4$*$7H_2O$, aciclovir, 96% ethanol and distilled water were used as solvents. The synthesis process was carried out in an open laboratory. By taking 10 ml of a 0.1 molar aqueous solution of $CoSO_4$ and adding 0.2 M, 0.4 M and 0.6 molar aciclovir in ethanol, the compounds were synthesized on a shaker for 2 hours and 22 minutes. H_2SO_4 was used in order to ensure pH = 5 in the environment of $ZnSO_4$ solutions.

In order to get rid of sulfuric acid, an equivalent amount of 0.01 molar solution of $Ba(NO_3)_2$ was used. The entire synthesis process was carried out in the temperature range of 50-60 ^{0}C. The color of the isolated complex was reddish blue. The solution was filtered to get rid of BaSO4 precipitation from the obtained solution. To reduce the water and ethanol in the solution, the solution was evaporated in a water bath. When the solvents were sufficiently reduced, acetone was added to separate the complex compound from the remaining solution. As a result, crystals formed at the bottom of the container[14,15]. The IK-spectrum, SEM and elemental analysis of the obtained complexes of both Co(II) and Zn(II) were studied.

3.Results

3.1. IR Spectrum Analysis of Zn(II) Complex with Acyclovir

The physico-chemical analysis, composition and structure of the synthesized [Zn(L)2] complex was studied using an IR-spectrum device FTIR (Perkin Elmer, Llantrisant, Great Britain). FTIR spectra of aciclovir showed a peak at 3439 cm^{-1} due to -OH stretching vibrations (Fig. 1). The peaks of extension vibration-NH, aliphatic-CH, -C=O, -C=N and –C-O-C functional groups are 3184 cm^{-1}, 2918 cm^{-1}, 1707 cm^{-1}, 1487 cm^{-1} and 1182 cm^{-1} for acyclovir, respectively. It was confirmed to be 1182 cm^{-1}.

3.2. IR spectrum analysis of Co(II) complex with acyclovir.

The physico-chemical analysis, composition and structure of the synthesized [Co(L)2] complex were studied using an IR-spectrum device FTIR (Perkin Elmer, Llantrisant, Great Britain).

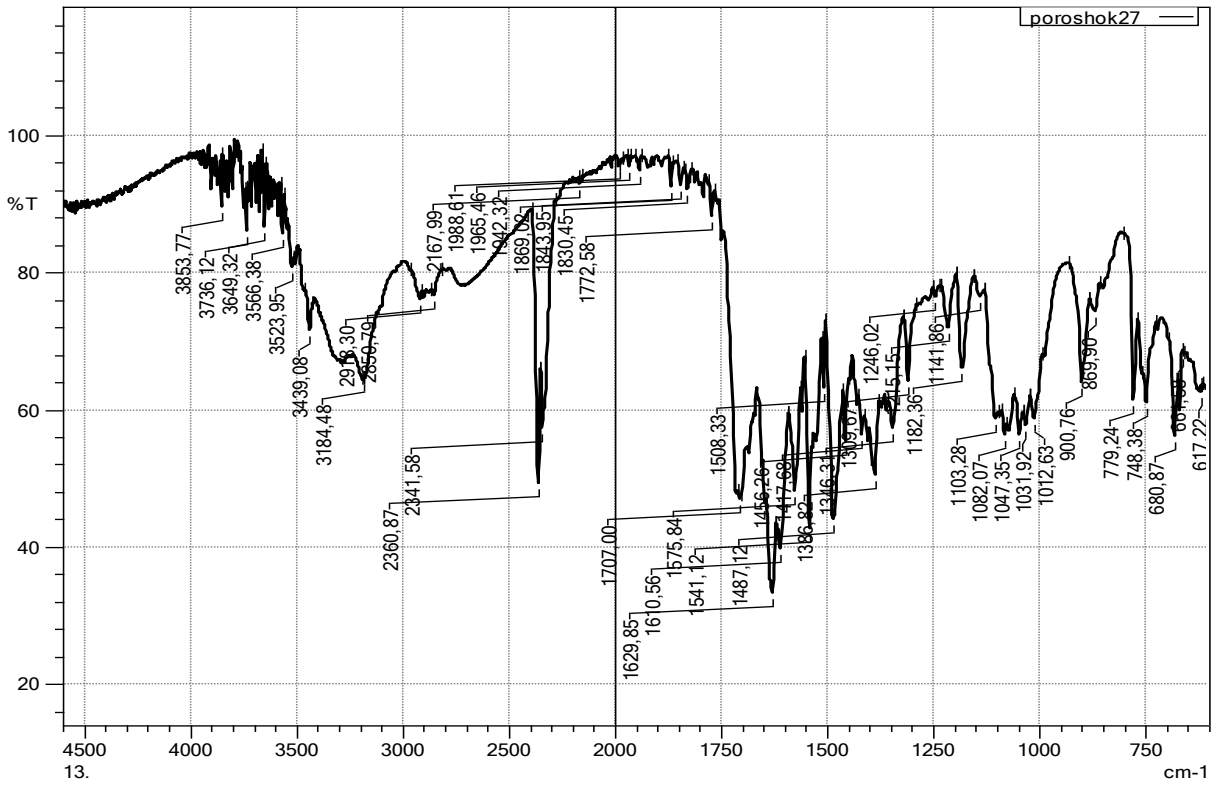

Fig. 1 IR spectrum analysis of [Zn(L)2] ligand.

Table 1. Analysis of [Zn(L)2] ligand.

Wavenumber	Chemical bonds	Material
3439.08	ν(O-H)	Aciclovir
3184.48	ν(N-H)	Aciclovir
2918.30	ν(C-H)	Aciclovir
1707.00	ν(C=O)	Aciclovir
1487.12	ν(C=N)	Aciclovir
1182.36	ν(C-O-C)	Aciclovir

Table 2. Analysis of the complex compound [Zn(L)2]

Wavenumber	Chemical bonds	Material
3329.14	ν(O-H)	Aciclovir
3182.55	ν(N-H)	Aciclovir
1712.79	ν(C-H)	Aciclovir
1633.71	ν(C=O)	Aciclovir
1047.35	ν(C-O-C)	Aciclovir

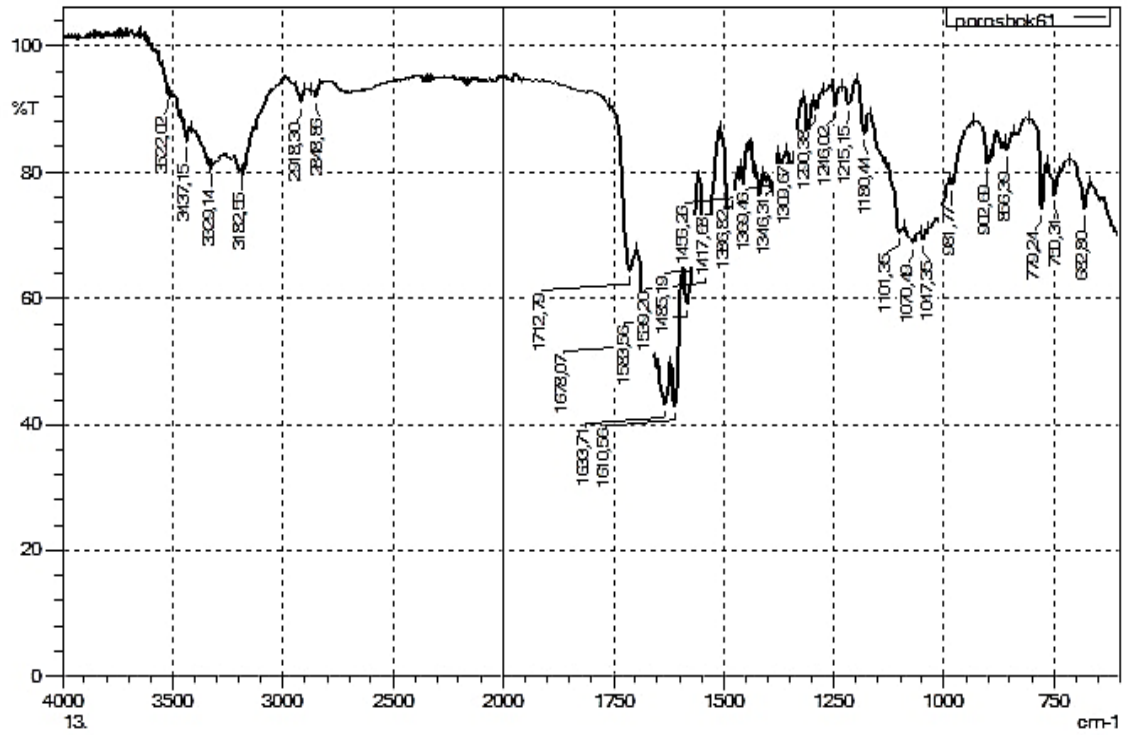

Fig. 2 IR-spectrum analysis of the complex compound [Zn(L)2]

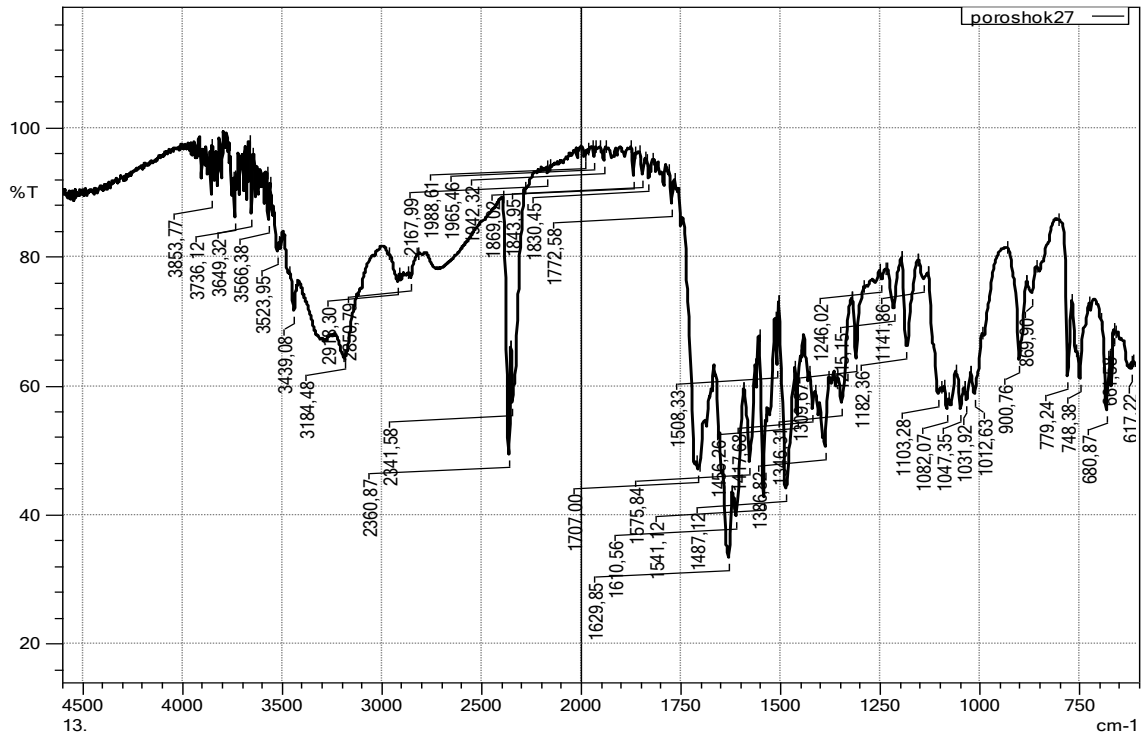

Fig. 3 IR spectrum analysis of [Co(L)2] ligand

Table 3. Analysis of [Co(L)2] ligand

Wavenumber	Chemical bonds	Material
3439	ν(O-H)	Aciclovir
3184	ν(N-H)	Aciclovir
2361	ν(C-H)	Aciclovir
1707	ν(C=O)	Aciclovir
1487	ν(C=N)	Aciclovir
1182	ν(C-O-C)	Aciclovir

Table 4. Analysis of [Co(L)2] complex compound

Wavenumber	Chemical bonds	Material
3308	ν(O-H)	Aciclovir
2918	ν(N-H)	Aciclovir
2359	ν(C-H)	Aciclovir
1636	ν(C=O)	Aciclovir
1047	ν(C-O-C)	Aciclovir

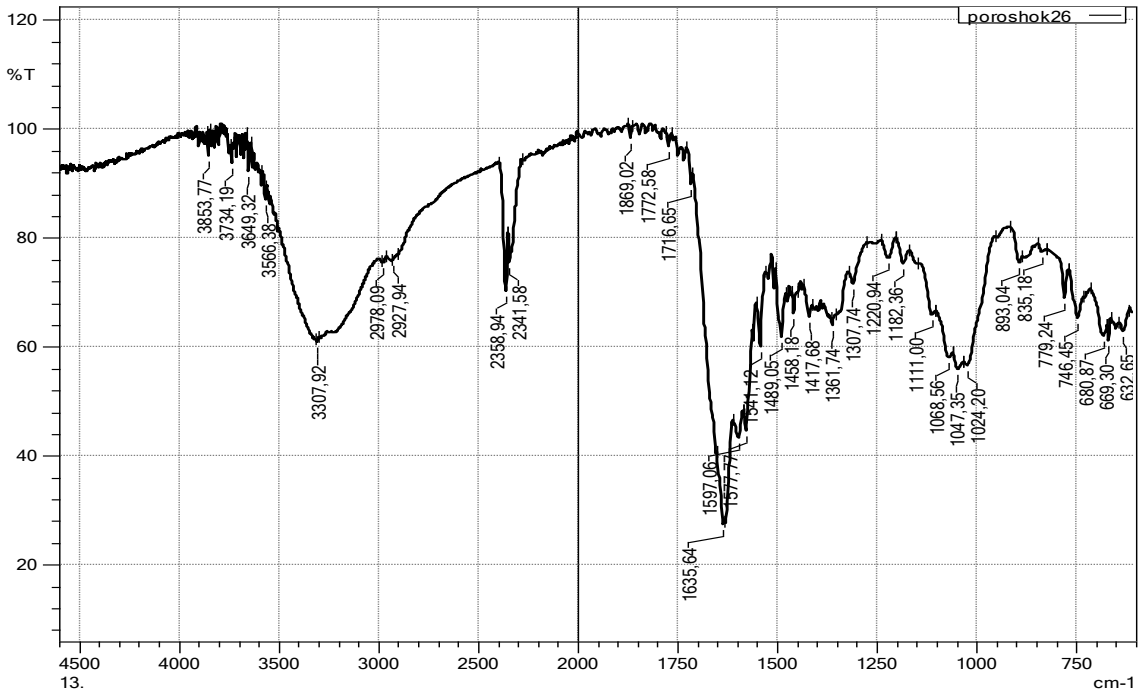

Fig. 4 IR spectrum analysis of [Co(L)2] complex compound

IR-spectR of aciclovir showed a peak at 3439 cm^{-1} due to -OH stretching vibrations (Fig. 3). The peaks of extension vibration-NH, aliphatic-CH, -C=O, -C=N and –C-O-C functional groups are 3184 cm^{-1}, 2918 cm^{-1}, 1707 cm^{-1}, 1487 cm^{-1} and 1182 cm^{-1} for acyclovir, respectively.

The figure 4 shows the infrared spectra of the cobalt complex with acyclovir. The reflection zone of the complex at 3308 cm^{-1}, 2918 cm−1, 2359 cm^{-1}, 1636 cm^{-1}, and 1047 cm^{-1} is O-H stretching, N-H stretching, CH stretching, C=O stretching, and related to the C-O-C stretch. acyclovir swing.

On the other hand, the reflective band at 1487 has disappeared due to the C=N bond. This phenomenon can be suggested by the formation of a new chemical bond between N and Co[16].

3.2. Scanning Electron Microscope Analysis

The morphology of the surface of this synthesized $[(C_8N_5O_3H_{10})_2Zn]$ complex was also studied using SEM analysis. It was also determined that the composition of the obtained $[(C_8N_5O_3H_{10})_2Zn]$ complex, which was studied by elemental analysis, has the correct percentage of elements by mass. The mass ratio of the elements in the synthesized complex showed C-37.4%, N-27.3%, O- 18.7%, and Zn-12.6% in percent. (Fig. 5), which shows that the gross formula of the synthesized complex is $[(C_8N_5O_3H_{10})_2Zn]$.

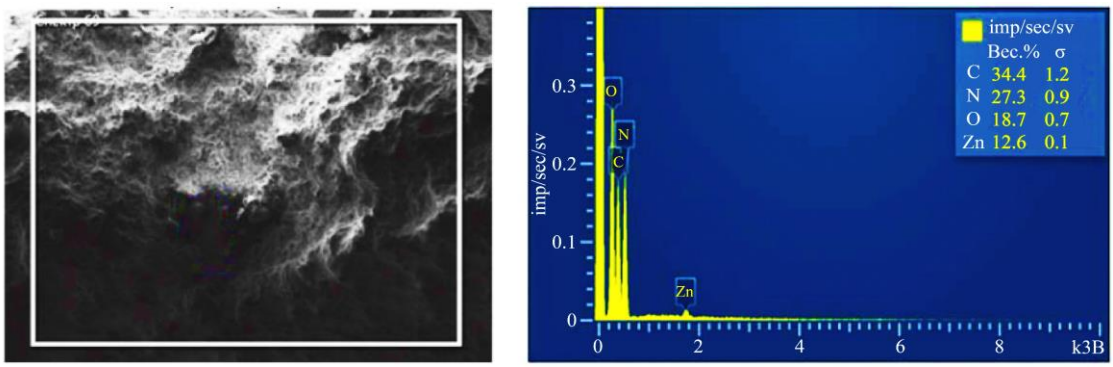

Fig. 5 Scanning electron microscope (a) and elemental analysis (b) analysis of the complex containing $[(C_8N_5O_3H_{10})_2Zn]$

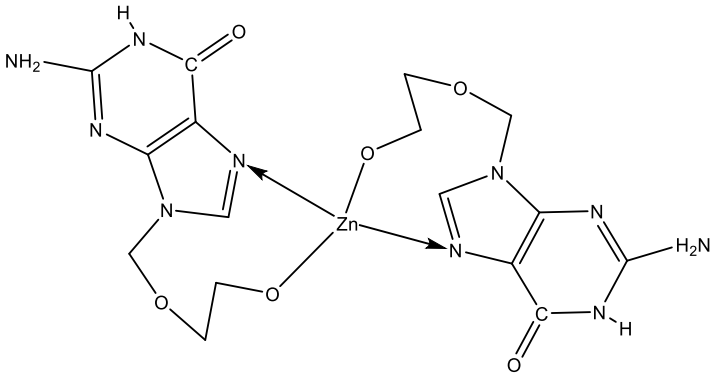

Fig. 6 Graphical structure of the complex compound [Zn(L)2]

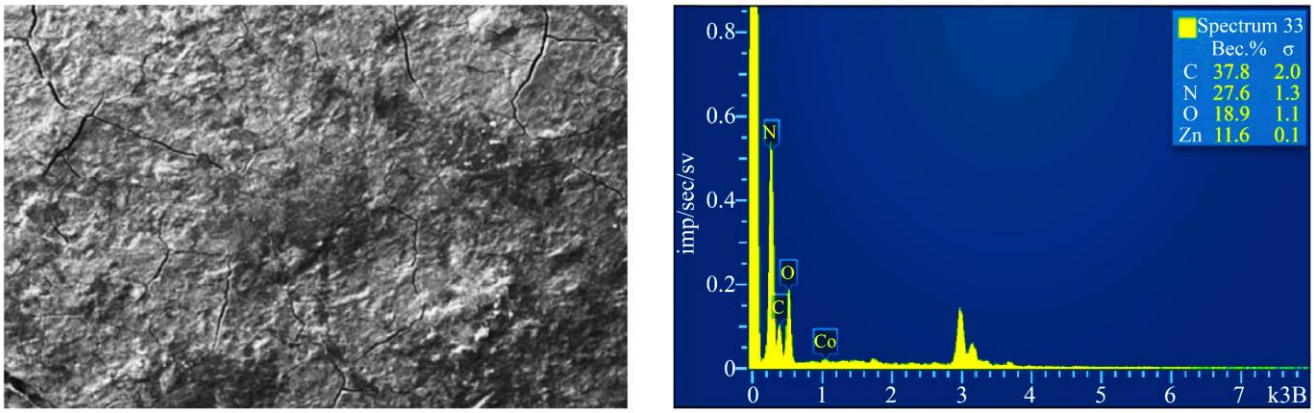

Fig. 7 Scanning electron microscope (a) and Elemental analysis (b) Analysis of the [(C8N5O3H10)2Co] complex

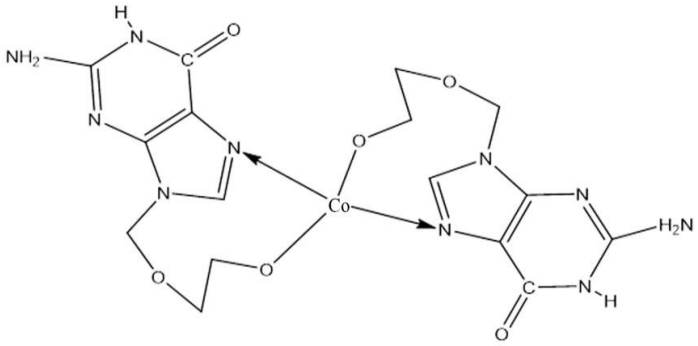

Fig. 8 Graphical structure of the complex compound [Co(L)2]

The composition of the synthesized complex was studied using the SEM-EDX method. The mass ratio of the elements in the synthesized complex showed that C- 37.8%, N- 21.6%, O- 18.9%, and Co- 11.6%. (Fig. 6), which shows that the gross formula of the synthesized complex compound is $[(C_8N_5O_3H_{10})_2Co]$.

3.3. Thermal Analysis of Zn(II) Complex with Acyclovir

The thermal stability of the synthesized substance was analyzed by differential-thermal and thermogravimetric methods on the DTG-60 device of the Japanese company SHIMADZU.

It was studied in the derivativeograph at a speed of 10 degrees/min, with the sensitivity of T-900, TG-200, DTA-1/10, and DTG-1/10 galvanometer, by an automatic recording of the derivativeogram[17].

The derivative diagram of the complex compound is presented in Figure 4, which consists of 2 curves. The thermogravimetric analysis (TGA) curve (curve 1) analysis showed that the TGA curve mainly occurs in the 3 intensive decomposition temperature ranges. The first thermal decomposition starts at 39.41 ^{0}C, takes 12.28 minutes to reach 147.45 0C, and ends with 5.570% mass loss due to the vaporization of the gas in the compound. The second thermal decomposition takes 26.32 minutes from 153,62 ^{0}C to 288,85 ^{0}C. It ends with a mass loss of 22.705% due to the decomposition of additives in the mixture. The third thermal decomposition takes 77.97 minutes from 287.76 ^{0}C to 790.99% ^{0}C with a 44.265% mass reduction. It can be seen from the differential thermal analysis of the complex compound that 4 endothermic process effects were observed at temperatures of 59,20 ^{0}C, 161,39 ^{0}C, 203,28 ^{0}C, 264,09 ^{0}C and 713,73 ^{0}C.

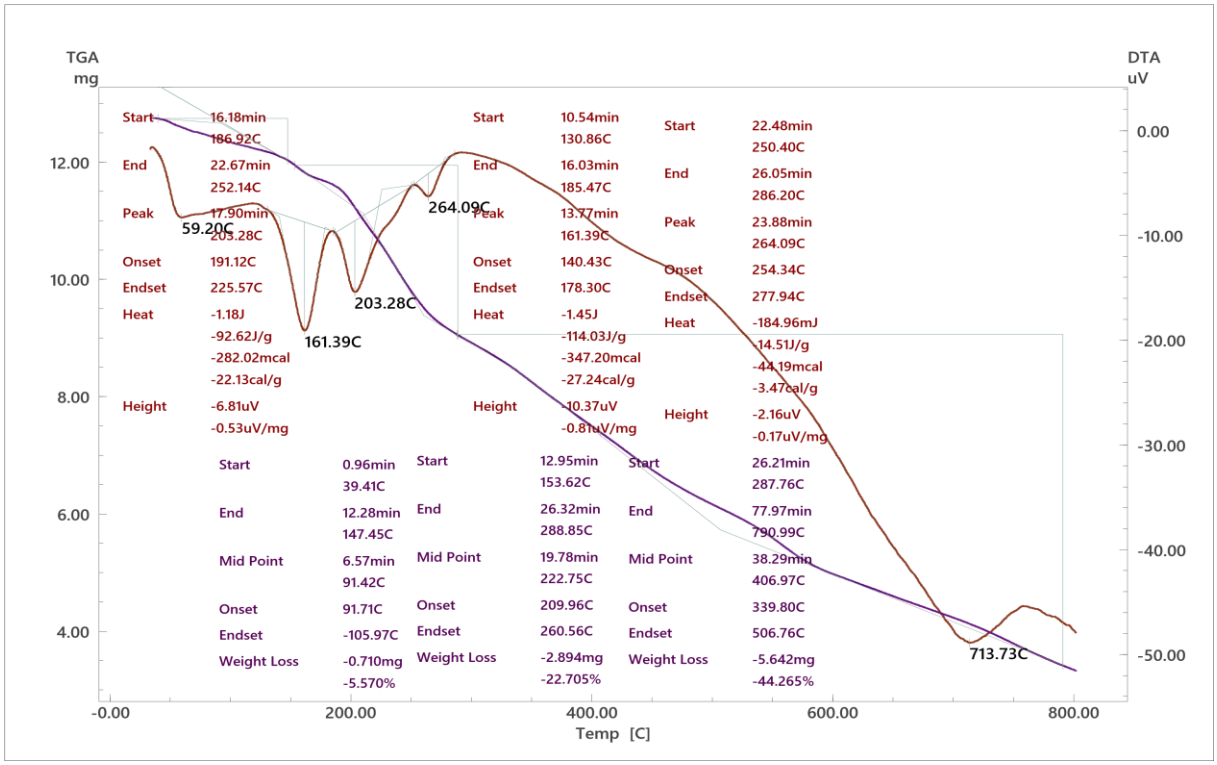

Fig. 9 Thermogravimetric (TGA) and differential thermal analysis (DTA) derivatogram of [Zn(L)2] complex compound

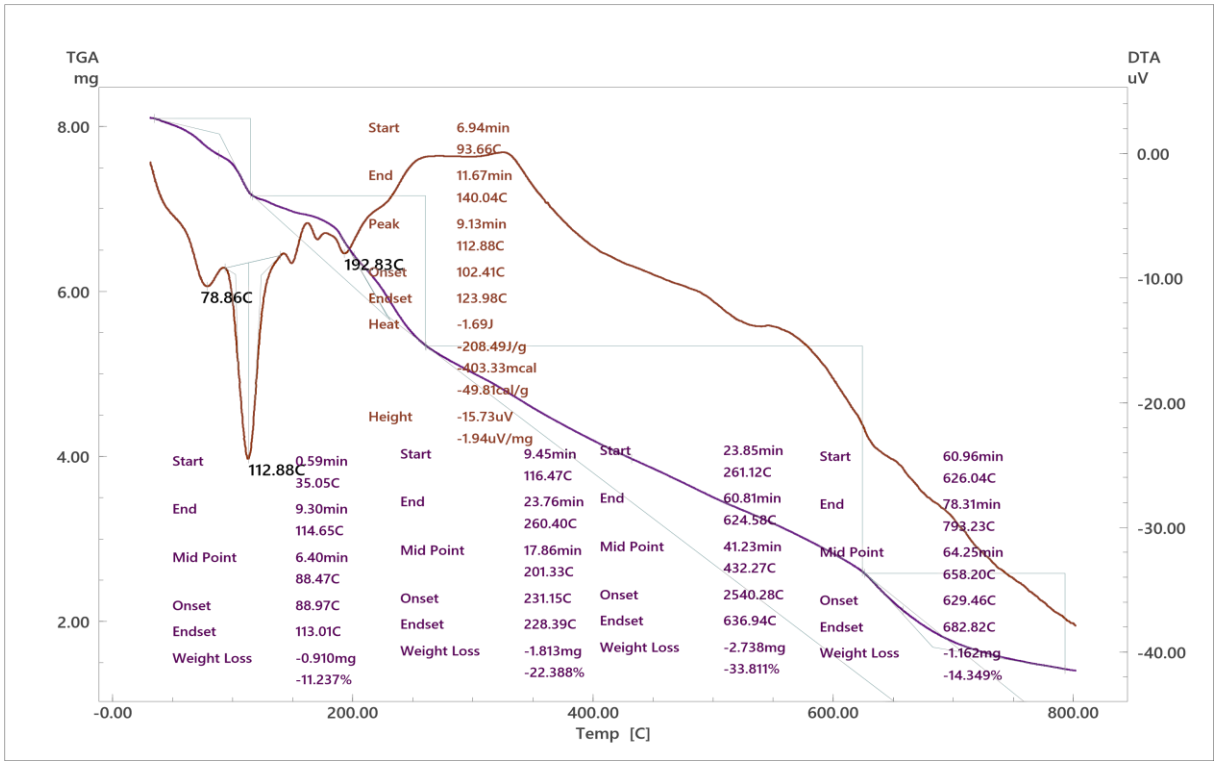

Fig. 10 Thermogravimetric (TGA) and differential thermal analysis (DTA) derivatogram of the complex compound [Co(L)2]

3.4. Thermal Analysis of Co(II) Complex with Acyclovir

The thermal stability of the synthesized substances was analyzed by differential-thermal and thermogravimetric methods on the device of the Japanese company SHIMADZU-DTG 60. It was studied in the derivativeograph at a speed of 10 degrees/min, with the sensitivity of T-900, TG-200, DTA-1/10, and DTG-1/10 galvanometer, by the automatic recording of the derivativeogram. Thermal analysis of [Co(L)2] complex compound. 8,098 mg was taken for thermogravimetric analysis of the complex compound, and the process was studied at a temperature of 20-800 ^{0}C.

The obtained analysis showed that the complex compound synthesized on the basis of Co^{2+} and acyclovir is thermally decomposed in 4 stages. The first thermal

decomposition starts at 35,05 ^{0}C and takes 9.30 minutes to reach 114,65 ^{0}C and ends with a mass loss of 11.237% due to the vaporization of the compound gas. The second thermal decomposition takes 23.76 minutes from 116,47 ^{0}C to 260,40 ^{0}C. It ends with a mass loss of 22.388% due to the decomposition of water vapor in the mixture. The third thermal decomposition takes 60.81 minutes from 261.120C to 624.58 ^{0}C and ends with a mass loss of 33.811% due to the decomposition of additives in the mixture. The fourth thermal decomposition took 78.31 minutes from 626.04 ^{0}C to 793.23 ^{0}C, reducing the mass by 14.349%. It can be seen from the differential thermal analysis of the complex compound that 3 endothermic process effects were observed at temperatures of 78,86 ^{0}C, 112,88 ^{0}C, and 192,83 ^{0}C.

4. Conclusion

In conclusion, it can be said that the optimal conditions for the complex formation of Zn(II) and Co(II) with acyclovir were studied. Extraction of the obtained complexes from the solution and their structure and other properties were studied and analyzed using various physico-chemical (Scanning Electron Microscope, IR-spectrum, DTA and TGA) analyses. Based on the results of the analysis, an approximate structural formula of the obtained complex was proposed.

Acknowledgment

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