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SYNTHESIS AND CHARACTERIZATION OF COMPLEXES FORMED BY Fe(III), Cr(III), Co(II), Cu(II), Cd(II), AND Ag(I) IONS WITH THE DRUG CAPTOPRIL AND THE AMINO ACID GLYCINE

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ABSTRACT. The capability of Fe(III), Cr(III), Co(II), Cu(II), Cd(II), and Ag(I) ions to form stable mixed-ligand complexes was examined. The ligands are the antihypertensive drug captopril (L_1) and the glycine amino acid (L_2). The characterization data suggest that Fe(III), Cr(III), Co(II), Cu(II), and Cd(II) ions react with the L_1 and L_2 ligands in a ratio of 1:1:1 (metal ion: L_1:L_2), whereas the Ag(I) ions interacted with the ligands in a 2:1:1 ratio (metal ion: L_1: L_2). Results suggest that the L_1 ligand capture the metal ions using the S atom of the mercpto (SH) group and the O atom of the amide (C=O) group, whereas the L_2 ligand captures the metal ions using the O and N atoms of the carboxylate and amino groups, respectively. The XRD analysis demonstrated that Fe(III), Cr(III), Co(II) and Cu(II) complexes had well-defined and well-crystallized morphology, whereas the Cd(II) and Ag(I) complexes mainly possessed an amorphous structure. The microscopic characterizations indicate that the particles of Fe(III), Cr(III), Co(II), and Cu(II) complexes had rod-like shaped morphology with well-defined and clear shapes. The morphology of Cd(II) and Ag(I) complexes did not form short or long rods but rather contained particles in small aggregated shapes.

KEY WORDS: Drug captopril, Mixed-ligand complex, Glycine, Metal ion, Thermal decomposition

INTRODUCTION

Metallodrugs constitute a class of interesting chemical compounds that contain a drug molecule and a metal ion, especially a transition metal ion. The coordination chemistry of this class of compounds has attracted considerable interest from pharmacists, biologists, and chemists alike. Numerous metal-based complexes and metallodrugs have been proven to possess potential biological activities, such as antiviral, antifungal, antibacterial, and anticancer [1-5], and these potential pharmaceutical properties are useful for treating various human diseases and for use as chemotherapeutics, such as cisplatin, for cancer treatment. Metal-based complexes of transition metal ions have been utilized as therapeutic agents and drugs for the treatment of neurological disorders, diabetes, inflammation, infection control, and carcinomas [6-12]. Two effective properties of transition metals enabling the design and development of more biologically active metallodrugs and metal-based complexes: (1) the capability of transition metals to exhibit different oxidation states, and (2) the capability of transition metals to interact with multiple metal-binding sites [12-15].

One of the leading causes of death across the world is hypertension. A broad diversity of antihypertensive drugs used for the treatment of the “silent killer” includes several classes of drugs: (1) beta blockers (such as tenormin, corgard, lopressor inderal); (2) calcium channel blockers (such as diltiazem, verapamil, nifedipine); (3) angiotensin-converting enzyme inhibitors (such as captopril, enalapril, lisinopril); (4) angiotensin receptor blockers (such as losartan,

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*Corresponding authors. E-mail: msrefat@tu.edu.sa valsartan); (5) alpha agonists (such as clonidine, catapres, aldamet); (6) alpha-1 blockers (such as doxazosin, terazosin, prazosin); and (7) direct vasodilating agents (such as nitroprusside) [16]. Captopril, a widely used hypertensive drug belongs to the angiotensin-converting enzyme inhibitor family, is a white to off-white powder with a melting point of 104 to 108 °C, an empirical formula of $C_9H_{15}NO_3S$, a molecular weight of 217.29 g/mol, and a chemical name of *N*-[(S)-3-mercapto-2-methylpropionyl]-L-proline. Captopril is an orally active drug used therapeutically for the treatment of high blood pressure [17]. Glycine is the simplest amino acid and is the only amino acid that does not have optical isomers. Its molecular structure indicates that it is composed of a single carbon bonded to an amino group on one side and to a carboxylic group on the other side (NH_2CH_2COOH). In the human body, glycine contributes to hormones assembly, enzyme and muscle protein structures, antibody production, and calcium absorption [18].

We believe that manufacturing new metallodrugs that contain two ligands, a drug and a vital molecule, such as an amino acid, may be a crucial step in developing effective metal-based drugs. Therefore, this study focused on several parameters: (1) Synthesizing six mixed-ligand complexes that containing two ligands, namely, a drug (captopril; referred to as L_1), and an amino acid (glycine; referred to as L_2). The two ligands (L_1 and L_2) were complexed with Fe(III), Cr(III), Co(II), Cu(II), Cd(II), and Ag(I) metal ions in a MeOH:H_2O media with a 1:1:1 (metal ion: L_1:L_2) ratio at 70°. (2) Exploring the mode of interactions and the chelating properties of L_1 and L_2 toward the metal ions in question based on the data collected from ultraviolet/visible (UV), Fourier-transform infrared (FT-IR), nuclear magnetic resonance (^{1}H NMR), and electron spin resonance (ESR) spectra in addition to elemental analyses results. (3) Observing the thermal decomposition behavior of the synthesized mixed-ligand complexes by thermogravimetry (TG/DTG) and the microstructure and phase purity of the complexes based on results from XRD and scanning and transmission electron microscopy (SEM and TEM, respectively) techniques.

EXPERMENTAL

Chemicals

The ligands were L_1: Captopril ($C_9H_{15}NO_3S$; 217.29 g/mol; purity ≥ 98%), and L_2: Glycine (NH_2CH_2COOH; 75.07 g/mol; purity ≥ 99%). The investigated metal ions were: Fe(III): $FeCl_3\cdot 6H_2O$ (270.30 g/mol; purity ≥ 98%), Cr(III): $CrCl_3\cdot 6H_2O$ (266.45 g/mol; purity ≥ 98%), Co(II): $CoCl_2\cdot 6H_2O$ (237.93 g/mol; purity 99.9%), Cu(II): $CuCl_2\cdot 2H_2O$ (170.48 g/mol; purity ≥ 99.0%), Cd(II): $CdCl_2\cdot xH_2O$ (183.32 g/mol, anhydrous basis; purity 98.0%), and Ag(I): AgCl (143.32 g/mol; purity 99.0%). The ligands were obtained from Fluka (Seelze, Germany), and the metal ion slats of analytical grade were obtained from Merck KGaA (Darmstadt, Germany) and Sigma-Aldrich (St Louis, MO, USA).

Analytical methods

The UV/Vis (200–1000 nm) data, FT-IR (400–4000 cm^{-1}), ^{1}H NMR (600 MHz; DMSO-d_6), and electron spin resonance (ESR) spectra, as well as the elemental analyses results, were obtained using a Perkin-Elmer Lambda 25 UV/Vis spectrophotometer, a Shimadzu FT-IR spectrophotometer, a Bruker DRX-250 Digital FT-NMR spectrometer, a Jeol JES-FE2XG ESR-spectrometer, and a Perkin-Elmer 2400 series CHN elemental analyzer, respectively. The thermal decomposition behavior of the mixed-ligand complexes, particle morphology, particle sizes, and phase purity of the complexes were established based on data collected from the TG and DTG thermograms (25–800 °C), XRD patterns (2θ 5–90°), and SEM and TEM images. These data were obtained using a Shimadzu TG/DTG-50H thermal analyzer, an X'Pert Philips X-ray diffractometer, a Quanta FEI 250 SEM, and a JEOL JEM-1200 EX II TEM.

Synthesis of complexes

Six 100-mL beakers containing 2 mmol of $FeCl_3\cdot 6H_2O$, $CrCl_3\cdot 6H_2O$, $CoCl_2\cdot 6H_2O$, $CuCl_2\cdot 2H_2O$, $CdCl_2\cdot xH_2O$, and AgCl dissolved in 20 mL deionized water were prepared. A hot methanolic solution of L_1 (2 mmol, 20 mL) was added gradually to each beaker. The six mixtures were stirred with a magnetic stirrer at 60 °C. While the mixtures were continuously stirring, a 20 mL methanolic solution containing 2 mmol of L_2 was added slowly. A 5% ammonium solution was used to optimize the pH value of the mixtures to pH = ~7–8. Next, each mixture was refluxed on a hotplate at ~70 °C for 3 to 4 h under stirring. Upon cooling, colored precipitates were formed. The six systems were left overnight to ensure the complete precipitation process. All products were separated and thoroughly washed with methanol and diethyl ether to obtain pure products. The pure products were then collected and dried in vacuum desiccators over anhydrous $CaCl_2$ for 72 h. The complexes were collected as brown crystals representing Fe(III) ions, greenish-blue colored crystals representing Cr(III) ions, dark brown colored crystals representing Co(II) ions, green-colored crystals indicating Cu(II) ions, off-white colored powder indicating Cd(II) ions, and reddish-brown powder indicating Ag(I) ions.

RESULTS AND DISCUSSION

Reaction chemistry

Six mixed-ligand complexes were synthesized by refluxing methanolic solutions of L_1 and L_2 with the aqueous solutions of the Fe(III), Cr(III), Co(II), Cu(II), Cd(II), and Ag(I) metal ions. The reaction ratio was 1:1:1 (Metal ion: L_1:L_2), and the reaction proceeded in a neutral medium at approximately 70 °C. The refluxing of the mixtures yielded colored precipitates that were collected, purified, and dried. The resulting products are the complexes Fe(III)-L_1-L_2, Cr(III)-L_1-L_2, Co(II)-L_1-L_2, Cu(II)-L_1-L_2, Cd(II)-L_1-L_2, and Ag(I)-L_1-L_2. A CHN elemental analyzer was used to determine the contents (%) of hydrogen, chlorine, nitrogen, and carbon in the mixed-ligand complexes, whereas the contents of the metal and water in these complexes were determined gravimetrically. Table 1 lists the elemental results of the synthesized mixed-ligand complexes. The reaction of L_1 and L_2 ligands with the Fe(III), Cr(III), Co(II), Cu(II), and Cd(II) ions proceeded via a 1:1:1 molar ratio (Metal ion: L_1:L_2). The ligands reacted with the Ag(I) ions via 2:1:1 molar ratio (Metal ion: L_1:L_2). The general compositions of Fe(III), Cr(III), Co(II), Cu(II), Cd(II), and Ag(I) complexes are $[FeL_1L_2(H_2O)Cl]\cdot 6H_2O$, $[CrL_1L_2(H_2O)Cl]\cdot 7H_2O$, $[CoL_1L_2(H_2O)_2]\cdot 4H_2O$, $[CuL_1L_2(H_2O)_2]$, $[CdL_1L_2(H_2O)_2]$, and $[Ag_2L_1L_2(H_2O)_2]$. The corresponding gross formulas of these complexes are $C_{11}H_{32}N_2O_{12}SFeCl$ (507.66 g/mol), $C_{11}H_{34}N_2O_{13}SCrCl$ (521.81 g/mol), $C_{11}H_{30}N_2O_{11}SCo$ (457.29 g/mol), $C_{11}H_{22}N_2O_7SCu$ (389.91 g/mol), $C_{11}H_{22}N_2O_7SCd$ (438.76 g/mol), and $C_{11}H_{22}N_2O_7SAg_2$ (542.10 g/mol), respectively. The Fe(III), Cr(III), Co(II), Cu(II), and Cd(II) ions have six-coordinate chelation modes, and their complexes possess octahedral stereochemistry. The Ag(I) ion has a three-coordinate chelation mode. The following equations can be proposed to represent the reaction of L_1 and L_2 with the metal ions under investigation:

$$FeCl_3\cdot 6H_2O + L_1 + L_2 + H_2O \rightarrow [FeL_1L_2(H_2O)Cl]\cdot 6H_2O + 2HCl$$

$$CrCl_3\cdot 6H_2O + L_1 + L_2 + 2H_2O \rightarrow [CrL_1L_2(H_2O)Cl]\cdot 7H_2O + 2HCl$$

$$CoCl_2\cdot 6H_2O + L_1 + L_2 \rightarrow [CoL_1L_2(H_2O)_2]\cdot 4H_2O + 2HCl$$

$$CuCl_2\cdot 2H_2O + L_1 + L_2 \rightarrow [CuL_1L_2(H_2O)_2] + 2HCl$$

$CdCl_2{\cdot}xH_2O + L_1 + L_2 \rightarrow [CdL_1L_2(H_2O)_2] + 2HCl + (x\text{-}2)H_2O$

$2AgCl + L_1 + L_2 + 2H_2O \rightarrow [Ag_2L_1L_2(H_2O)_2] + 2HCl$

Table 1. Elemental results of the synthesized mixed-ligand complexes.

Complex	Elemental results (%) found (calculated)						
	C	H	N	Cl	S	Metal	H_2O
Fe(III)	26.18 (26.0)	6.19 (6.30)	5.37 (5.52)	7.20 (6.98)	6.56 (6.30)	11.15 (11.0)	24.60 (24.82)
Cr(III)	25.19 (25.30)	6.71 (6.52)	5.15 (5.37)	7.03 (6.79)	6.30 (6.13)	9.73 (9.97)	27.32 (27.60)
Co(II)	29.02 (28.87)	6.79 (6.56)	5.98 (6.12)	-	7.16 (7.00)	12.66 (12.89)	23.77 (23.62)
Cu(II)	33.60 (33.85)	5.52 (5.64)	7.36 (7.18)	-	8.45 (8.21)	16.02 (16.30)	9.12 (9.23)
Cd(II)	30.20 (30.08)	5.22 (5.01)	6.24 (6.38)	-	7.56 (7.29)	25.37 (25.62)	8.00 (8.20)
Ag(I)	24.30 (24.35)	4.23 (4.06)	5.06 (5.17)	-	15.11 (5.90)	39.92 (39.80)	6.90 (6.65)

UV-Visible spectral analysis

The dimethylsulfoxide (DMSO) solutions of the mixed-ligand complexes were scanned by a UV/Vis spectrophotometer over the 200–1000 nm wavelength range and the resulted UV/Vis spectra are presented in Figure 1. All complexes displayed an absorption band with maximum wavelengths (λ_{max}) in the range of 250 to 350 nm and can be attributed to the $\pi \rightarrow \pi^*$ transitions. Complexation of L_1 and L_2 with Cd(II) and Ag(I) ions generated the widest and most intense absorption bands with λ_{max} of 330 and 317 nm, respectively. Complexation with Co(II) ions displayed an absorption band with intensity similar to those of Cd(II) and Ag(I) but with widening approximately equal to half that seen with Cd(II) and Ag(I) ions. The λ_{max} for the Co(II) complex was 313 nm. The widening and intensity decreased greatly when L_1 and L_2 formed complexes with Cu(II), Cr(III), and Fe(III) ions. The λ_{max} of Cu(II), Cr(III), and Fe(III) complexes were observed at 288, 275, and 268 nm, respectively. Widening of the absorption bands decreased in a specific order: Ag(I) > Cd(II) > Co(II) > Cr(III) > Fe(III) > Cu(II).

ESR spectral analysis

The DMSO solution of the Cu(II) complex was scanned using an ESR spectrometer. Based on the ESR spectrum, the $g_{\perp}$ and $g_{\parallel}$ value of the complex were 1.8387 and 2.1546, respectively. Kivelson and Neiman [19] reported a $g_{\parallel}$ value > 2.3 for a metal–ligand bond with ionic character, and < 2.3 for a metal–ligand bond with covalent character. These characteristics indicate that the synthesized Cu(II) complex possess a covalent character similar to the L_1-Cu and L_2-Cu bonds. The results suggests that the Cu(II) ion in the synthesized complexes has a $d_{x^2-y^2}$ ground state characteristic of a square pyramidal or octahedral geometry.

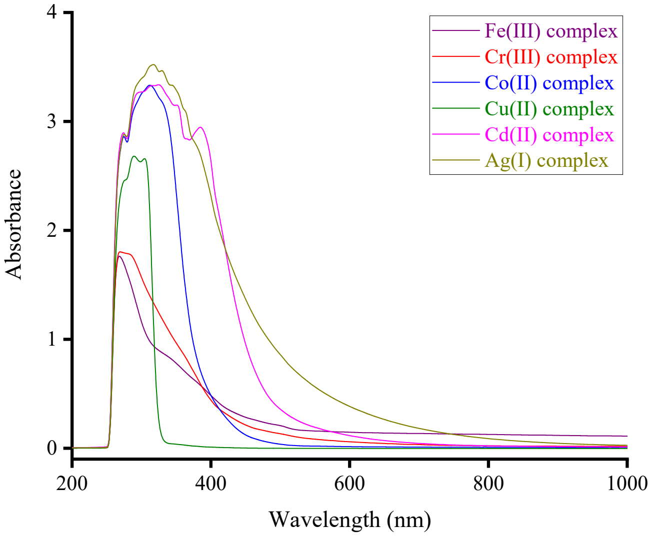


Figure 1. The UV-Visible spectra of the synthesized mixed-ligand complexes.

FT-IR spectral analysis

The characteristic FT-IR spectral bands for the free ligands and synthesized mixed-ligand complexes are listed in Table 2. The free L1 ligand displayed five characteristics IR spectral bands at 3300, 2562, 1592, 1648, and 1446 cm^{-1} attributed to the vibrations of ν(O–H); carboxylic group, ν(S–H), ν_{asym}(COO), ν(C=O); amide, and ν_{sym}(COO), respectively. The free L_2 ligand displayed three characteristic IR spectral bands at 3153 ν(NH_2), 1497 ν_{asym}(COO), and 1400 ν_{sym}(COO) [20]. Data in Table 2 reveal changes in the intensities and positions of some absorption bands in the IR spectra of the synthesized complexes compared to those from L_1 and L_2 ligands alone. The most pronounced changes were observed in the absorption bands corresponding to the mercpto (SH) and amide (C=O) groups of the L_1 ligand, and amino (–NH_2) and carboxylic (COOH) groups of the L_2 ligand. The absorption band due to the SH group in the free L_1 ligand was absent in the IR spectra of the complexes, indicating loss of the SH proton and the participation of the deprotonated SH in the coordination with the metal ions by forming metallo-sulfur bond (–S–M). The band resulted from the ν(C=O) vibration that appeared at 1648 cm^{-1} in the IR spectrum of the free L_1 was shifted to 1600, 1615, 1607, 1612, 1610, and 1603 cm^{-1} in the IR spectra of the Fe(III), Cr(III), Co(II), Cu(II), Cd(II), Ag(I) complexes, respectively. This suggests that the amide (C=O) group formed a complex with the metal ion (–C=O…M). Shifts were also observed in the vibrations resulting from the amino (–NH_2) and carboxylate [ν_{asym}(COO) and ν_{sym}(COO)] groups of L_2 ligand. The values of the band shift, Δν [ν_{asym}COO - ν_{sym}COO], in all complexes, suggests a unidentate coordination mode for the carboxylate group and participation of the carboxylate group in the complexation process with the metal ions [21]. The deprotonated COOH group formed a metallo-oxygen bond with the metal ion (–COO–M), whereas the –NH_2 group formed a coordination bond with the metal ion (H_2N…M). The weak absorption bands observed in the range 544-513 and 445-425 cm^{-1} in the IR spectra of the complexes could be attributed to the stretching vibrations of the M–O and M–N frequencies, respectively [20]. The broad absorption bands centered in the 3440-3360 cm^{-1} region resulted from hydrogen-bonding of coordinated or uncoordinated water molecules, whereas the bands observed at 880-840 cm^{-1} region were assigned to coordinated water molecules [21].

Table 2. Characteristics FT-IR bands of the free ligands and the synthesized mixed-ligand complexes.

Assignments (cm^{-1})	Free ligands		Complexes					
	L_1	L_2	Fe(III)	Cr(III)	Co(II)	Cu(II)	Cd(II)	Ag(I)
ν(O–H); water	-	-	-	3407	3366	3441	3406	3380
ν(O–H); carboxylic	3300	-	3254	3222	3201	3246	-	3240
ν(N–H); NH_2	-	3153	3178	3186	-	3170	3189	3177
ν(S–H)	2562	-	-	-	-	-	-	-
ν(C–O); amide	1648	-	1600	1615	1607	1612	1610	1603
ν_{asym}(COO)	1592	1497	1588 1445	1595 -	- 1442	1591 1448	1590 1444	1593 1440
ν_{sym}(COO)	1446	1400	1410	1409	1407	1411	1410	-
ν(M–O)	-	-	542	537	520	513	544	517
ν(M–N)	-	-	-	430	-	445	425	433

^{1}H NMR spectral analysis

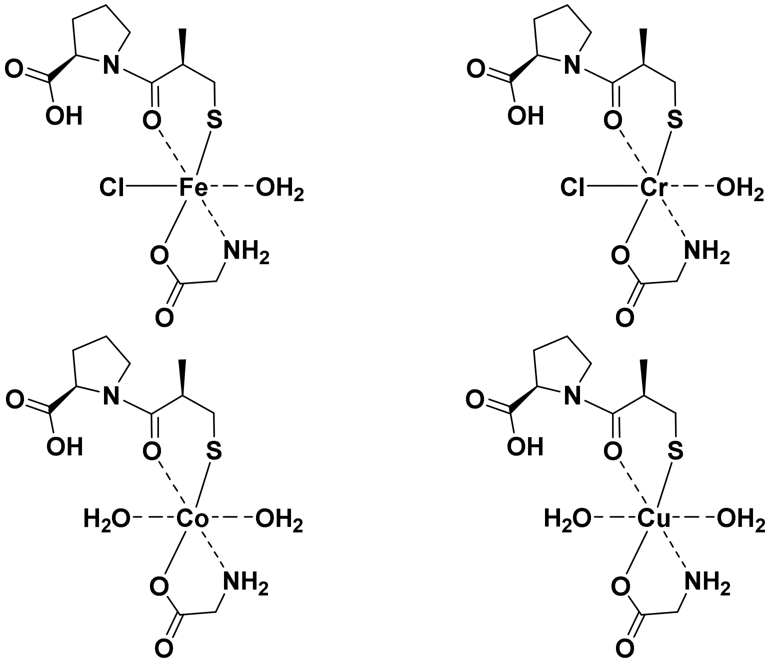
The ^{1}H NMR spectrum of the $[CrL_1L_2(H_2O)Cl]\cdot 7H_2O$ complex was recorded at room temperature in DMSO-d_6 solvent. Free L_2 molecule gives only one peak at ^{1}H NMR spectrum at $\delta = 3.567$ ppm, originated from the two alpha protons (Hα1 and Hα2) in the molecule. These two protons represent strong coupling and the same chemical environment and have equal chemical shift. In the ^{1}H NMR of the Cr(III) complex, the signal of L_2 ligand was observed at $\delta = 3.329$ ppm. The free L_1 molecule presented two sharp singlet signals at 1.90 and 8.53 ppm due to protons of –SH, and –COOH groups, respectively [22]. The signal due to the –SH group no longer observed in the ^{1}H NMR spectrum of the Cr(III) complex due to deprotonation of –SH group. The signal due to the –COOH group was shifted upfield and appeared at ~7.45 ppm in the ^{1}H NMR spectrum of the Cr(III) complex. The signals located at 2.268 and 2.267 ppm could be attributed to protons of $-CH_2$ moieties in L_1 molecule.

Thermogravimetry

Thermogravimetry was applied to confirm the compositions and structures of the synthesized mixed-ligand complexes. The thermal decomposition data of the synthesized complexes yielded several findings: i) The Cu(II) complex exhibited good thermal stability up to 180 °C. ii) Complexation of L_1 and L_2 ligands with the Cu(II), Ag(I), Cd(II), and Cr(III) ions formed stable complexes, and these complexes start to decompose at ~ 180 °C, ~ 120 °C, ~ 110 °C, and 100 °C, respectively. iii) Complexation of L_1 and L_2 ligands with the Co(II), and Fe(III) ions formed unstable complexes, and these complexes started to thermally decompose at around ~ 70 °C, and 60 °C, respectively. iv) Complexes of Co(II) and Ag(I) ions decomposed in three-stage degradation steps, whereas the complexes of Fe(III), Cr(III), Cu(II), and Cd(II) ions exhibited a two-stage degradation process. v) Thermal decomposition of Fe(III), Cr(III), Cu(II) and Cd(II) complexes were characterized by a very strong endothermic peak at DTG_{max} of 476, 265, 235, and 166 °C, respectively. vi) Thermal decompositions of Co(II), and Ag(II) complexes were characterized by two (255, 470 °C) and three (170, 295, 400 °C) very strong endothermic peaks, respectively. vii) Thermograms of Fe(III), Co(II), and Cd(II) show two medium strong endothermic peaks at (107, 135 °C), (115, 168 °C), and (380, 462 °C), respectively. viii) The final decomposition products of all complexes were metal oxides, except Ag(I) complex, which leaves Ag metal. ix) Decomposition of the complexes was almost complete with only residual CoO, CuO, CdO from the Co(II), Cu(II), and Cd(II) complexes, respectively. Fe_2O_3 and Cr_2O_3 were the final decomposition products from the thermal degradation of Fe(III) and Cr(III) complexes, respectively. x) The final decomposition residues of Fe(III), Co(II), Cu(II), and Cd(II) complexes were contaminated with some residual carbons. The decomposition of the Cr(III) and Ag(I) complexes was almost complete without any residual carbons.

Complexation modes

Characterization data (analytical, spectral, and thermal) suggest that the bidentate coordination of L_1 ligand to the metal ions under investigation occurred through the S atom of the mercpto (SH) group and the O atom of the amide (C=O) group. The L_2 ligand acts as a bidentate ligand coordinating to the investigated metal ions through its O atom of the carboxylate group and the N atom of the amino group. Fe(III), Cr(III), Co(II), Cu(II), and Cd(II) ions form six-coordinate complexes, all with octahedral geometry. The Ag(I) ion forms a three-coordinate complex, and its complex with L_1 and L_2 contains two Ag ions. The suggested chemical structures of the synthesized mixed-ligand complexes are presented in Figure 2.



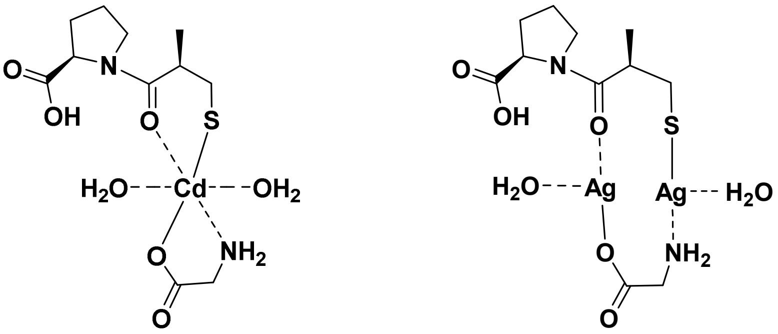


Figure 2. Proposed chemical structures of the synthesized mixed-ligand complexes.

XRD, SEM, and TEM results

Figures 3-8 contain the powder XRD diffraction patterns along with the SEM and TEM images for the L_1 and L_2 complexes with Fe(III), Cr(III), Co(II), Cu(II), Cd(II), and Ag(I) ions, respectively. The XRD diffractograms of Fe(III), Cr(III), and Cu(II) complexes suggest that these complexes have higher degree of crystallinity with well-defined and well-crystallized morphology. The Fe(III) complex had one very strong diffraction line at Bragg's angle 2θ 17.483° and three medium-strong lines at 5.807°, 8.557°, and 10.014°. The XRD diffractogram of Cr(III) complex showed a very strong diffraction line at Bragg's angle 2θ 25.383° and five medium-strong lines at 12.107°, 15.841°, 23.885°, 27.066°, and 34.001°. A group of seven medium-strong lines were observed for Co(II) complex in the range 2θ 17°-30°. Among this group, the most intense lines were at 19.391° and 24.316°, which had approximately the same intensity. Complex containing the Cu(II) ions had only one very strong diffraction line at 2θ 37.921°. No medium–strong or medium intensity lines were observed for this complex, but it contained six low-intensity lines at different Bragg's angles. The XRD patterns of the Cd(II) and Ag(I) complexes were low-intensity and displayed one broad peak ranged from 2θ 18° to 35° for the Cd(II) complex and from 14° to 40° for the Ag(I) complex. The absence of sharp strong sharp and intense lines in the XRD profiles of Cd(II) and Ag(I) complexes suggest that the complexes mainly possess an amorphous structure.

The SEM images of Fe(III), Cr(III), and Cu(II) complexes indicate that the particles of these complexes have a distinct size and morphology as all showed a long rod-like morphology. The SEM images of Co(II) complex revealed that the particles of this complex had short rod-like shaped structure. The rods of Fe(III), Cr(III), Co(II), and Cu(II) complexes were well-developed and had clear features, shapes, and dimensions. The morphology of Cd(II) and Ag(I) complexes indicate that their particles had different shapes mixed between short, long, and broken rods and small aggregates. Some of the complex's particles showed no complete development into short or long rods. The small aggregates had different granule shapes and sizes. The TEM images of Fe(III), Cr(III), and Cu(III) complexes show that several particles have rod-like shaped morphology. The TEM images of Co(II), Cd(II), and Ag(I) complexes indicate that most of their particles were mixed spherical and elliptical-shaped. Some particles have different polygonal and rectangular shapes. According to the TEM images, most of the particles of the synthesized complexes exhibit diameters in the range of 40 to 80 nm.

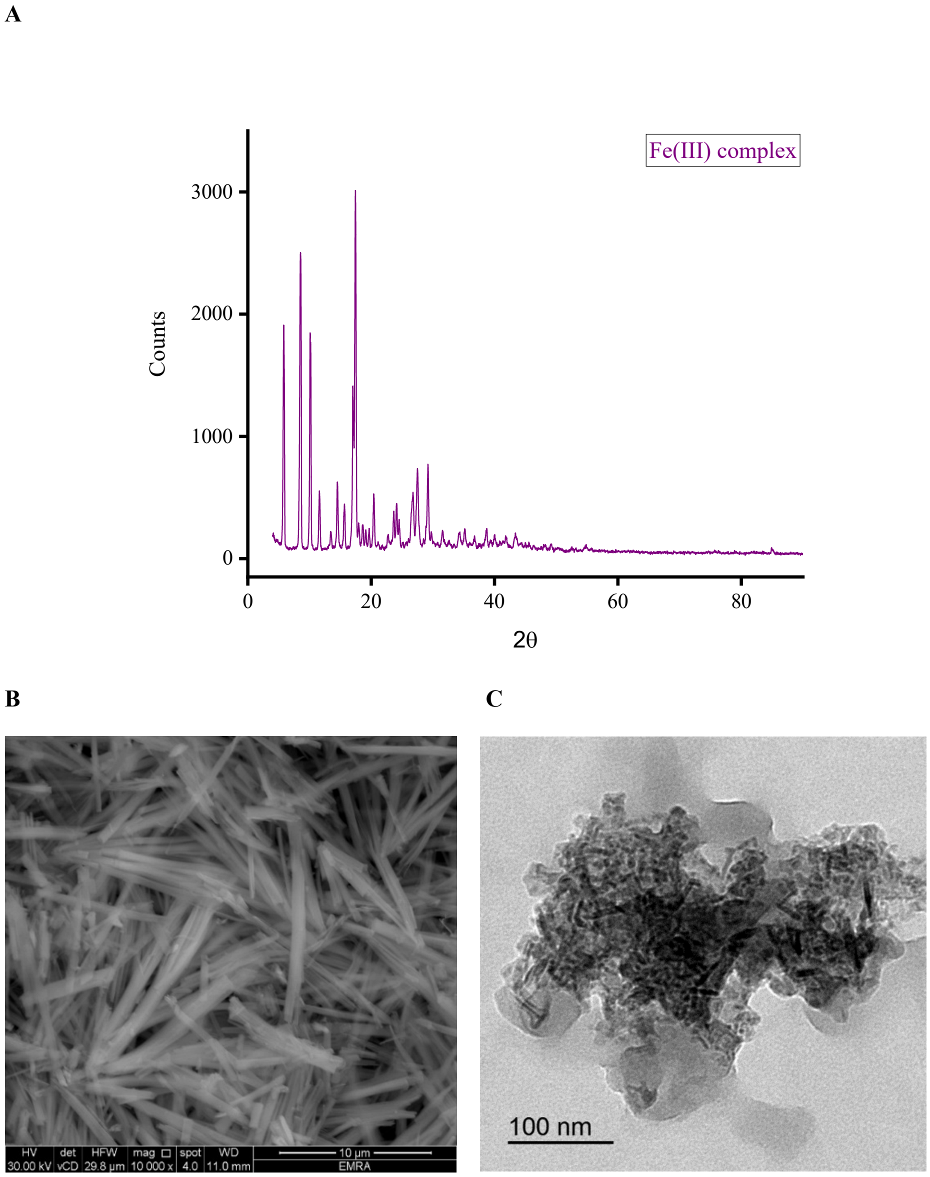


Figure 3. The XRD, SEM, and TEM results of the Fe(III) complex: A) XRD spectrum, B) SEM image, and B) TEM image.

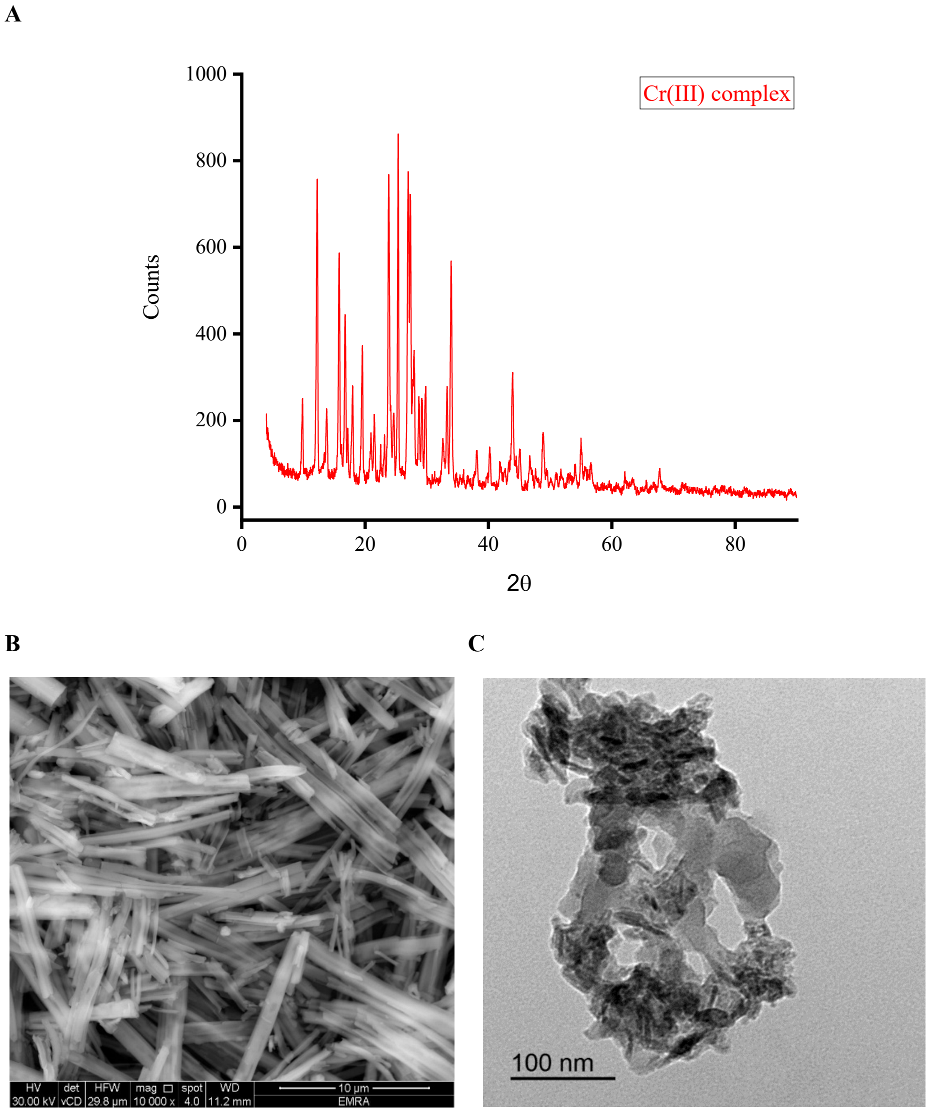


Figure 4. The XRD, SEM, and TEM results of the Cr(III) complex: A) XRD spectrum, B) SEM image, and B) TEM image.

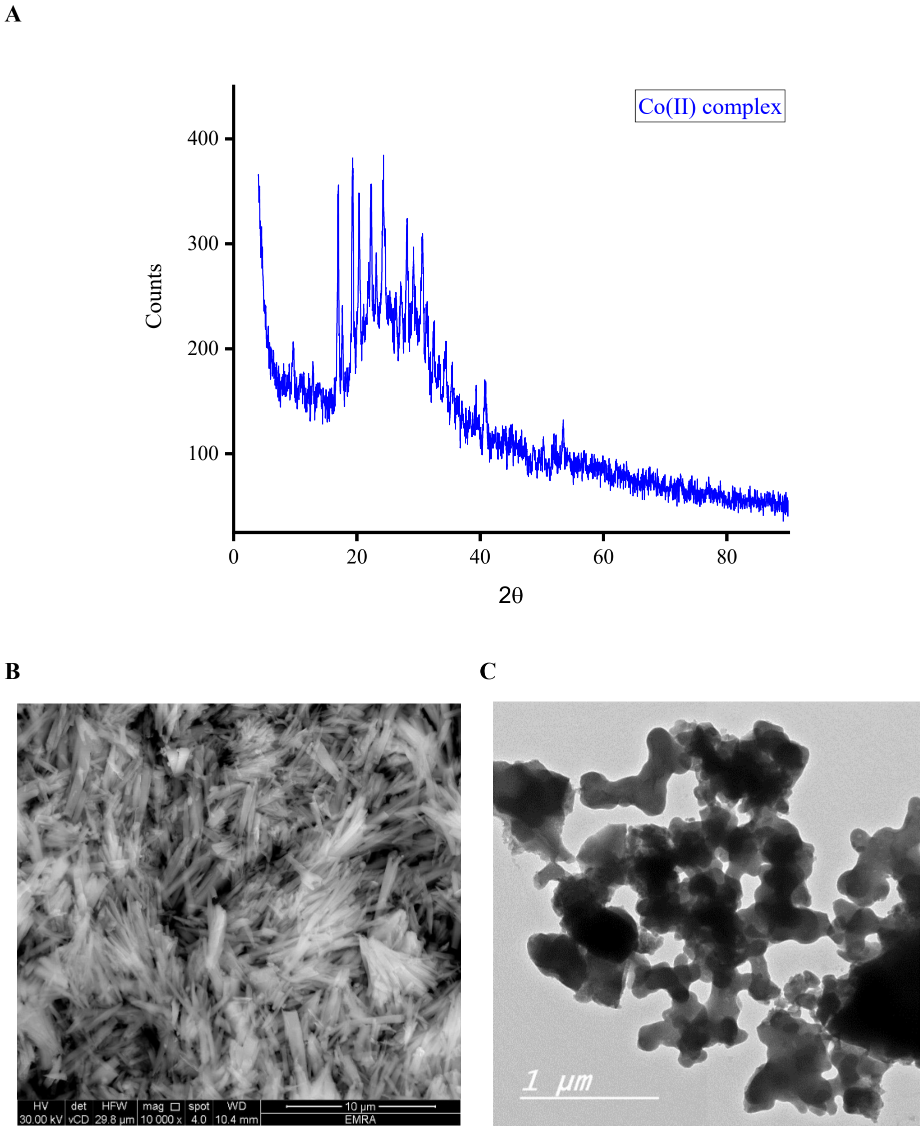


Figure 5. The XRD, SEM, and TEM results of the Co(II) complex: A) XRD spectrum, B) SEM image, and B) TEM image.

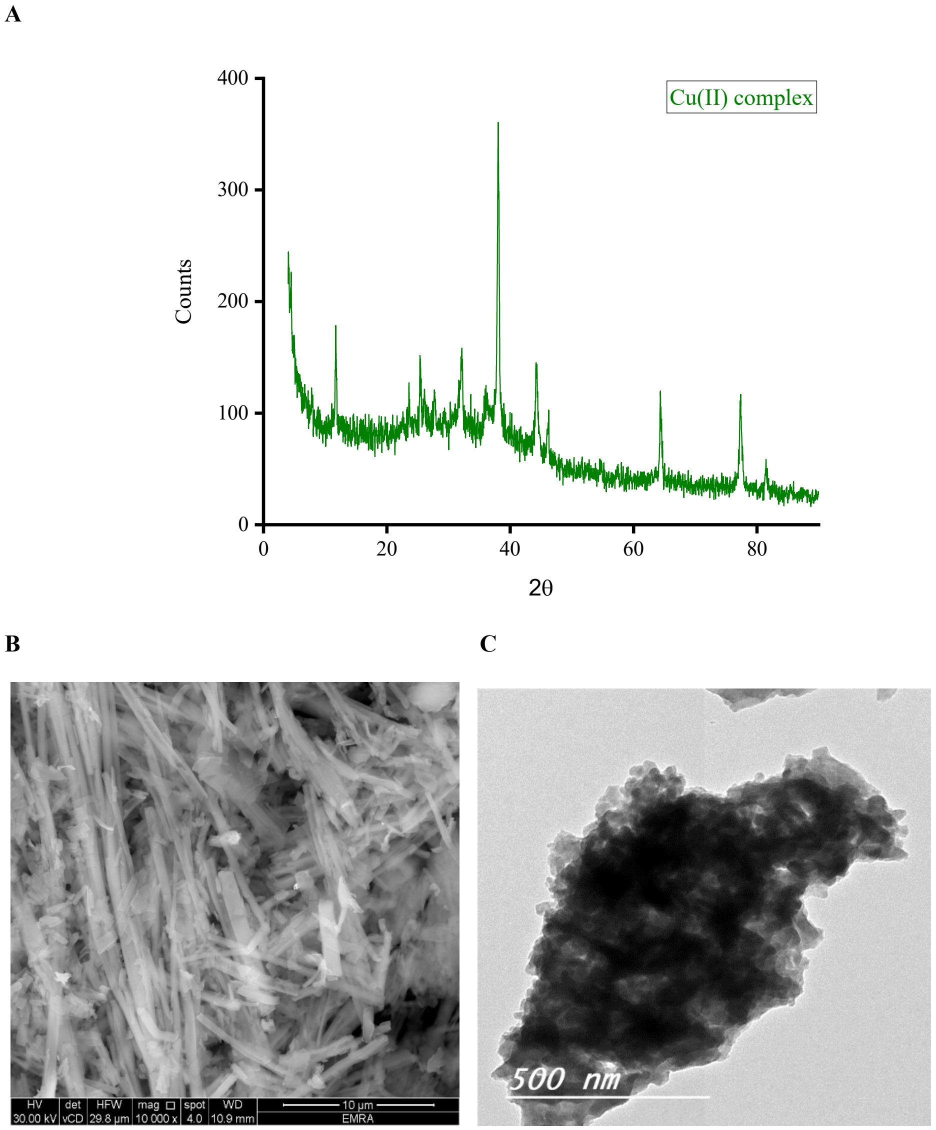


Figure 6. The XRD, SEM, and TEM results of the Cu(II) complex: A) XRD spectrum, B) SEM image, and B) TEM image.

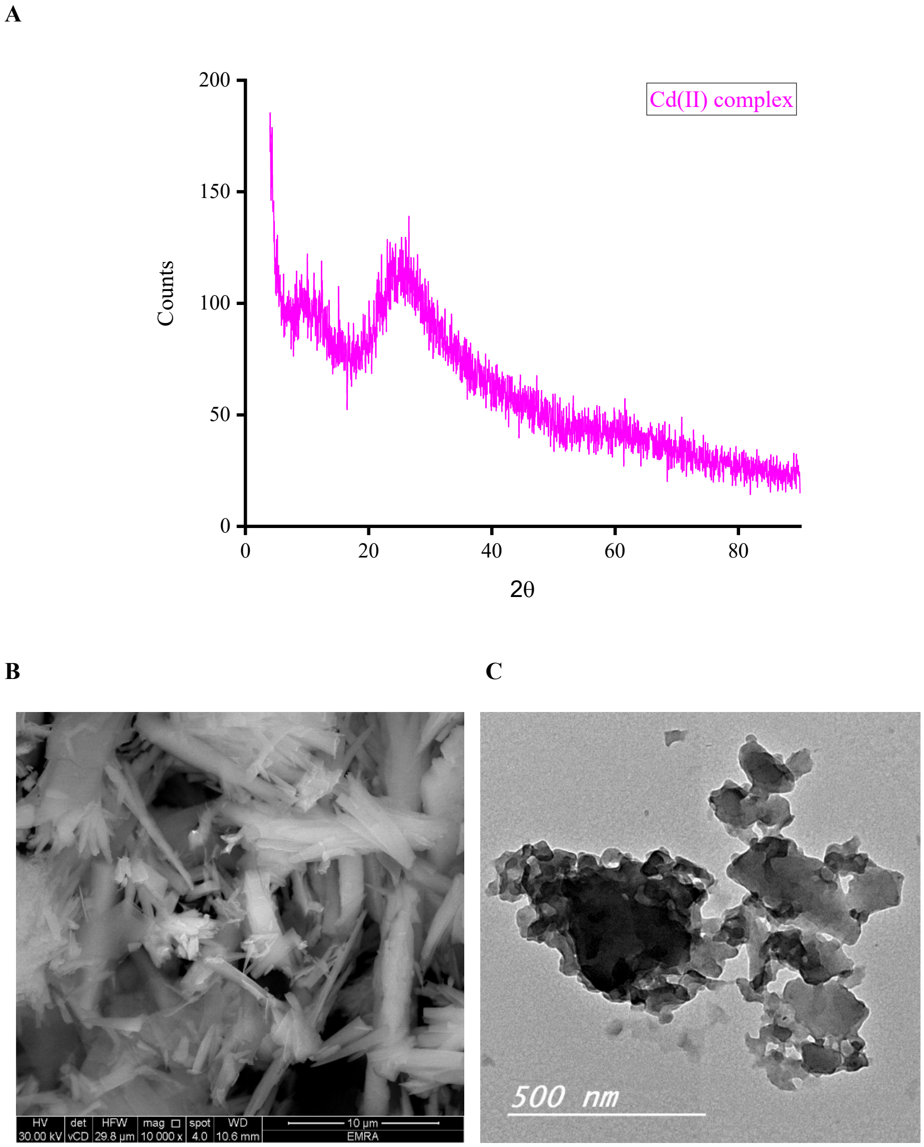


Figure 7. The XRD, SEM, and TEM results of the Cd(II) complex: A) XRD spectrum, B) SEM image, and B) TEM image.

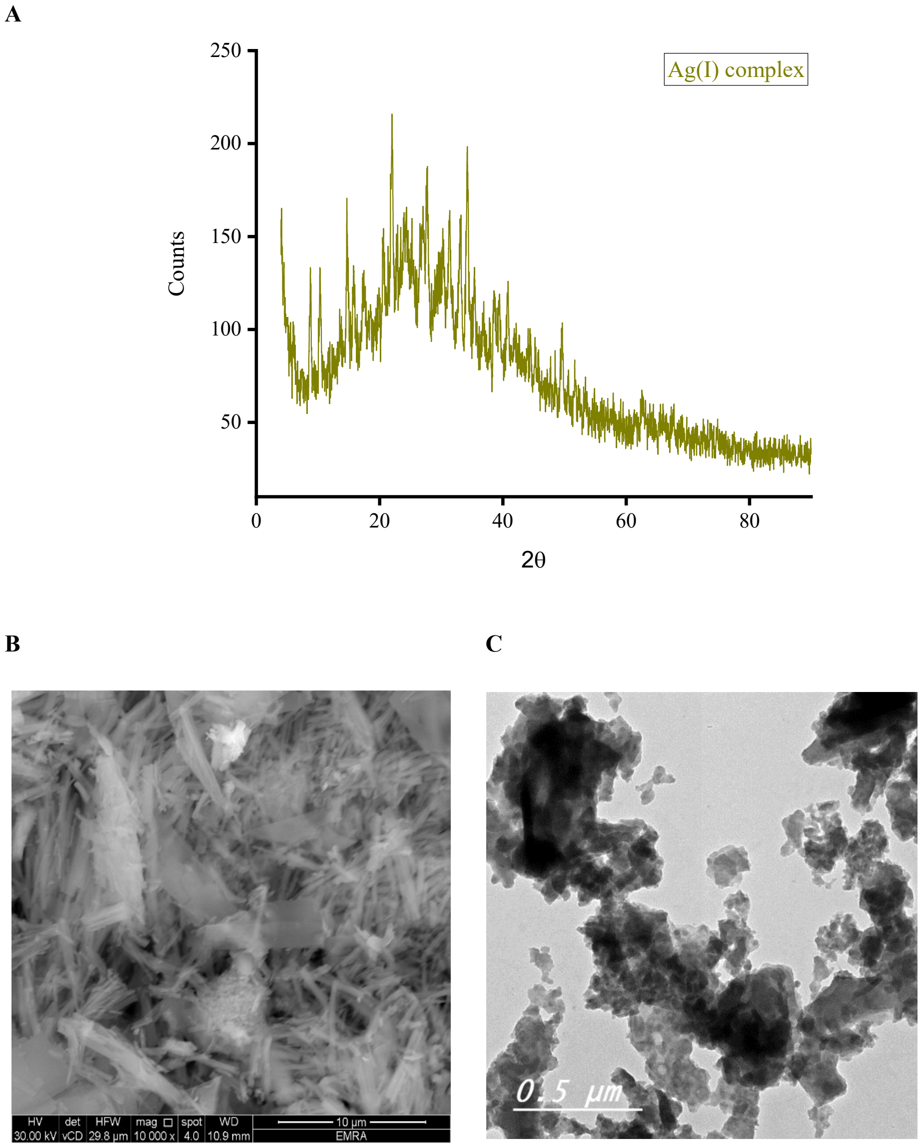


Figure 8. The XRD, SEM, and TEM results of the Ag(I) complex: A) XRD spectrum, B) SEM image, and B) TEM image.

CONCLUSIONS

We believe that manufacturing new metallodrugs that continue two ligands, a drug and a vital molecule, may play a crucial role in developing effective metal-based drugs. Therefore, in this study, we manufactured six mixed-ligand complexes that contained two ligands: (1) drug (captopril; referred to as L_1) and (2) an amino acid (glycine; referred to as L_2). The two ligands (L_1 and L_2) were complexed with Fe(III), Cr(III), Co(II), Cu(II), Cd(II), and Ag(I) metal ions in a MeOH:H_2O media at 70 °C. The resulting complexes were formulated as $[FeL_1L_2(H_2O)Cl]\cdot6H_2O$, $[CrL_1L_2(H_2O)Cl]\cdot7H_2O$, $[CoL_1L_2(H_2O)_2]\cdot4H_2O$, $[CuL_1L_2(H_2O)_2]$, $[CdL_1L_2(H_2O)_2]$, and $[Ag_2L_1L_2(H_2O)_2]$, respectively. Thermal analysis indicates that all complexes are thermally stable except those containing Fe(III) and Co(II) ions. Complexes of Fe(III), Cr(III), Co(II), and Cu(II) ions presented a rod-like shaped morphology with well-defined shapes, dimensions, and features. The S atom of (SH) group and the O atom of (C=O) group in L_1 ligand and the O atom of (COOH) group and the N atom of (NH_2) group in L_2 ligand captured the metal ion. The Fe(III), Cr(III), Co(II), Cu(II), and Cd(II) ions have six-coordinate chelation modes, whereas the Ag(I) ion has a three-coordinate chelation mode. The next level of this study involves investigation of the biological activities of the synthesized mixed-ligand complexes by screening them for antibacterial activity against several Gram-positive and -negative bacteria and for cytotoxic activity against different human cancer cell lines.

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