Chapter 7

Metal Complexes of Pharmaceutical Substances

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Abstract

Significant progresses have been made in the inorganic and organic chemistry up to the present concerning the synthesis, characterization, and application of the metal complexes of pharmaceutical substances. From the wide range of fields in which these coordination compounds find their application, many efforts were focused on the study of their importance in the biological processes. The coordination complexes of many pharmaceutical substances having different pharmacological effects e.g., pyrazinamide (PZA), nicotinamide (NAM), nicotinic acid (NIC), theophylline (TEO), captopril (CPL), tolbutamide (TBA), clonidine (CLN), guanfacine (GUAF), etc. with transition metals were synthesized and used in order to improve their pharmacological and pharmacotechnical properties and also for the drug analysis and control. Several techniques such as Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy, surface-enhanced Raman spectroscopy (SERS), X-ray spectroscopy, mass spectrometry, ultraviolet-visible (UV-Vis) spectrophotometry, electron paramagnetic resonance (EPR) spectroscopy, X-ray diffraction, elemental analysis, electrochemical methods, thermal methods, and scanning electron microscopy were used for the physicochemical characterization of the complex composition. A significant interest in the development of metal complex-based drugs with unique research and therapeutic and diagnostic opportunities is currently observed in the medicinal inorganic chemistry area.

Keywords: coordination complexes, transition metals, pharmaceutical substances, characterization methods, medicinal chemistry

1. Introduction

The coordination complexes have been studied since 1798 starting with the Tassaert studies, and till nowadays significant progresses have been made in the inorganic and organic

chemistry concerning the synthesis, characterization, and application of this large group of metal complexes. Concerning their structure, complexes were considered those compounds which do not fit within the classical theory of valence, meaning that the combination ratio of the elements exceeded their valences. This coordination theory elaborated by Alfred Werner indicated that the secondary valences of the elements are involved in the formation of the second-order combinations leading to the actual representation of the complexes formed by the first coordination sphere marked between brackets [central atom (ligand)] and the second coordination sphere (ionization sphere) coming outside of the brackets. The central atom can be any chemical element; meanwhile, the ligands can be ions, atoms, or neutral molecules, which can act as donors [1]. Neutral molecules or mono-/polyatomic anions which have one or more unshared electron pairs can act as mono-/polydentate ligands, the latter ones form complexes with cyclic structure known as chelates. A large number of pharmaceutical substances behave in vivo or in vitro conditions as ligands and chelating agents [2].

The number and the large structural variety of these complexes could not allow a rigorous systematization, even though some attempts by using certain classification criteria have been made such as the number of the central atoms, the charge of the complex ion, the type of ligands, and the coordination number. The coordination compounds were classified into Werner complexes, complexes with metal-metal bonds, metal carbonyls, clusters, complexes with macrocyclic ligands, molecular complexes (adducts, clathrates), chelates, and metal-organic complexes [1].

Natural metal complexes consisting of a central metal atom or ion (especially of the 3D transition metals) are involved in a plenty of biological mechanisms among which photosynthesis, transport of oxygen in blood, coordination of some metabolic processes, pathological states, enzymatic reactions, etc., even though the metallic ions represent only 3% of the body composition. Many biomolecules (amino acids, peptides, carboxylic acids, etc.) can form metal complexes with different stabilities having biomedical importance. Some drugs have a certain therapeutic effect (e.g., antimicrobial, diuretic, antidepressant) due to the complexation of the metallic ion (Cu^{2+}, Zn^{2+}, Fe^{2+}, Mg^{2+}, etc.) essential for a certain biochemical process. Metal complexes and products containing oligoelements are widely used in therapy due to their pharmacodynamic properties, bioavailability enhancement, and toxicity decrease of some metal ions [1].

The main aspects concerning the formation of complexes between pharmaceutical substances and various ligands are supported by several observations. According to the biological, physiological, and pathophysiological role of metal ions and ligands with pharmacological effect, metal ions present a great importance in carrying out the vital functions of living organisms acting as complexes or chelates and also in the analysis and control methods of drug substances by forming complexes that can be detected by spectral techniques. The use of ligands, chelating agents, or complexes in medicine and biology concerns several purposes such as antidotes in poisoning with metal ions or hydrocyanic acid or cyanides; introduction in the living organisms of some essential metal ions found to be deficient; depriving bacteria, viruses, or microbial enzyme systems of micronutrients essential for their work; or providing toxic metals for the pathogenic agents [2].

Many coordination complexes have been used in medicine containing metals such as platinum (cisplatin as anticancer chemotherapy drug), gold (as auranofin used for rheumatoid arthritis), technetium and rhenium (as radiopharmaceuticals used in imaging and radiotherapy), ruthenium (as anticancer drug), gadolinium, cobalt, lithium, bismuth, iron, calcium, lanthanum, gallium, tin, arsenic, rhodium, copper, zinc, aluminum, lutetium, vanadium, manganese, etc. [3, 4]. Only a reduced number of Co(III) complexes can be mentioned as having biochemical properties: vitamin B_{12}, a natural organometallic complex of Co(III) with glyoxime. Other important examples are the series of Co(III) complexes containing N- and O-donor ligands based on a chelating Schiff base (imidazole, methylimidazole) with efficiency in the treatment of epithelial herpetic keratitis (the molecular target is supposed to be a virus protease containing histidine), adenovirus keratoconjunctivitis, and human immunodeficiency virus type 1. $[Co(NH_3)_6]Cl_3$ presents potent antiviral activity (against Sindbis virus). Some studies reported also the antibacterial activity of Co(II) and Co(III) complexes against *Bacillus subtilis*, *Enterobacter aeruginosa*, *Escherichia coli*, *Staphylococcus aureus*, etc. [3].

It was demonstrated that the antibacterial activity was increased upon chelation making the ligand a more powerful agent [5, 6]. The complexation of derivatives of sterically hindered *o*-diphenols and *o*-aminophenols with Cu(II), Co(II), Ni(II), and Zn(II) ions exhibited antioxidant, antiviral, and antimicrobial activity with low toxicity. Their synthesis, their separation as crystalline powders, the composition, and physicochemical characteristics of the complexes were also studied in Ref. [7].

Metal complexes have become an emerging tool in drug discovery being widely used as therapeutic compounds to treat several human diseases such as carcinomas, lymphomas, infection control, diabetes, anti-inflammatory, and neurological disorders [8, 9]. Due to various implications and applications of complexes (especially the chelates) in the biomedical field, many aspects are required to be studied such as their nature, their stability, the factors determining their formation and stability, and possibilities for preventing some reactions and for releasing a metal ion from a complex; all these are necessary in order to understand how they act in biological processes [2].

2. Physicochemical characterization of metal complexes of some pharmaceuticals

The coordination complexes of a wide range of pharmaceutical substances [pyrazinamide (PZA), nicotinamide (NAM), nicotinic acid (NIC), tolbutamide (TBA), theophylline (TEO), captopril (CFL), clonidine (CLN), and guanfacine (GUAF)] with transition metals [Cu(II), Cd(II), Ni(II), Mn(II), Zn(II), and Co(II)] were synthesized and then characterized by using various techniques such as elemental analysis, spectral, electrochemical, thermal, and microscopic methods.

2.1. Metal complexes of pyrazinamide

Pyrazinamide (PZA) (pyrazine carboxamide) is a nicotinamide analogue used as a first-line drug to treat tuberculosis. The complexes of PZA with Cu(II) were assessed by different techniques

such as elemental analysis, spectral methods [Fourier transform infrared spectroscopy (FTIR), FT-Raman spectrometry, mass spectrometry], and scanning electron microscopy (SEM) coupled with X-ray spectroscopy [energy-dispersive spectroscopy (EDS)] [1, 10–13].

The elemental analysis indicated that the combination ratio of metal:ligand (Me:L) is 1:2 for $[Cu(PZA)_2]Cl_2$ and $[Cu(PZA)_2](C_6H_5COO)_2$ complexes. The mass spectra of the complex of PZA with Co(II) benzoate revealed the identity and the purity of PZA and of the complex fragments confirming its structure (**Figure 1**) [1, 10].

The FTIR spectra of the complexes highlighted that –C═O groups and nitrogen from the pyrazine ring are implied in the coordination process (**Table 1**) [11]. Comparing the Raman spectra of PZA and of $[Cu(PZA)_2]Cl_2$, another analytical evidence for the complex formation is obtained. The appearance of new band characteristic for the Me:L bonds can be observed analyzing in detail the spectral region of low values of wave number (**Figure 2**) [1, 11, 12].

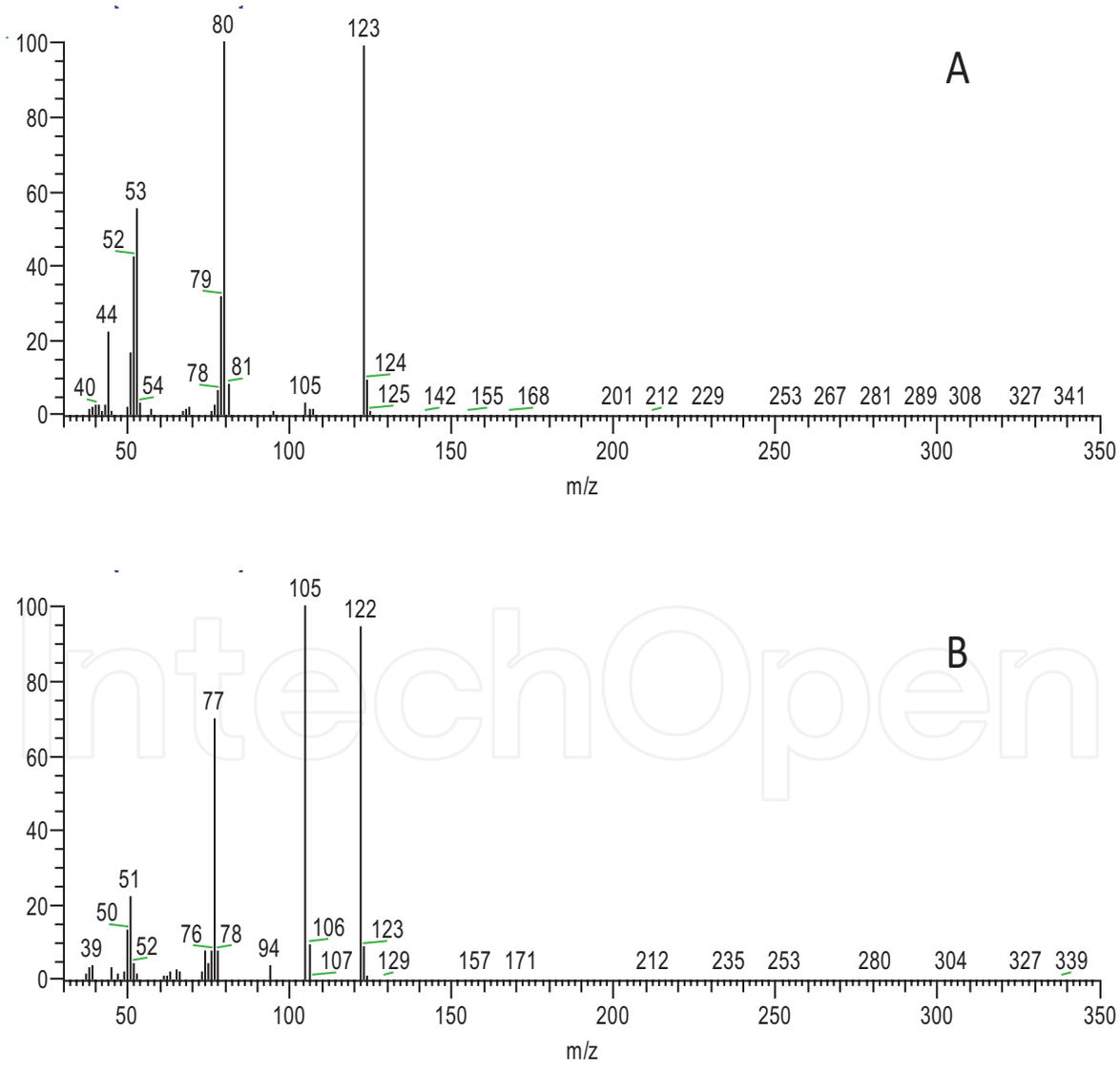

Figure 1. The mass spectra of PZA (A) and $[Cu(PZA)_2](C_6H_5COO)_2$ (B) [1, 10]. Reprinted with permission of Revista de Chimie and of Editura Universităţii din Oradea.

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PZA	$[Cu(PZA)_2](C_6H_5COO)_2$	$[Cu(PZA)_2]Cl_2$	Assignment
3410s	3610w	3430s	ν_{as} NH_2
3140m	3170m	3110m	ν_s NH_2
3080	3065m	3070m	νCH
1705s	1915w	1700s	νC═O(1)
1600m	1590m	1590m	δNH_2(2)
1570	1585m	1585m	ν ring
1530	1545s	1510w	ν ring
1375s	1380s	1385s	νCN(III)
1150w	1180w	1170m	δCH
1090m	1085w	1080w	ϱ NH_2
870w	850w	870m	δ ring
665w	680m	670w	ϱ NH_2

Note: v, very; s, strong; m, medium; w, weak; ν, stretching; δ, in plane bending; ϱ, rocking.
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Table 1. Assignment of the characteristic IR bands of the metal complexes of PZA [1, 14].

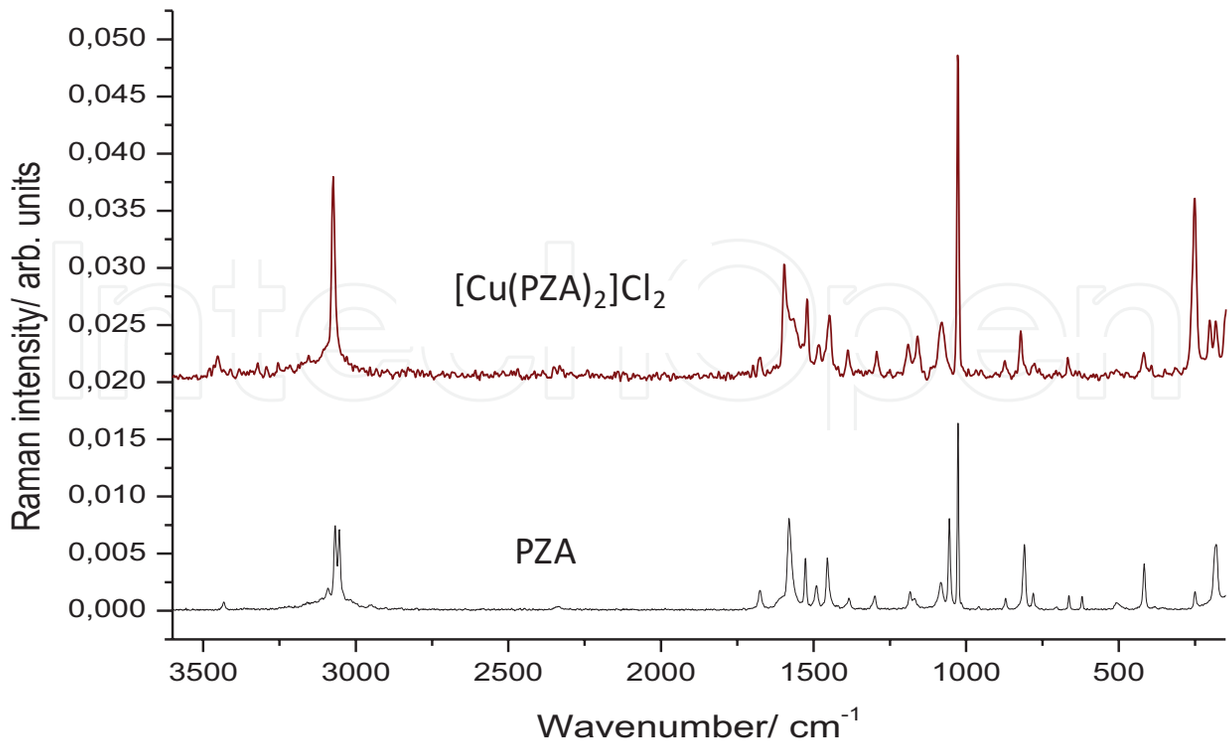

Figure 2. Raman spectra of PZA and of $[Cu(PZA)_2]Cl_2$ [1, 12]. Reprinted with permission of Studia Universitatis Babes-Bolyai and of Editura Universităţii din Oradea.

The morphology and the crystal structure of the two complexes were revealed by the SEM images and EDS spectra (**Figures 3** and **4**). The first complex, $[Cu(PZA)_2](C_6H_5COO)_2$, presented irregular conglomeration with different shapes and dimensions (**Figure 3A**); meanwhile, the second one, $Cu(PZA)_2]Cl_2$, presented acicular and elongated particles with an average size of about 1.5 microns (**Figure 4A**) [1, 14].

2.2. Metal complexes of nicotinamide

Nicotinamide (NAM) (3-pyridine carboxylic acid amide) is the amide of nicotinic acid playing an important role in the biosynthesis of pyridine nucleotides, and it is a reactive moiety of the coenzyme nicotinamide adenine dinucleotide, a soluble electron carrier in biochemical reactions. The NAM complexes with transition metals [Cu(II), Cd(II), Hg(II)] were synthesized and characterized by using elemental analysis, UV-Vis, and FTIR spectroscopy [1, 15, 16]. The spectral data confirmed tetradentate coordination of NAM with Hg(II), Cd(II), and hexadentate coordination with Cu(II). In the FTIR spectra of these complexes, it can be observed that the characteristic bands of NAM are slightly shifted after coordination (**Table 2**) [16]. The slight shifting of the bands from NAM complexes with Hg may be explained by the stereochemistry of $HgCl_2$, which is less bulky than $Cu(C_6H_5COO)_2$ and $Cd(SCN)_2$.

2.3. Metal complexes of nicotinic acid

Nicotinic acid (NIC) (pyridine-3-carboxylic acid) known as vitamin B_3, niacin, has two important pharmacological properties: peripheral vasodilator and hypocholesterolemic drug. Its complexes with Co(II) and Cu(II) were synthesized and characterized by elemental analysis and spectral methods [FTIR spectroscopy, Raman spectroscopy, and surface-enhanced

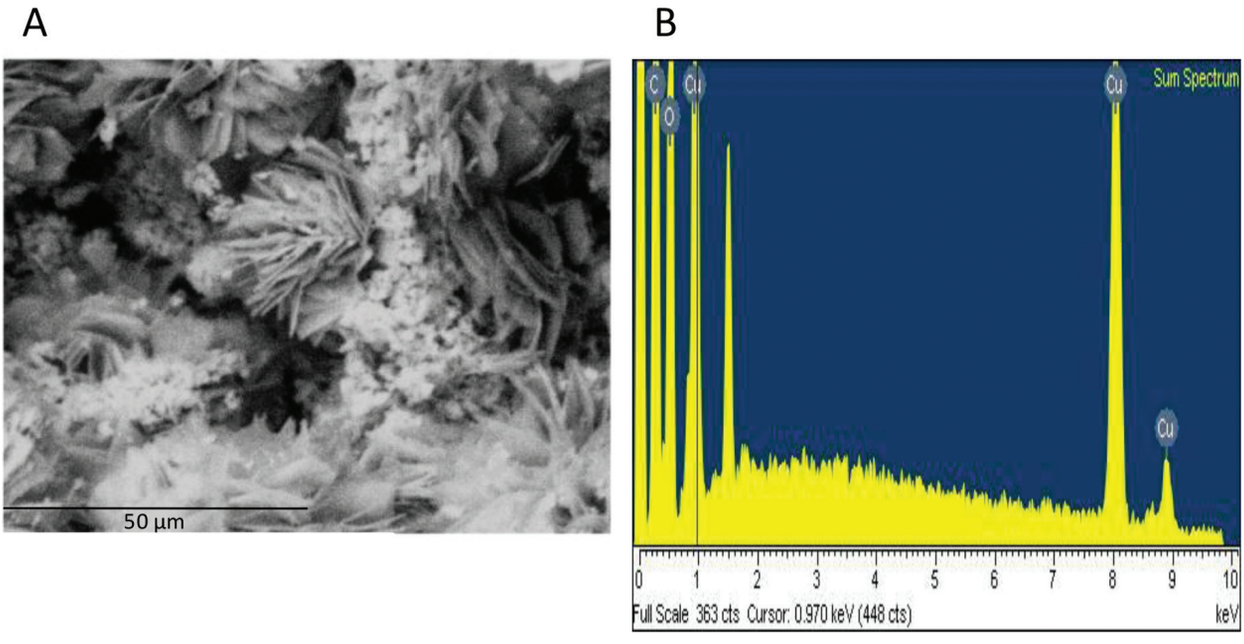

Figure 3. SEM image (A) and EDS spectrum (B) of $[Cu(PZA)_2](C_6H_5COO)_2$ [1, 14]. Reprinted with permission of Farmacia and of Editura Universităţii din Oradea.

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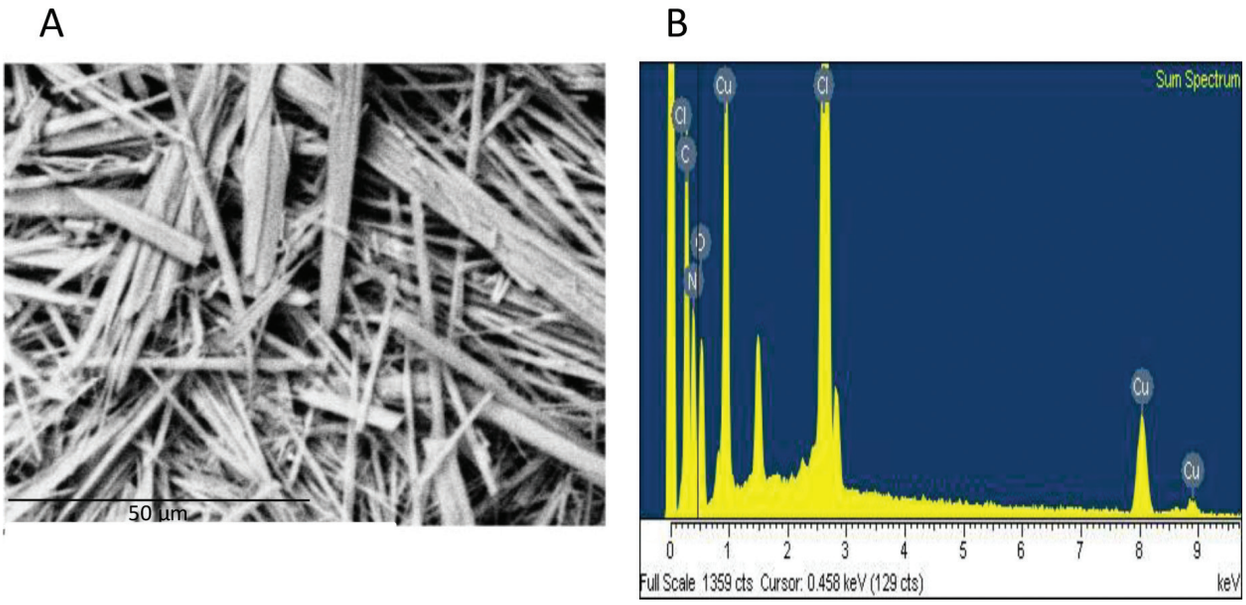

Figure 4. SEM image (A) and EDS spectrum (B) of $[Cu(PZA)_2]Cl_2$ [1, 14]. Reprinted with permission of Farmacia and of Editura Universităţii din Oradea.

Raman spectroscopy (SERS)] (**Figure 5**). The significant differences observed from the spectral data of the metal complexes can be attributed to the coordination process with the metal ions: the stretching vibrations ν(C—C) from the pyridine ring (1500–1600 cm^{-1}) and ν(ring) of NIC (1037 cm^{-1}) are shifted; meanwhile, the vibration band γ(CH) of the ring at 811 cm^{-1} is shifted and also splitted indicating the ring deformation during the coordination process. There appear new bands corresponding to the Me:L bonds (at about 500 cm^{-1}) (**Table 3**). The spectral results confirmed the monodentate coordination of NIC with Cu(II) and Co(II) [17].

2.4. Metal complexes of guanfacine

Guanfacine (GUAF) (*N*-(diaminomethylidene)-2-(2,6-dichlorophenyl)acetamide), used as antihypertensive drug, is able to form colored complexes (combination ratio Me:L 1:2) with Mn(II) and Cd(II) having different spectral characteristics. These complexes were analyzed by using spectral techniques such as FTIR and Raman spectroscopy. The imine group vibration from the FTIR data of GUAF ($\nu_{C=N}$ at 1700 cm^{-1}) was shifted (Δ = 10–60 cm^{-1}) in the spectra of GUAF complexes with Mn(II) ($\nu_{C=N}$ at 1710 cm^{-1}) and Cd(II) ($\nu_{C=N}$ at 1760 cm^{-1}) showing the imine group involvement in the complex formation. The formation of new bonds Me:L was observed at around 500 cm^{-1} in the case of the two mentioned complexes. Significant differences appeared in the Raman spectra of the complexes in the region 1100–1250 cm^{-1} due to the electronic delocalization from NH═C—NH_2 (**Figure 6**). After coordination, in the case of both complexes, two distinct bands were revealed at 1212 cm^{-1} for NH—C—NH_2 and at 1174 cm^{-1} for NH═C—NH_2. The spectral data indicated that GUAF is coordinated by nitrogen atoms, and the results confirmed a tetradentate coordination of Cd(II) complexes [18].

NAM	$[Hg(NAM)_2]Cl_2$	$[Cu(NAM)_2](C_6H_5COO)_2 2H_2O$	$[Cd(NAM)_2](SCN)_2$	Assignment
			3531w	(OH)
3364vs	3363s	3369s	3479s	$\nu_{as}(NH_2)$
3167s	3171s	3207vs	3176m	$\nu_s(NH_2)$
3065sh	3071sh	3071sh	3072w	ν(CH)
1654s	1654vs	1668vs	1667vs	ν(CO)
1622ws	1623ws	1632ws	1618m	$\delta(NH_2)$
1577ws	1577vs	1596s	1577s	ν(CN) + ν(CC)
1449m	1449m	1490s	1485m	β(CH)
1395ws	1400m	1377vs	1400s	ν(CN) amide
1297m	1296m	1301w	1331m	ν(CC)
1178m	1179m	1193w	1204s	ν(ring) NAM
1141m	1142s	1153sh	1153m	ν (CN)
1120m	1119s	1116m	1112m	$\rho(NH_2)$
1022m	1024w	1025m	1040m	υ(CNS)
–	919m	928w	937w	γ(CH) ring
–	844s	853m	840m	$\nu_{as}(C{-}CH_3)$
771m	786s	775w	770s	γ(CH) ring
698m	700ws	719w	719w	$\omega(NH_2)$
684m	686ws	687s	687ws	δ(ring)NAM
633s	641s	655w	657ws	γ(NH)

Note: v, very; s, strong; m, medium; w, weak; sh, shoulder; sp, splitting; ν, stretching; β, in-plane bending; γ, out-of-plane bending; δ, in-plane bending; ω, out-of-plane wag.

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Table 2. Assignment of the characteristic IR bands of the metal complexes of NAM [16].

2.5. Metal complexes of theophylline

Theophylline (TEO) (3,7-dihydro-1,3-dimethyl,1H-purine-2,6-dione) also known as 1,3-dimethyl-xanthine belongs to the class of peripheral and cerebral vasodilator drugs. Metal complexes of TEO were synthesized having the general formula: $[Me_n(TEO)_x]A_m \cdot yH_2O$, where Me = Cu(II), Co(II), Cd(II), Zn(II), and Ni(II) and A = CH_3COO^-, $C_6H_5COO^-$; n = 1, x = 1 or 2, m = 2, and y = 2 or 4. The combination ratio was determined by using elemental analysis and conductometric titration; meanwhile, the number of water molecules was determined by using thermal analysis [2, 19–22].

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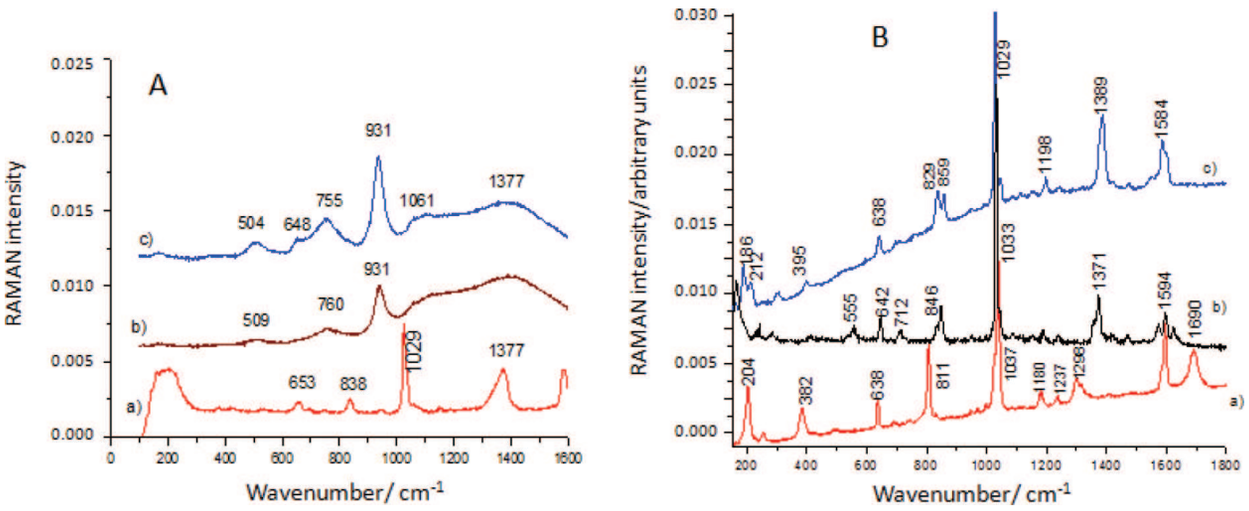

Figure 5. Raman (A) and SERS (B) spectra of NIC (a) and its complex with Cu(II) (b) and Co(II) (c) [17]. Reprinted with permission of Revista de Chimie.

Assignment (cm^{-1})	NIC Raman (cm^{-1})	NIC SERS (cm^{-1})	$Cu(NIC)_2(CH_3COO)_2$ Raman (cm^{-1})	$Cu(NIC)_2(CH_3COO)_2$ SERS (cm^{-1})	$Co(NIC)_2(CH_3COO)_2$ Raman (cm^{-1})	$Co(NIC)_2(CH_3COO)_2$ SERS (cm^{-1})
ν(OH) acid	–	–	–	–	–	–
ν(CH)	–	–	–	–	–	–
νC=O	1690m	–	–	–	–	–
ν(ring) NIC	1594m	1594m	1594m	–	1584m	–
ν(CN)	–	–	–	–	–	–
	–	1377m	1371m	1377wv	1389s	1377wv
ν(CC)	1298m	–	–	–	–	–
δ(CN)	1180m	–	–	–	1198m	–
ν(ring)NIC	1037vs	1029s	1033vs	1060wv	1029vs	1061wv
δ(OH)acid	–	–	–	931m	–	931m
γ(CH) ring	811m	838wv	846m	760wv	829m	755wv
δ(CH) ring	638m	653wv	642m	–	638m	648wv
νMe-O	–	–	555wv	509wv	–	504wv

Note: v, very; s, strong; m, medium; w, weak; ν, stretching; γ, out-of-plane bending; δ, in-plane bending.
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Table 3. Assignment of the characteristic Raman and SERS bands of the metal complexes of NIC [17].

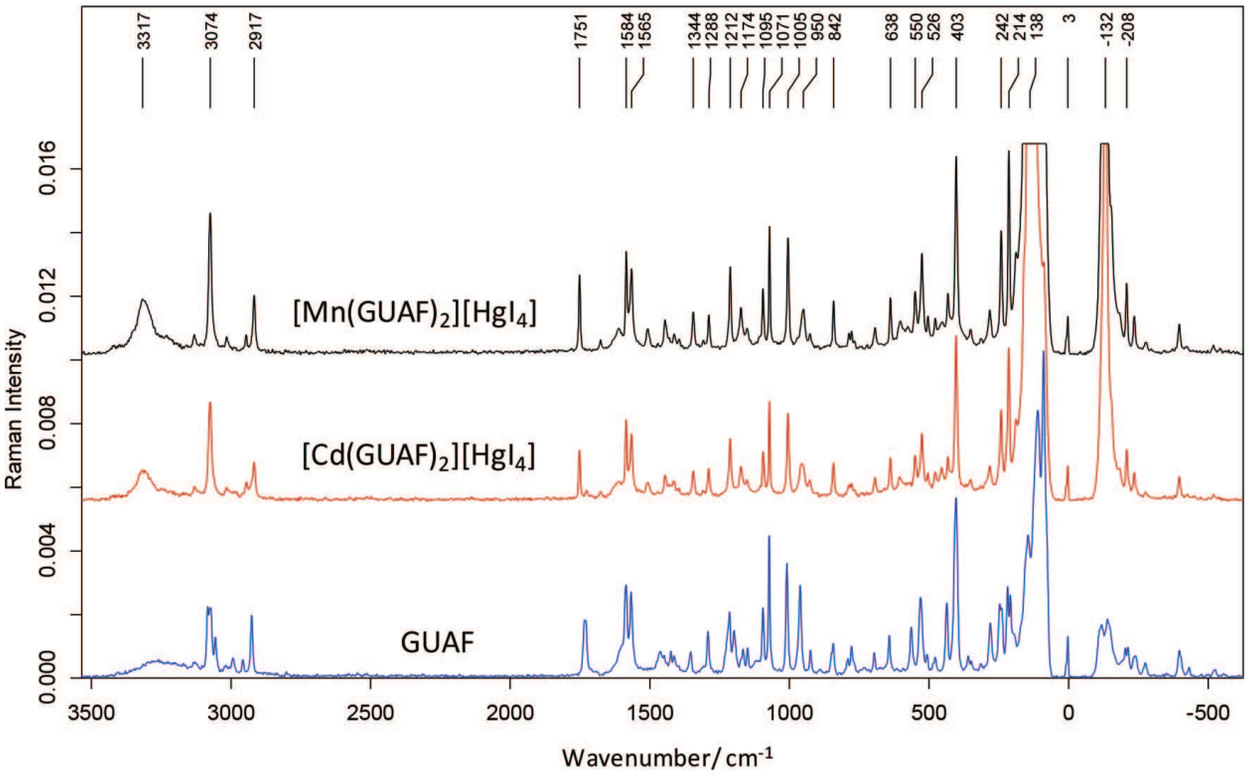

Figure 6. Raman spectra of GUAF and of its metal complexes [19].

The combination ratio Me:TEO is 1:2 for the complexes having the acetate anion. The complex $[Cu(TEO)_2](CH_3COO)_2$ has a high thermal instability even at 40°C, its thermal decomposition being already started. On the thermal curves, eight stages of decomposition, all scarcely separable, can be observed. The first five were weakly endothermic, and three were strongly exothermic. The X-ray diffractogram revealed that this complex crystallizes in the monoclinic system. The microscopic analysis showed a mixture of particles with different shapes: acicular, flake, irregular, and lamellar (**Figure 7**) [2, 19–22].

In the case of $[Cd(TEO)_2](CH_3COO)_2$, the last stage of thermal decomposition was not achieved in the investigated temperature range; therefore, heating was required up to a higher temperature (850°C) when constant weight was reached corresponding to the cadmium oxide. The complex crystallizes in the monoclinic system, and it presents microcrystals with parallelepiped shape (**Figure 8**) [2, 19, 21, 22].

The thermal decomposition of $[Co(TEO)_2](CH_3COO)_2$ takes place in four stages: one endothermic and three exothermic. It presents monoclinic crystal system, and the microcrystals have a tabular form (**Figure 9**). The complex $[Zn(TEO)_2](CH_3COO)_2$ presented similar properties as $[Cd(TEO)_2](CH_3COO)_2$ complex [2, 19, 21, 22].

The endothermic peak at 272°C, which is characteristic for TEO decomposition, is not found in the differential scanning calorimetry (DSC) curves of the complexes, being a credible argument for the complex synthesis and not as a simple mechanical mixture (**Figure 10**) [2, 19].

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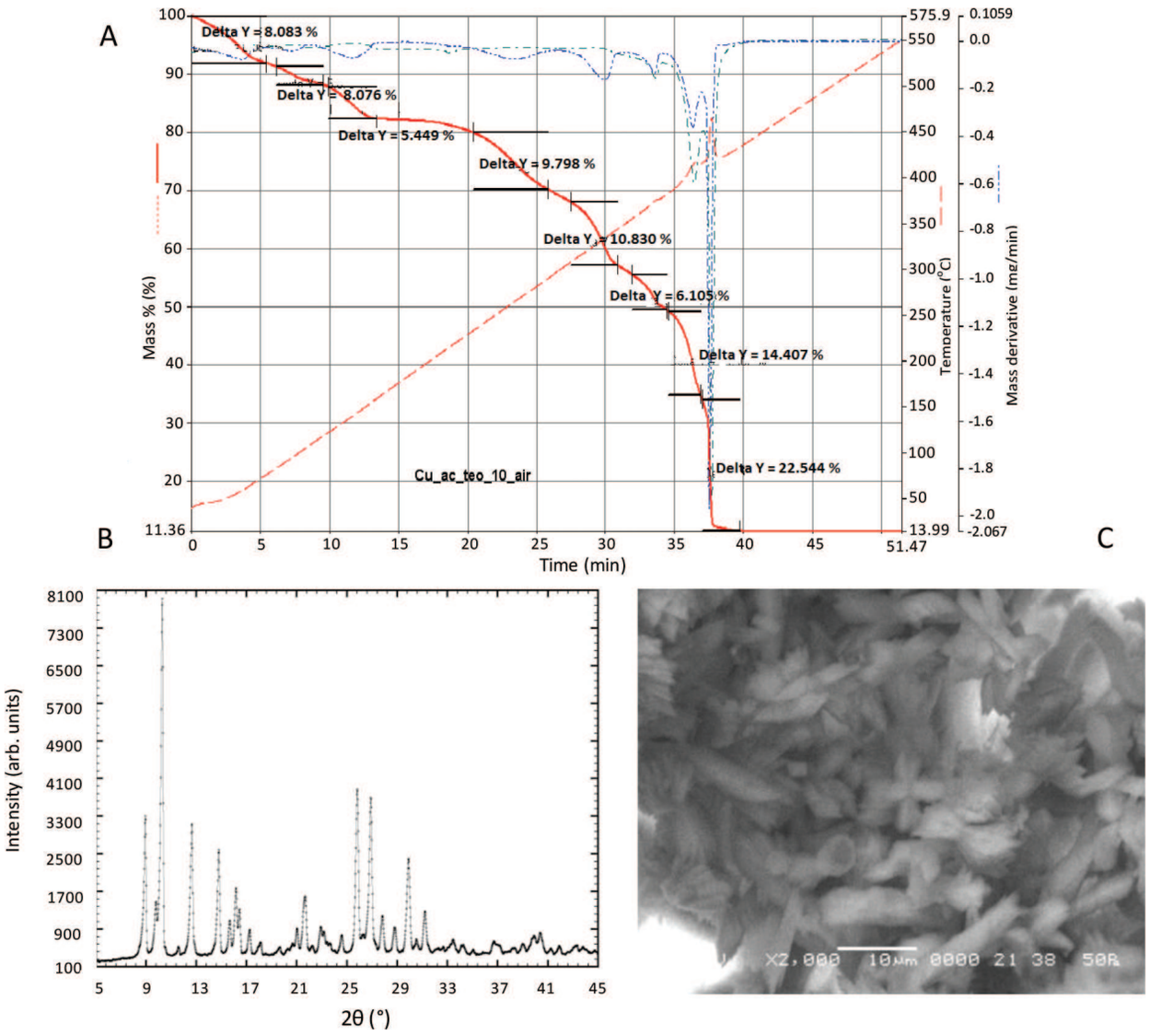

Figure 7. Thermogramms TG, DTG, and DTA (A); X-ray diffractogram; (B) and SEM images (C) of $[Cu(TEO)_2](CH_3COO)_2$ [2, 19, 21, 22]. Reprinted with permission of Revista de Chimie, Farmacia and of Editura Politehnica Timişoara.

The FTIR data also indicated the complex formation: the disappearance of the symmetric vibration band of ─C═O from TEO at 1717 cm^{-1} in the complexes spectra indicating that this bond is involved in the formation of Me:TEO coordinative bond; the deformation vibration of Me:N bond found at 570–685 cm^{-1}, the appearance of symmetric and asymmetric stretching vibrations of the ─COOH group (1260–1250 and 1535–1530 cm^{-1}), and the possibility of coordinating also the water of crystallization (appearance of large bands at 3050–3500 cm^{-1}) (**Figure 11**) [2, 19, 21, 22].

The combination ratio Me:TEO is 1:1 for the complexes having the benzoate anion: $[Co(TEO)](C_6H_5COO)_2 \cdot 2H_2O$, $[Ni(TEO)](C_6H_5COO)_2 \cdot 2H_2O$, and $[Cu(TEO)](C_6H_5COO)_2 \cdot 2H_2O$. Their thermal decomposition takes place in four stages, the first one being the stage of loss of water of crystallization (**Figure 12A**). The FTIR data are similar with those of the complexes mentioned above (having the acetate group as anion); in addition, the specific vibration band

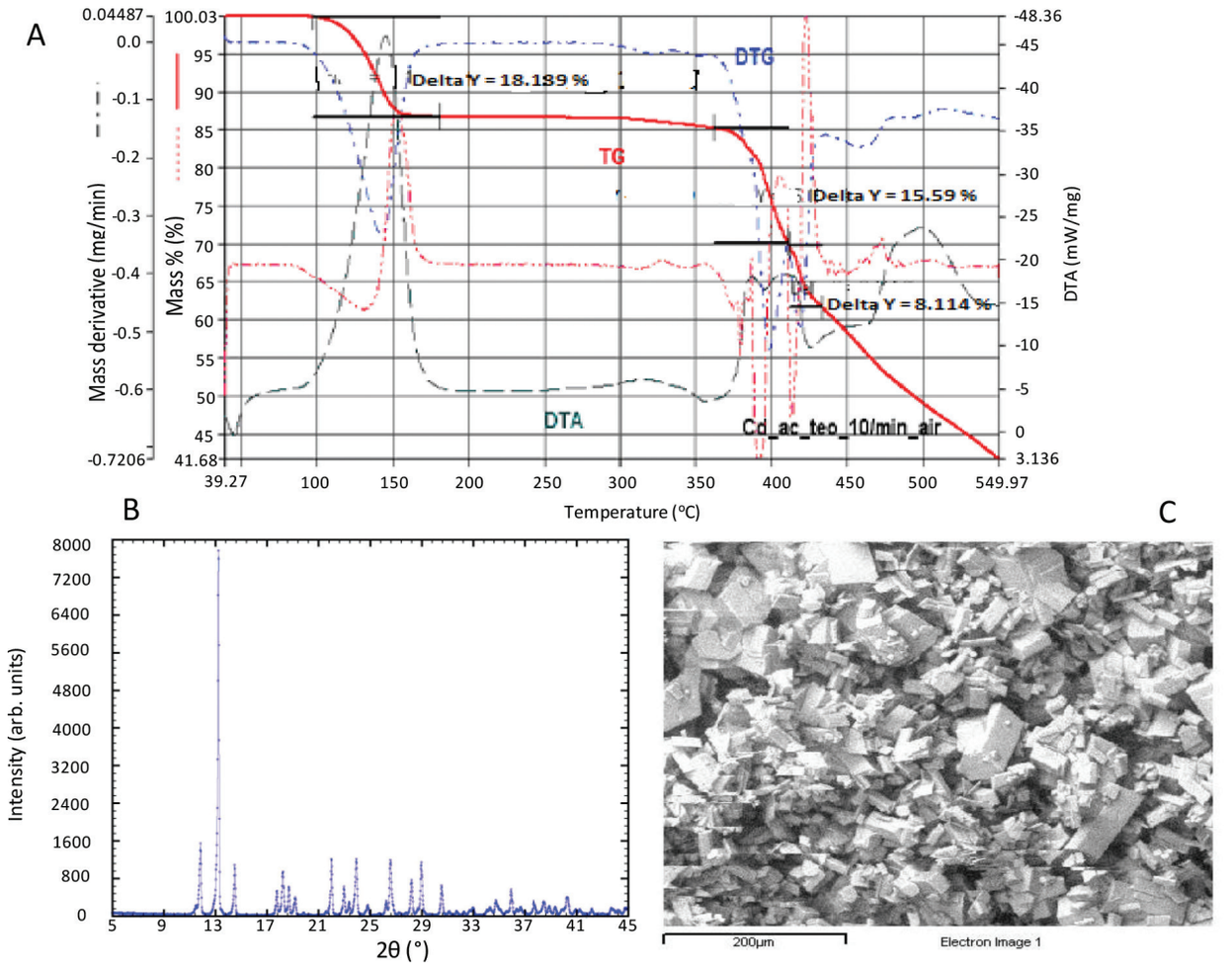

Figure 8. Thermogramms TG, DTG, and DTA (A); X-ray diffractogram; (B) and SEM images (C) of $[Cd(TEO)_2](CH_3COO)_2$ [2, 19, 21, 22]. Reprinted with permission of Revista de Chimie, Farmacia and of Editura Politehnica Timişoara.

of the aromatic ring (1438, 1442, 1440 cm^{-1}) appears. The microscopic image of [Co(TEO)] $(C_6H_5COO)_2$ showed the acicular shape of the particles (**Figure 12B**) [2, 20].

2.6. Metal complexes of captopril

The chemical structure of captopril (CPL), a dipeptide derivative of *L*-alanine-*L*-proline with antihypertensive effect, contains bonds such as —C═O and —N(—CH_2)$_2$ with donor atoms capable of forming Me:L bonds. The interaction between the metal ions such as Mn(II), Co(II), Zn(II), Ni(II), and Cd(II) with N and O atoms from the peptide (which act as donors) leads to the formation of stable chelate cycles. These complexes were characterized by elemental analysis obtaining the results presented in **Table 4** [23, 24].

CPL forms complexes with transition metals mentioned above in the presence of tetraiodomercurate anion, $[HgI_4]^{2-}$. The formation and the structure of these complexes are observed in the data of the elemental analysis and in the UV and IR spectra of the complexes with changes of the wavelength values and of absorbance due to the presence of Me:CPL bonds. In the IR spectra of the complexes, a diminution of the band at 1748 cm^{-1} of —C═O from the carboxyl group, in comparison with the IR spectrum of CPL, was observed. A wider band appeared

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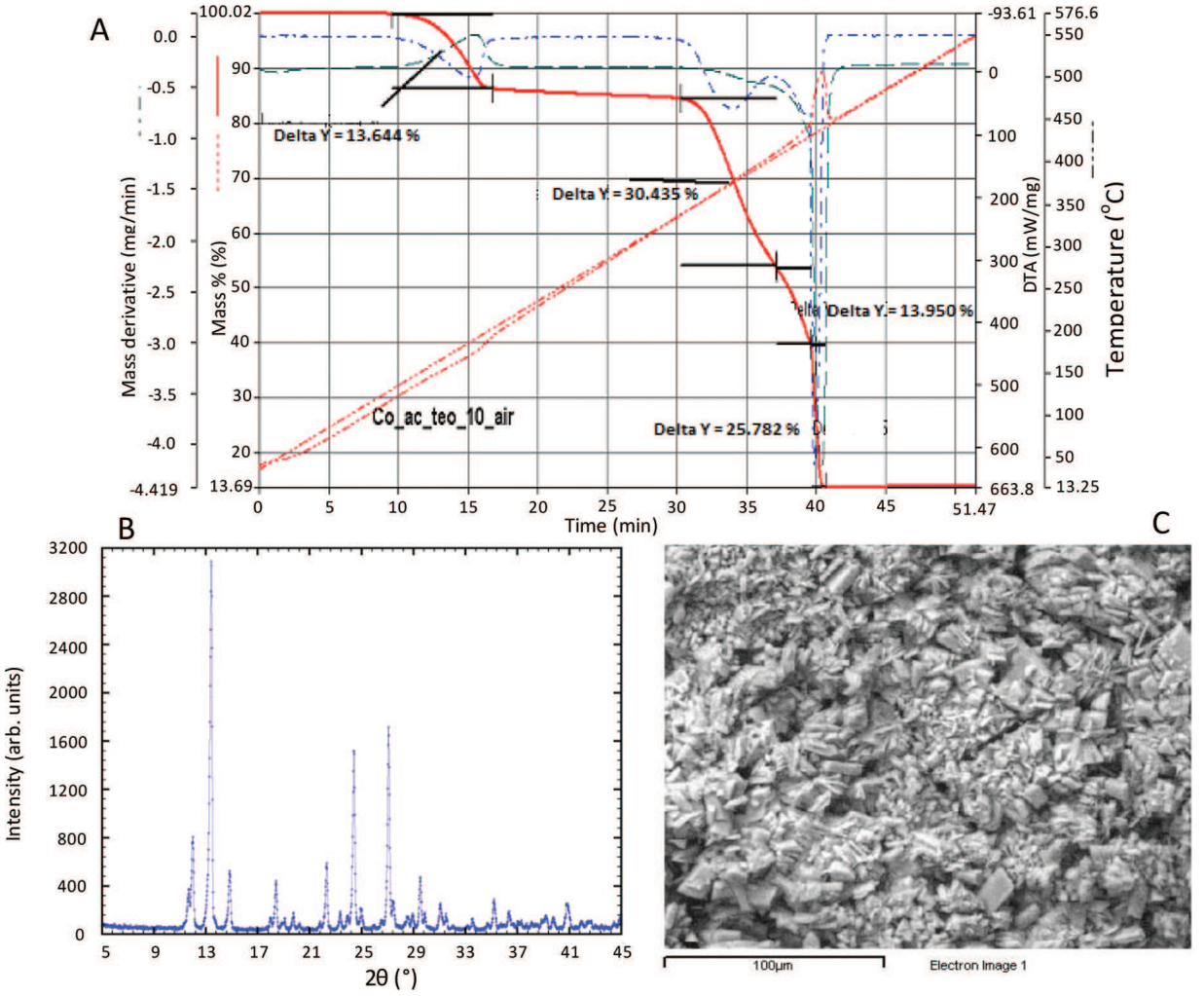

Figure 9. Thermogramms TG, DTG, and DTA (A); X-ray diffractogram; (B) and SEM images (C) of $[Co(TEO)_2](CH_3COO)_2$ [2, 19, 21, 22]. Reprinted with permission of Revista de Chimie, Farmacia and of Editura Politehnica Timişoara.

at 1600 cm^{-1} due to the overlapping of the bands corresponding to —C═O from the amide group. In addition, a new band is observed at 1450 cm^{-1} due to —C═O from the carboxyl group (—COO^-). In the IR spectra of the Zn:CPL complex, the band corresponding to —C═O from carboxyl group decreased. It is possible that the reaction with some metals was not completely performed or some degradation products of CPL may be involved in the complexation reaction. In the case of the complex $Cu_2^{II}CPL_2(H_2O)_2$, the IR spectra have indicated the participation of —COOH, —C═O, and —SH groups in coordination along with H_2O included in the inner coordination sphere [23, 24].

The UV spectra of the complexes were compared to the UV spectrum of CPL in dimethylformamide establishing the parameters presented in **Table 5** ($A^{\%}_{1\,cm}$ = 190 for 2.5 µg% CPL) [23, 24].

2.7. Metal complexes of tolbutamide

Tolbutamide (TBA) (*N-p*-tolylsulfonyl-*N'-n*-butylcarbamide) is the first generation of sulfonylurea oral hypoglycemic drug. Three complexes of TBA with Cu(II) were synthesized,

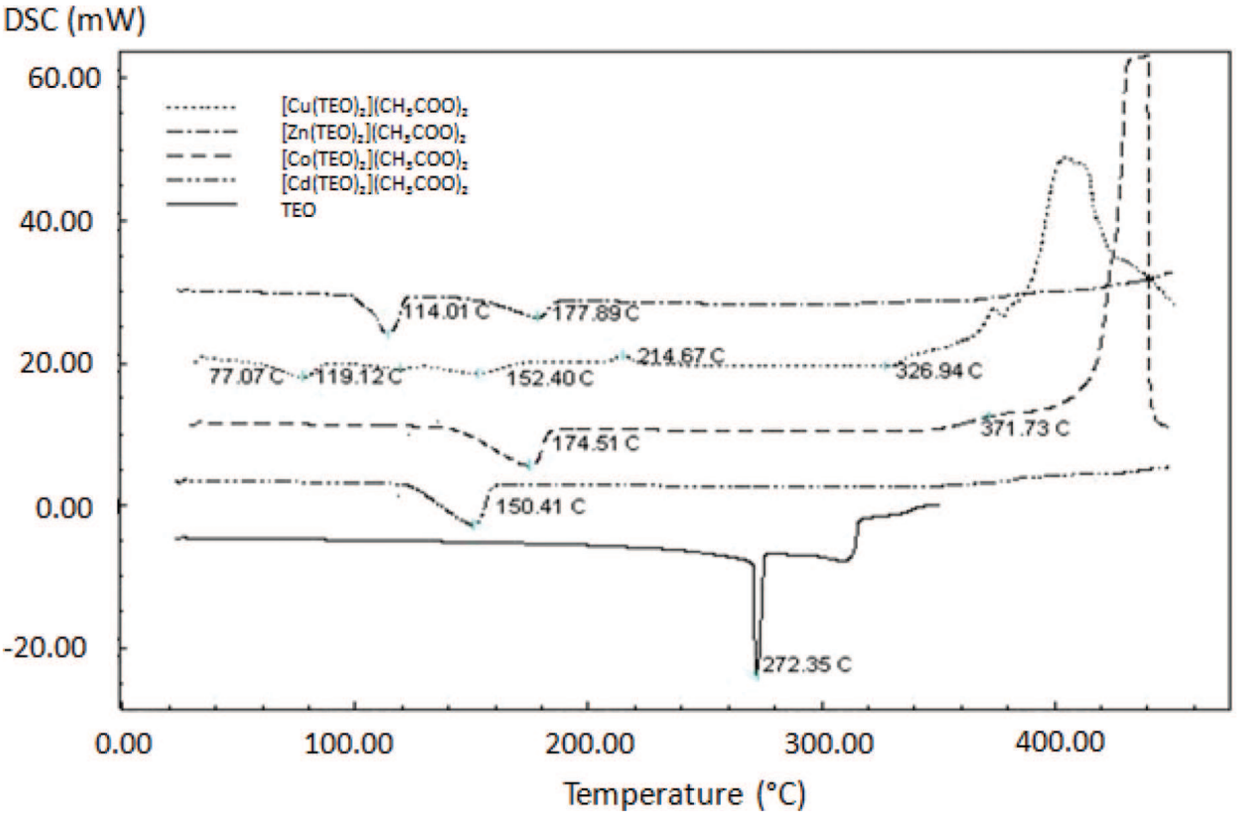

Figure 10. DSC thermogramms of metal complexes of TEO [2, 19]. Reprinted with permission of Revista de Chimie and of Editura Politehnica Timişoara.

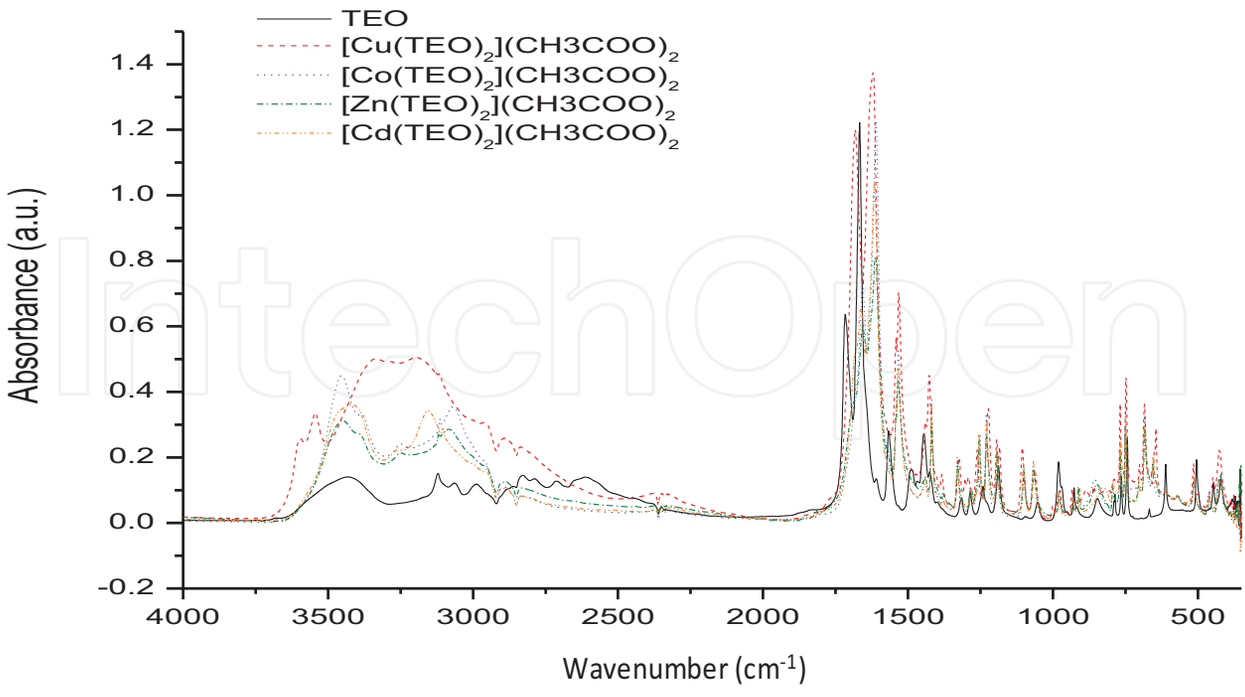

Figure 11. FTIR spectra of TEO and of its metal complexes (acetate anion).

http://dx.doi.org/10.5772/65390

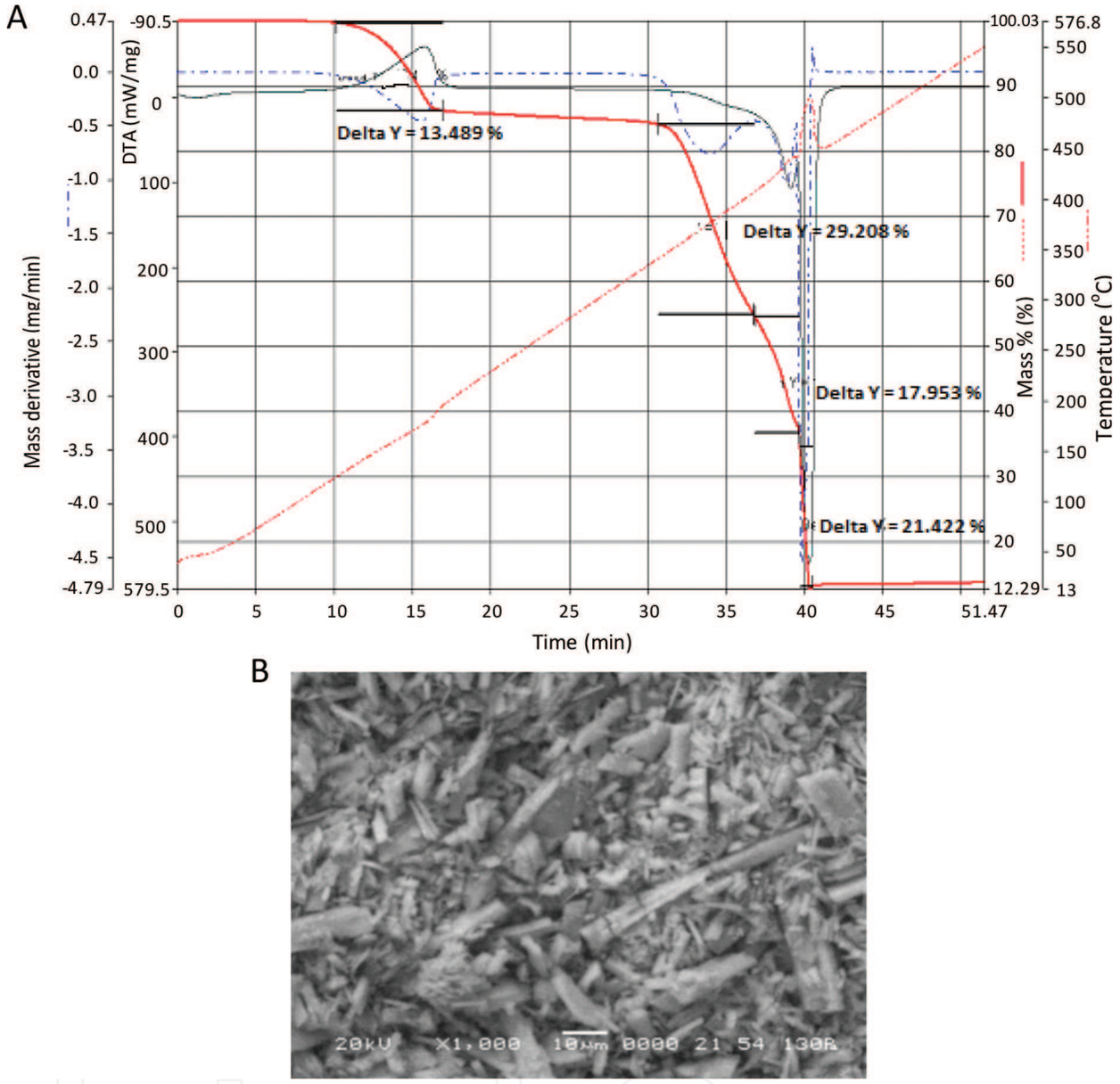

Figure 12. Thermogramms TG, DTG, and DTA (A) and SEM images (B) of $[Co(TEO)](C_6H_5COO)_2$ [2, 20]. Reprinted with permission of Revista de Chimie and of Editura Politehnica Timişoara.

$[Cu(TBA)_2](SCN)_2$, $[Cu(TBA)_2]Cl_2 \cdot 2H_2O$, and $[Cu(TBA)_2][Hg(SCN)_4] \cdot H_2O$ and then were characterized by elemental analysis, FTIR spectroscopy, electron paramagnetic resonance (EPR) spectroscopy, and thermal methods establishing the combination ratio Cu:TBA 1:2, the presence of water of crystallization, and the coordination system. The FTIR spectral studies indicated that the three mentioned complexes were coordinated through the carbonyl group. The EPR spectra showed that the Cu^{2+} ions were disposed in an octahedral vicinity of axial symmetry with a different hyperfine structure of the three complexes [25–27].

The molecular formula and weight	Color	Melting point (°C)	C% Found/ calculated	H% Found/ calculated	N% Found/ calculated	S% Found/ calculated
$[Cd(CPL)_2][HgI_4]$ M = 1255.18	White	210	17.09/17.21	2.56/2.39	1.881/2.23	5.579/5.099
$[Zn(CPL)_2][HgI_4]$ M = 1244.18	White	165	16.94/17.8	3.019/2.48	1.866/2.31	5.547/5.29
$[Ni(CPL)_2][HgI_4]$ M = 1199.48	Greenish yellow	170	18.07/18.01	3.022/2.5	1.955/2.33	6.083/5.33
$[Co(CPL)_2][HgI_4]$ M = 1199.68	Light pink	180	17.84/18.01	2.866/2.51	1.938/2.31	6.148/5.43
$[Mn(CPL)_2][HgI_4]$ M = 1195.68	White crystals	182	18.04/18.06	2.648/2.50	1.946/2.34	5.85/5.35

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Table 4. Physicochemical characterization of the metal complexes of CPL [23, 24].

Complex	λ (nm)	$A^{\%}_{1\,cm}$	Concentration (μg %)
CPL–Cd	300	270	5
CPL–Zn	300	400	5
CPL–Ni	300	475	4
CPL–Co	300	250	8
CPL–Mn	321	520	4.5

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Table 5. The parameters of the metal complexes of CPL from UV spectra [23].

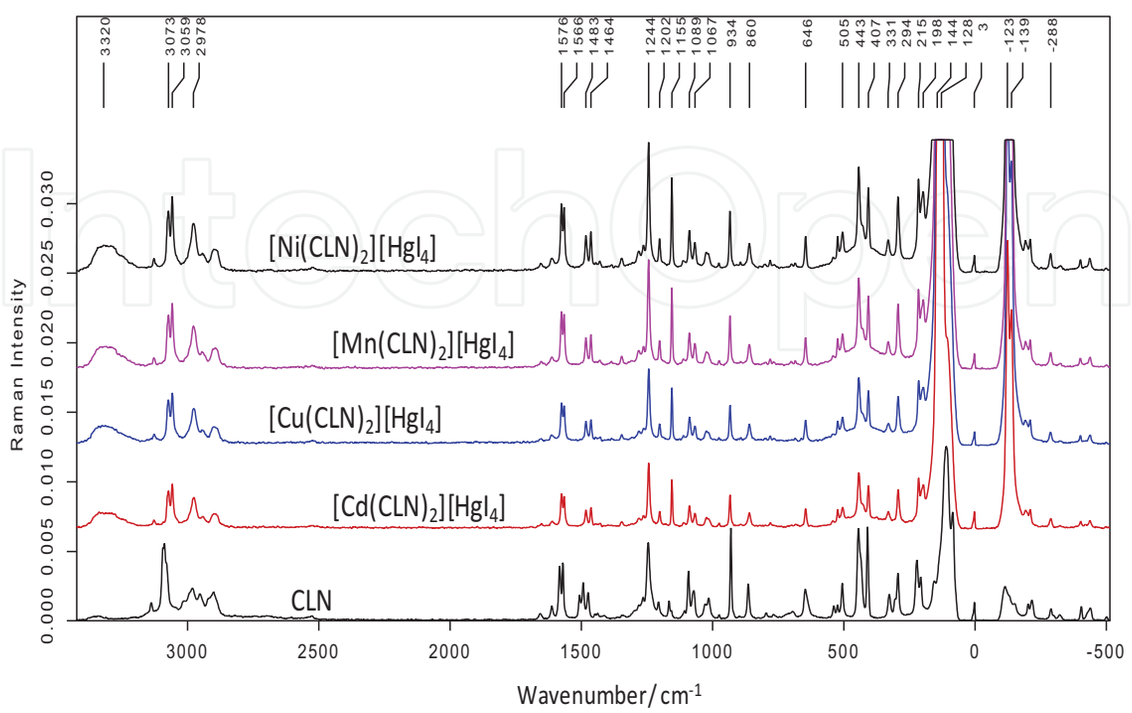

Figure 13. Raman spectra of CLN and of its metal complexes.

2.8. Metal complexes of clonidine

Clonidine (CLN) (2[(2,6-dichlorophenyl)imino]-imidazolidine) is a centrally acting α_2 adrenergic agonist used as antihypertensive drug. Metal complexes of CLN such as $[Me(CLN)_2][HgI_4]$ where Me = Cd(II), Mn(II), Ni(II), and Cu(II) were synthesized and studied by elemental analysis, FTIR spectroscopy, Raman spectroscopy (**Figure 13**), and EPR spectroscopy confirming the structure and the changes in the complex conformation [28].

3. Biomedical significance of metal complexes with pharmaceuticals

The study of the complexes structure and of their biological importance represented the major research interest toward the use of organic drugs as ligands in coordination chemistry for their application in the biomedical field.

The molecules of the pharmaceutical substances have one or more unshared electron pairs that can function as ligands. In fact, many of the basic components of living organisms (amino acids, peptides, proteins, hormones, lipids, carbohydrates, etc.) may function as ligands because they contain donor atoms in their molecules such as nitrogen, oxygen, sulfur, and phosphorus. It is well known that many molecules of drug substances act as ligands both in vitro and in vivo conditions. It is noteworthy to mention that in vivo these ligands will compete for a particular metal ion with a variety of other ligands determining that the extrapolation of this in vitro behavior should be done with moderation. It should always be taken into consideration that the therapeutic effect will be mainly influenced by the conformation of the drug ligands molecules and by their ability to combine with receptors.

Thus, the use of these metal complexes in the biomedical field can be realized by various purposes such as the introduction in the body of deficient metal ions, the use of the ligands as antidotes in various intoxications with metals, and the acquirement of pharmacotherapy effects by blocking metal ions essential for some enzymatic systems. Metal ions are of great importance not only in the vital functions of living organisms, but also they can be intensively used in analysis and control methods for pharmaceutical substances by forming complexes that can be detected by using different physicochemical methods such as spectroscopy, chromatography, microscopy, etc.

4. Conclusions

Transition metal complexes find their application in catalysis, material synthesis, photochemistry, therapy, and diagnostics. Various chemical, optical, and magnetic properties of the metal complexes of some pharmaceutical substances (pyrazinamide, nicotinamide, nicotinic acid, tolbutamide, theophylline, captopril, clonidine, and guanfacine) have been studied by using a wide range of techniques. The spectral methods such as Fourier transform infrared spectroscopy, Raman spectroscopy, surface-enhanced Raman spectroscopy, X-ray spectroscopy, mass spectrometry, ultraviolet-visible spectrophotometry, electron paramagnetic resonance spectroscopy, and X-ray diffraction provided information about the complexes

and ligand structure. Other techniques such as elemental analysis, electrochemical, and thermal methods were also employed for the assessment of the complexation ratio. The scanning electron microscopy images revealed the morphology of the metal complexes underlying their crystalline or amorphous character. Many studies were conducted concerning the synthesis and the investigation of metal complexes in which the pharmaceutical substances play the role of ligand highlighting their increasing clinical and commercial importance.

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