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Research Article

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Mn(II), Co(II), Fe(III) And Cu(II) Complexes of Antihistaminic "Fexofenadine" and Amucolytic "Carbocysteine" Drugs: Synthesis, Spectroscopic and Thermal Studies

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Abstract: Complexes of Mn(II), Co(II), Fe(II) and Cu(II) with fexofenadine and carbocysteine drug were synthesized and characterized by elemental analysis, conductivity, UV–Vis, IR spectroscopy and thermal analysis, as well as screened for antimicrobial activity. The IR spectral data suggested that the fexofenadine and carbocysteine ligands behave as monobasic bidentate ligand coordinated to the metal ions via the deprotonated carboxylate O atom. From the microanalytical data, the stoichiometry of the fexofenadine and carbocysteine complexes reacts with Mn(II), Co(II), Fe(II) and Cu(II) by molar ratios (2:1) and (1:1) (drug:metal ion), respectively. The thermal behavior (TG/DTG) of the complexes was studied.

Keywords: Fexofenadine; Carbocysteine; Transition Metal; Thermal Analysis; Antimicrobial Activity.

1. INTRODUCTION

A number of drugs and potential pharmaceutical agents also contain metal-binding or metal-recognition sites, which can bind or interact with metal ions and potentially influence their bioactivities and might also cause damages on their target biomolecules [1-10]. A histamine antagonist: is an agent that serves to inhibit the release or action of histamine. Antihistamine can be used to describe any histamine antagonist, but it is usually reserved for the classical antihistamines that act upon the H_1 histamine receptor. Fexofenadine was an antihistamine drug used in the treatment of hay fever and similar allergy symptoms (Fig. 1A). It was developed as a successor of an alternative to terfenadine (brand names include Triludan and Seldane), an antihistamine with potentially serious contraindications. Fexofenadine, like other second and third-generation antihistamines, does not readily cross the blood-brain barrier, and so causes less drowsiness than first-generation histamine-receptor antagonists. It works by being an antagonist to the H_1 receptor [11]. It has been described as both second-generation [12] and third-

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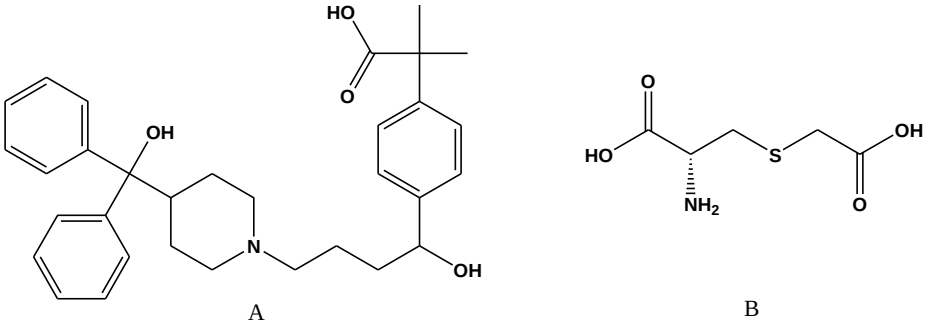

Figure 1. Structure of Fexofenadine (A) and Carbocysteine (B) drug

generation [13]. An expectorant increases bronchial secretions and mucolytics help loosen thick bronchial secretions. Expectorants reduce the thickness or viscosity of bronchial secretions thus increasing mucus flow that can be removed more easily through coughing. Mucolytics break down the chemical structure of mucus molecules. The mucus becomes thinner and can be removed more easily through coughing [13]. Carbocisteine was a mucolytic that reduces the viscosity of sputum and so can be used to help relieve the symptoms of Chronic Obstructive Pulmonary Disorder (COPD) and bronchiectasis by allowing the sufferer to bring up sputum more easily (Fig. 1B) [14]. Carbocisteine should not be used with antitussives (cough suppressants) or medicines that dry up bronchial secretions. The great importance that S-carboxymethyl-l-cysteine (carbocysteine, ccys) has in medicine and biology can be immediately appreciated by the several papers that can be found by simply keying one of its numerous synonyms in some web search engines. In fact, this aminoacid represents one of the most common drugs, mainly used as “mucolytic” agent. However, new studies were continuously performed with the aim of discovering new properties and functions: for example, carbocysteine inhibits virus infections and bacteria attachment in human epithelial cells of respiratory apparatus [15,16], it was used in the management of herbicide poisoning [17], and, very important from an environmental point of view, it was employed in soil remediation by complexometric extraction of metal contaminants (mainly copper) [18], thanks to its ability to form quite stable complexes with several metal cations [19-21]. Metal chelation by carbocysteine represents a very interesting subject not only for environmental chemists, but for biochemists too, because this bio-ligand may modify bioavailability of some metals in vivo [20]. Also unfortunately, to our knowledge, few papers report protonation constants for this ligand [19-21], in evident contrast with the number of studies dealing with carbocysteine metal complexes in aqueous solution.

The goal of this paper was to get a wide understanding of the structural and spectral properties as well as microbial activities of fexofenadine and carbocysteine and their Mn(II), Co(II), Fe(II) and Cu(II) metal ion complexes (Fig. 2 and Fig. 3). Metallo-fexofenadine/carbocysteine complexes were investigated by spectral and thermal techniques.

2. EXPERIMENTAL

2.1 Materials

All chemicals used were of the purest laboratory grade (Merck) and both fexofenadine and carbocisteine were presented from Egyptian international pharmaceutical industrial company (EIPICo.)

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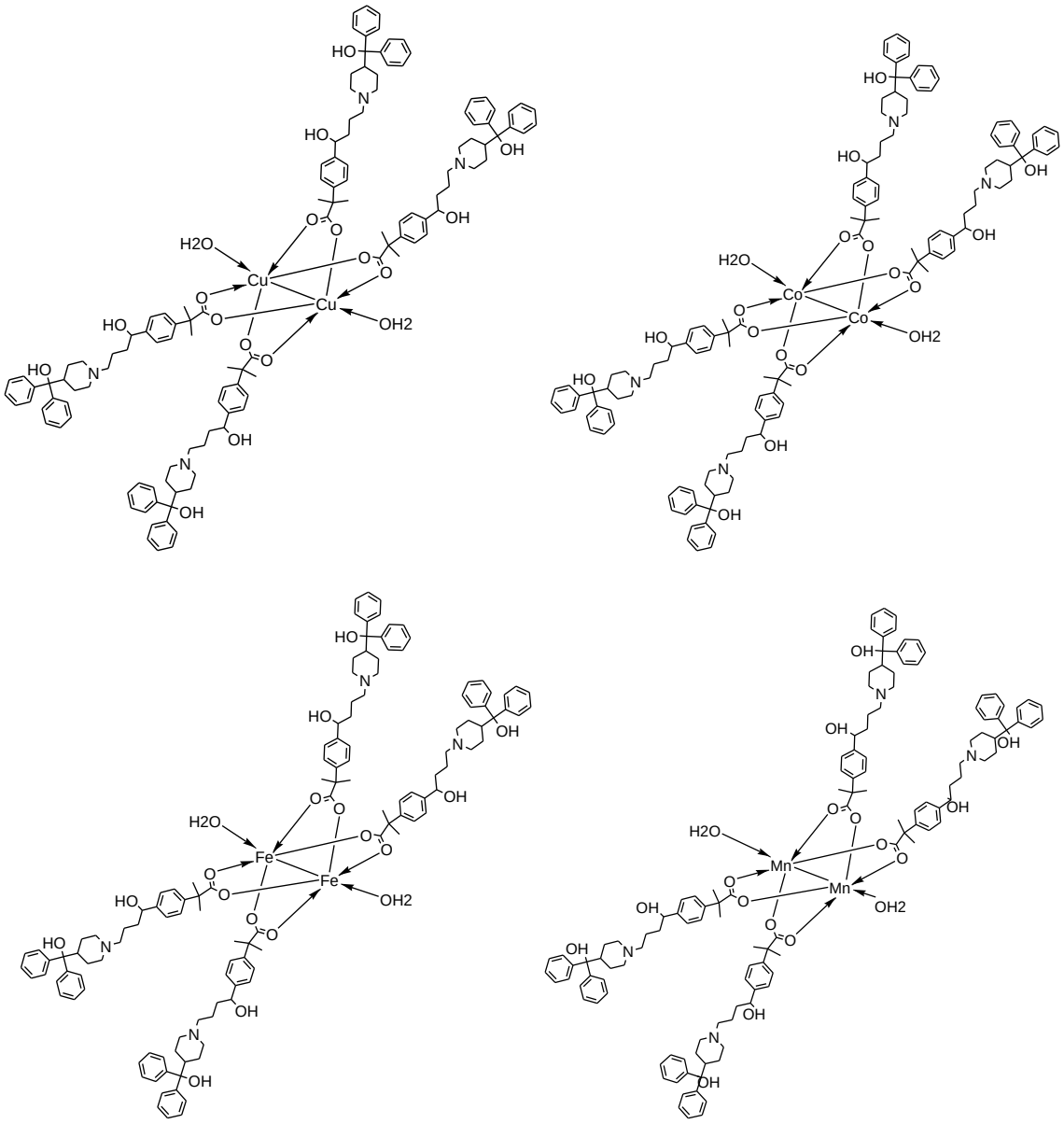

Figure 2. Structure of the Fexofenadine complexes

2.2 Synthesis of fexofenadine and carbocysteine metal complexes

For all preparations, doubly distilled water employed as solvent. All used reagents were of analytical grade and employed without further purifications. Cu(II) chloride, Fe(II) chloride, Mn(II) chloride and Cobalt(II) chloride (1 mmol, Fluka) were dissolved in 20 cm^3 of water and then the prepared solutions were slowly added to 25 cm^3 of an aqueous solution with 1 mmol of ligand solution under magnetic stirring. The pH of each solution adjusted to 6-8 by addition of ammonium hydroxide. The resulting solutions heated at 50 ^oC and left to evaporate slowly at room temperature overnight. The obtained precipitates were filtered-off, washed with hot water and then dried at 60 ^oC.

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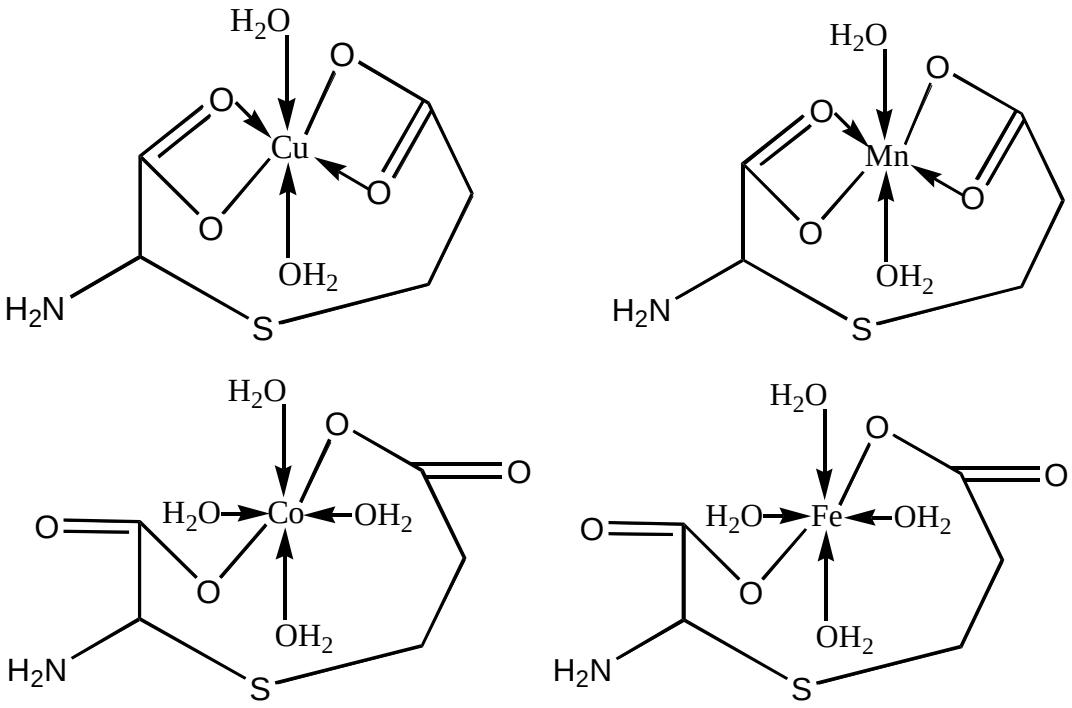

Figure 3. Structure of the Carbocysteine complexes

2.3 Microanalytical and instrumental techniques

Carbon and hydrogen contents were determined using a Perkin-Elmer CHN 2400. The metal content found gravimetrically by converting the compounds into their corresponding oxides. Chloride content in all prepared complexes determined potentiometrically by the titration against a standard $AgNO_3$ Materials. Mn(II), Co(II), Fe(II) and Cu(II) were determined atomic absorption technique. Molar conductivities of freshly prepared 1.0×10^{-3} mol/dm^{-3} DMSO solutions measured using Jenway 4010 conductivity meter. IR spectra were recorded on Bruker FTIR Spectrophotometer (4000–400 cm^{-1}) in KBr pellets. The UV–vis, spectra were determined in the DMSO solvent with concentration (1.0×10^{-3} M) for the free ligands and their complexes using Jenway 6405 Spectrophotometer with 1cm quartz cell, in the range 200–800 nm. Thermogravimetric analyses (TG) carried out in the temperature range from 25 to 800 ^{o}C in a steam of nitrogen atmosphere by Shimadzu TGA 50H thermal analysis. The experimental conditions were: platinum crucible, nitrogen atmosphere with a 30 ml/min flow rate and a heating rate 10 ^{o}C/min.

2.4 Microbiological investigation

The investigated isolates of bacteria were seeded in tubes with nutrient broth (NB). The seeded NB (1 cm^3) was homogenized in the tubes with 9 cm^3 of melted (45 ^{o}C) nutrient agar (NA). The homogeneous suspensions were poured into Petri dishes. The discs of filter paper (diameter 4 mm) were ranged on the cool medium. After cooling on the formed solid medium, 2×10^{-5} dm^3 of the investigated compounds were applied using a micropipette. After incubation for 24 h in a thermostat at 25–27 ^{o}C, the inhibition (sterile) zone diameters (including disc) were measured and expressed mm. An inhibition zone diameter over 7 mm indicates that the tested compound is active against the bacteria under investigation [22]. The antibacterial activities of the investigated compounds were tested against Escherichia Coli

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(Gram -ve), Bacillus subtilis (Gram +ve) and antifungal (tricoderma and penicillium). The concentration of each solution was 1.0×10^{-3} mol dm^3. Commercial DMSO was employed to dissolve the tested samples.

Table 1. Analytical and physical data of Fexo and its metal complexes

Complex	Mwt	Formula	%C		%H		%N	
			Calc.	Found	Calc.	Found	Calc.	Found
$Mn_2(Fexo)_4(H_2O)_2$	2148.5	$C_{128}H_{156}Mn_2N_4O_{18}$	71.56	71.66	7.32	7.13	2.61	2.55
$Co_2(Fexo)_4(H_2O)_2$	2156.49	$C_{128}H_{156}Co_2N_4O_{18}$	71.29	71.45	7.29	7.77	2.60	2.82
$Fe_2(Fexo)_4(H_2O)_2$	2150.31	$C_{128}H_{156}Fe_2N_4O_{18}$	71.50	71.32	7.31	7.34	2.61	2.77
$Cu_2(Fexo)_4(H_2O)_2$	2165.72	$C_{128}H_{156}Cu_2N_4O_{18}$	70.99	70.36	7.26	7.34	2.59	2.66

Table 2. Analytical and physical data of Carbo and its metal complexes

Complex	Mwt	Formula	%C		%H		%N	
			Calc.	Found	Calc.	Found	Calc.	Found
$Mn(Car)(H_2O)_2$	268.15	$C_5H_{11}MnNO_6S$	22.40	22.28	4.13	4.21	5.22	5.70
$Co(Car)(H_2O)_4$	308.17	$C_5H_{15}CoNO_8S$	19.49	19.13	4.91	4.66	4.55	5.32
$Fe(Car)(H_2O)_4$	305.08	$C_5H_{15}FeNO_8S$	19.68	19.60	4.96	4.63	4.59	5.42
$Cu(Car)(H_2O)_2$	276.75	$C_5H_{11}CuNO_6S$	21.70	21.98	4.01	4.15	5.06	5.27

Table 3. IR spectra (4000-400 cm^{-1}) of Fexo and its metal complexes

Compound	ν(COO) (s)	*ν*(COO) (as)	Δ	ν(C=O)	*ν*(M-O) (COO)	ν(M-O) (H_2O)
Fexo	1592w	1448sh	144	1705sh	--	--
$Mn_2(Fexo)_4(H_2O)_2$	1587s	1469m	118	1702w	460s	525s
Co_2(Fexo)$_4(H_2O)_2$	1595m	1491s	104	1703w	463w	515s
Fe_2(Fexo)$_4(H_2O)_2$	1594m	1470sh	124	1703w	458s	523s
Cu_2(Fexo)$_4(H_2O)_2$	1578m	1470m	108	1717w	460w	546s

3. RESULTS AND DISCUSSION

3.1 Elemental analysis and conductivity measurements

The elemental analysis results are summarized in Table 1 and 2. These results, as well as the obtained mass spectra are in good agreement with the proposed formula. The melting points of the complexes are higher than that of the free ligand, revealing that the complexes are much more stable than ligand. The molar conductance values of the fexofenadine complexes found to be in the range from 18-to-33 $\Omega^{-1}cm^2mol^{-1}$ at 25 ^oC, which indicates that the complexes are of a non-electrolytic nature . The solubility of Fexo and Car complexes is low in water, ethanol, chloroform, acetone and most organic solvents, but, on the other hand, they are soluble in DMSO, DMF and concentrated acids. The molar conductance values of the carbocysteine complexes found to be in the range from 18-to-36 $\Omega^{-1}cm^2mol^{-1}$ at 25 ^oC, which indicates that the complexes are of a non-electrolytic nature.

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Table 4. IR spectra (4000-400 cm^{-1}) of Car and its metal complexes

Compound	ν(COO) (s)	*ν*(COO) (as)	Δ	*ν*(M-O) (COO)	ν(M-O) (H_2O)
Carbocysteine	1510sh	1413sh	97	--	--
$Mn(Car)(H_2O)_2$	1565s	1411m	154	490s	535s
$Co(Car)(H_2O)_4$	1578m	1403s	175	470w	528s
$Fe(Car)(H_2O)_4$	1592m	1404sh	188	435s	526s
$Cu(Car)(H_2O)_2$	1522m	1402m	122	460w	528s

Table 5. Thermodynamic data of the thermal decomposition of Fexo metal complexes

Complex	TG range (°C)	DTG_{max} (°C)	Mass loss Found (Calcd.)	Assignment	Metallic residue
$Mn_2(Fexo)_4(H_2O)_2$	140-450	350	46.58(46.92)	-loss of $4H_2O,12C_6H_6$	MnO
	450-800	600	22.30 (22.71)	-loss of $7CO_2,4NH_3,4CH_4,24H_2$	
$Co_2(Fexo)_4(H_2O)_2$	120-450	300	45.28 (45.91)	-loss of $3H_2O,12C_6H_6$	CoO
	450-800	600	23.83 (23.46)	-loss of $7CO_2,4NH_3,4CH_4,24H_2,H_2O$	
$Fe_2(Fexo)_4(H_2O)_2$	140-450	350	46.27 (46.88)	-loss of $4H_2O,12C_6H_6$	FeO
	450-800	600	23.17(22.69)	-loss of $7CO_2,4NH_3,4CH_4,24H_2$	
$Cu_2(Fexo)_4(H_2O)_2$	140-450	350	44.53 (44.88)	-loss of $2H_2O,12C_6H_6$	CuO
	450-800	600	23.42(24.19)	-loss of $7CO_2,4NH_3,4CH_4,24H_2,2H_2O$	

Table 6. Thermodynamic data of the thermal decomposition of Car metal complexes

Complex	TG range (°C)	DTG_{max} (°C)	Mass loss %Found (Calcd.)	Assignment	Metallic residue
$Mn(Car)(H_2O)_2$	30-170	140	6.66(6.71)	-loss of H_2O	MnO
	170-800	600	48.55(48.85)	-loss of $2H_2O,CO_2,NH_3,H_2S$	
$Co(car)(H_2O)_4$	30-190	300	11.17(11.68)	-loss of $2H_2O$	CoO
	190-800	600	48.17(48.99)	-loss of $4H_2O,CO,NH_3,H_2S$	
$Fe(Car)(H_2O)_4$	30-140	350	11.89 (11.80)	-loss of $2H_2O$	FeO
	140-800	600	48.90(49.49)	-loss of $4H_2O,CO,NH_3,H_2S$	
$Cu(Car)(H_2O)_2$	30-140	350	6.28 (6.50)	-loss of H_2O	CuO
	140-800	600	47.34(47.33)	-loss of $2H_2O,CO_2,NH_3,H_2S$	

3.2 Infrared spectra

The IR data to fexofenadine and its complexes are listed in Table 3. The IR spectra of the complexes were compared with those of the free ligand in order to determine the coordination sites that may involve in chelation. There are some guide peaks, in the spectra of the ligand, which are useful in achieving this goal. The position and/or the intensities of these peaks are exepected to change upon chelation. No significant spectral changes were observed for the fexofenadine after their coordination to the metal ions, except for the frequencies related to the carboxylic (–COOH) groups [23]. The carbonyl stretching, *ν*(C=O), of the parent acids (1718 cm^{-1} for Fexofenadine) decrease to be very weak (near to disappear) in the correspondent metal complexes spectra. Instead, carboxylate ($–COO^-$) typical bands found at the region of 1590–1440 cm^{-1}. The values for Δ [*ν*(COO)– *ν*(COO)] are in the range of 104–118 cm^{-1}, corroborating the bridging coordination mode of the carboxylate ligands to the metal ion cores , in

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excellent agreement with those reported for Cu(II)–acetate complex.

The IR data to carbocysteine and its complexes are listed in Table 4. The absence of large systematic shifts of the $\nu(NH_2)$ and $\delta(NH_2)$ bands in the spectra of all the complexes compared with those of the ligand indicates that there is no interaction between the NH_2 group and the metal ions. The difference of bands of Fe(II) and Co(II) complexes ν_{as}(COO) and $\nu_{s.}$ (COO) compared to that of carbocysteine characterizes the carboxylate ligation. The ν_{as} (COO) and ν_s (COO) bands of carbocyteine complexes are at 1578-1592 and 1402-1403 cm^{-1} respectively. The difference $\Delta(\Delta = \nu_{as}.COO - \nu_s.COO)$ 190–170 cm^{-1} is close to the ionic value. The values Δ [ν(COO)– ν(COO)] for Mn(II) and Cu(II) are in the range of 122–154 cm^{-1}, corroborating the bridging coordination mode of the carboxylate ligands to the metal ion cores , in excellent agreement with those reported for Cu(II)–acetate complex.

3.3 Electronic absorption spectra

The formation of the metal fexofenadine complexes was also confirmed by UV-vis spectra. It can see that free fexofenadine has two distinct absorption bands. The first one at 290 nm may be attributed to $\pi\rightarrow\pi^*$ transition of the heterocyclic moiety and benzene ring. The second band observed at 400 nm is attributed to $n\rightarrow\pi^*$ electronic transition. Concerning carbocysteine complexes, the band observed at 290-310 nm is attributed to $n\rightarrow\pi^*$ electronic transition. In the spectra of the M complexes, the band are hypochromically affected obviously, suggesting the ligand has changed to the zwitterionic form. The results clearly indicate that the ligand coordinate to metal ions via carboxylic which is in accordance with the results of the FT-IR spectra.

3.4 Mass spectra

In the mass spectrum of $[Fe_2(Fexo)_4(H_2O)_2]$ intense mass peaks at *m/z* 501, 280, 107, 91 and 56 are detected. The first mass peak corresponds to the $[H\text{-}Fexo]^+$ ion, and the second one proceeds by formation of (1-methylpiperidin-4-yl)diphenylmethanol) from the molecular ion at *m/z* 280, then the elimination of methanol at *m/z*= 183. The molecular ion peak at *m/z*= 91 can be assigned to C_7H_7. In comparison between the fexofenadine (ligand) and the Fe(II) complexes, the peak assigned to molecular ion *m/z*= 501 of fexofenadine ligand is present complex, and new peaks appear at *m/z* = 56 can be assigned to Fe(II). These results are again consistent with the presence of direct metal-ligand bonding in the fexofenadine complexes. In the mass spectra of $[Co(Car)(H_2O)_4]$ intense mass peaks at *m/z* 181,161,116,92, and 58 are detected. The first mass peak corresponds to the $[H\text{-}Car]^+$ ion, and the second one proceeds by elimination of NH_3 from the molecular ion at *m/z* 161, then the elimination of CH_4 and CO_2 at *m/z*= 116. The. In comparison between the fexofenadine (ligand) and the Co(II) complexes, the peak assigned to molecular ion *m/z*= 501 of carbocysteine ligand is present complex, and new peaks appear at *m/z* = 58 can be assigned to Co(II). These results are again consistent with the presence of direct metal-ligand bonding in the carbocysteine complexes.

3.5 Thermogravimetric analysis

The heating rates were controlled at 10 °C min^{-1} under nitrogen atmosphere and the weight loss was measured from ambient temperature up to ≅ 1000 °C. The data are listed in Table 5. The weight losses for each chelate calculated within the corresponding temperature ranges. The thermal decomposition of $Mn_2(Fexo)_4(H_2O)_2$ occurs at two step. The degradation step take place in the range of 140-450 ^oC and it is corresponding to the loss of $4H_2O$ and $12C_6H_6$ molecules, representing a weight loss of 46.58% and its calculated value is 46.92%. The second step occurring at 450-800 ^oC and it is corresponds to the eliminated of $7CO_2$, $4NH_3$, $4CH_4$ and $24H_2$ molecules. The MnO polluted with some

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Table 7. Thermodynamic data of the thermal decomposition of Fexo metal complexes

Complex	Stage	Method	Parameter					r
			E (kJ mol^{-1})	A (s^{-1})	ΔS (Jmol^{-1}K^{-1})	ΔH (kJmol^{-1})	ΔG (kJmol$^{-1)}$	
Fexo	1nd	CR	9.63×10^{4}	3.34×10^{5}	-1.45×10^{2}	8.53×10^{4}	1.05×10^{5}	0.9938
		HM	2.32×10^{4}	3.16×10^{5}	-1.45×10^{2}	8.32×10^{4}	1.03×10^{5}	0.9982
		average	5.96×10^{4}	3.21×10^{5}	1.45×10^{2}	4.43×10^{4}	1.04×10^{5}	0.9960
Co	1st	CR	4.70×10^{4}	2.91×10^{3}	-1.41×10^{2}	4.43×10^{4}	1.63×10^{5}	0.9890
		HM	5.32×10^{4}	4.30×10^{2}	-1.19×10^{2}	4.05×10^{4}	1.60×10^{5}	0.9886
		average	5.01×10^{4}	2.30×10^{3}	-1.22×10^{2}	1.24×10^{4}	1.62×10^{5}	0.9988
Cu	2st	CR	3.56×10^{4}	2.59×10^{3}	-1.81×10^{2}	3.38×10^{4}	1.03×10^{5}	0.9731
		HM	4.65×10^{4}	2.48×10^{4}	-1.62×10^{2}	3.78×10^{4}	1.02×10^{5}	0.9762
		average	4.11×10^{4}	1.37×10^{4}	-1.72×10^{2}	3.58×10^{4}	1.01×10^{5}	0.9747
Fe	2nd	CR	1.63×10^{4}	61.77×10^{2}	-2.84×10^{2}	1.12×10^{4}	1.63×10^{5}	0.9877
		HM	2.61×10^{4}	3.64×10^{1}	-2.59×10^{2}	2.12×10^{4}	161×10^{5}	0.9952
		average	2.12×10^{4}	1.91×10^{2}	-2.72×10^{2}	1.62×10^{4}	1.62×10^{5}	0.9915
Mn	1st	CR	1.66×10^{4}	8.21×10^{4}	-1.51×10^{2}	4.05×10^{4}	1.61×10^{5}	0.9942
		HM	1.77×10^{4}	1.73×10^{6}	-1.26×10^{1}	4.65×10^{4}	1.58×10^{5}	0.9940
		average	1.72×10^{4}	9.06×10^{5}	-1.34×10^{2}	4.35×10^{4}	1.60×10^{5}	0.9941

Table 8. Thermodynamic data of the thermal decomposition of Car metal complexes

complex	method	parameter					r
		E (kJ mol^{-1})	A (s^{-1})	ΔS (Jmol^{-1}K^{-1})	ΔH (kJmol^{-1})	ΔG (kJmol$^{-1)}$	
Car	CR	1.16×10^{5}	8.06×10^{8}	-7.95×10^{1}	1.12×10^{5}	1.55×10^{5}	0.9860
	HM	1.27×10^{5}	1.50×10^{10}	-5.52×10^{1}	1.22×10^{5}	1.52×10^{5}	0.9899
	average	1.22×10^{5}	7.90×10^{9}	-6.74×10^{1}	1.17×10^{5}	1.54×10^{5}	0.9880
Fe^{3+}	CR	3.05×10^{4}	1.20×10^{2}	-2.06×10^{2}	2.76×10^{4}	9.95×10^{4}	0.9953
	HM	3.63×10^{4}	2.49×10^{3}	-1.81×10^{2}	3.34×10^{4}	9.65×10^{4}	0.9943
	average	3.34×10^{4}	1.31×10^{3}	-1.94×10^{2}	3.05×10^{4}	9.80×10^{4}	0.9948
Mn^{2+}	CR	4.87×10^{4}	1.05×10^{5}	-1.50×10^{2}	4.58×10^{4}	9.81×10^{4}	0.9910
	HM	5.45×10^{4}	2.01×10^{6}	-1.26×10^{2}	5.16×10^{4}	9.53×10^{4}	0.9906
	average	4.95×10^{4}	1.06×10^{6}	-1.38×10^{2}	4.87×10^{4}	9.67×10^{4}	0.9908
Cr^{3+}	CR	4.75×10^{4}	3.42×10^{5}	-1.40×10^{2}	4.48×10^{4}	8.99×10^{4}	0.9991
	HM	5.17×10^{4}	5.62×10^{6}	-1.17×10^{2}	5.60×10^{4}	8.79×10^{4}	0.9992
	average	4.96×10^{4}	2.98×10^{6}	-1.29×10^{2}	5.04×10^{4}	8.89×10^{4}	0.9992
Co^{2+}	CR	3.60×10^{4}	4.10×10^{3}	-1.76×10^{2}	3.33×10^{4}	9.03×10^{4}	0.9973
	HM	4.13×10^{4}	4.71×10^{4}	-1.55×10^{2}	3.86×10^{4}	8.86×10^{4}	0.9950
	average	3.87×10^{4}	4.41×10^{4}	-1.66×10^{2}	3.40×10^{4}	8.95×10^{4}	0.9966

carbon atoms is the final product remains and is stable until 800 ^{o}C. The cobalt(II) fexofenadine complex decomposed in two steps, the first one occurring at 120-450 ^{o}C and corresponding to the evolution of $3H_2O$ and $12C_6H_6$ molecules due to weight loss of 45.28% and its calculated value is 45.91%. The second step occurring at 450-800 ^{o}C is corresponding to the loss of $7CO_2$, $4NH_3$, $4CH_4$, $24H_2$ and H_2O molecules, representing a weight loss of 23.83% and its calculated value is 23.46 %. The final products resulted at 800 ^{o}C contain CoO polluted with some carbon atoms. The Fe(III) fexofenadine complex decomposed in two steps, the first one occurring at 140-450 ^{o}C and corresponding to the evolution of $4H_2O$ and $12C_6H_6$

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molecules, due to weight loss of 46.27% and its calculated value is 46.88%. The second step occurring at 450-800 ^{o}C is corresponding to the loss of $7CO_2$, $4NH_3$, $4CH_4$ and $24H_2$ molecules, representing a weight loss of 23.17% and its calculated value is 22.69%. The final products resulted at 800 ^{o}C contain FeO polluted with some carbon atoms. The thermal decomposition of $Cu(Fexo)_4(H_2O)_2$ occurs at two steps. The degradation step take place in the range of 140-450 ^{o}C and it is corresponds to the eliminated of $2H_2O$ and $12C_6H_6$ molecules due to a weight loss of 44.53% in a good matching with theoretical value 44.88%. The CuO is the final product remains stable until 800 ^{o}C polluted with some carbon atoms.

The weight losses for each carbocysteine chelate calculated within the corresponding temperature ranges (Table 6). The thermal decomposition of $Mn(Car)(H_2O)_2$ occurs at two step. The degradation step take place in the range of 30-170 ^{o}C and it is corresponding to the loss of H_2O molecule, representing a weight loss of 6.66% and its calculated value is 6.71%. The second step occurring at 170-800 ^{o}C and it is corresponds to the eliminated of $2H_2O$, CO_2, NH_3, and H_2S molecules. The MnO (polluted with one carbon atom) is the final product remains and is stable until 800 ^{o}C. The cobalt(II) carbocysteine complex decomposed in two steps, the first one occurring at 30-190 ^{o}C and corresponding to the evolution of $2H_2O$ molecules due to weight loss of 11.17% and its calculated value is 11.68%. The second step occurring at 190-800 ^{o}C is corresponding to the loss of $4H_2O$, CO, NH_3, and H_2S molecules, representing a weight loss of 48.17% and its calculated value is 48.99%. The final products resulted at 800 ^{o}C contain CoO polluted with few carbon atoms. The Fe(II) carbocysteine complex decomposed in two steps, the first one occurring at 30-140 ^{o}C and corresponding to the evolution of $2H_2O$, molecules, due to weight loss of 11.89% and its calculated value is 11.80%. The second step occurring at 140-800 ^{o}C is corresponding to the loss of $4H_2O$, CO, NH_3, and H_2S molecules, representing a weight loss of 48.90% and its calculated value is 49.49%. The final products resulted at 800 ^{o}C contain FeO polluted with few carbon atoms. The thermal decomposition of $Cu(Car)(H_2O)_2$ occurs at two steps. The degradation step take place in the range of 30-140 ^{o}C and it is corresponds to the eliminated of H_2O molecule due to a weight loss of 6.28% in a good matching with theoretical value 6.50%. The second step occurring at 140-800 ^{o}C is corresponding to the loss of $2H_2O$, CO_2, NH_3, and H_2S molecules, representing a weight loss of 47.34% and its calculated value is 47.33%. The CuO polluted with some carbon atoms is the final product remains stable until 800 ^{o}C. The polluted with carbon atoms for all the final residual products in Fexo and Car complexes are assigned to that thermogravimetric analyses operated under steam nitrogen which not let to achievement an excess amount of oxygen.

The different thermodynamic parameters were calculated upon Coats-Redfern [24] and Horowitz-Metzger [25] methods and listed in Tables 7 and 8. The activation energies of decomposition found to be in the range 1.66 $x10^4$- 9.63 $x10^5$ $kJmol^{-1}$. The high values of the activation energies reflect the thermal stability of the complexes. The entropy of activation found to have negative values in all the complexes, which indicate that the decomposition reactions proceed with a lower rate than the normal ones. On another meaning the thermal decomposition process of all Fexo complexes are non-spontaneous, i.e, the complexes are thermally stable. The correlation coefficients of the Arhenius plots of the thermal decomposition steps found to lie in the range 0.9731 to 0.9960, showing a good fit with linear function. The activation energies of decomposition for the carbocysteine complexes found to be in the range $3.05x10^4$-1.16 $x10^5$ $kJmol^{-1}$. The high values of the activation energies reflect the thermal stability of the complexes. The entropy of activation found to have negative values in all the complexes, which indicate that the decomposition reactions proceed with a lower rate than the normal ones. The correlation coefficients of the Arhenius plots of the thermal decomposition steps found to lie in the range 0.9860 to 0.9992, showing a good fit with linear function.

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3.6 Microbiological investigation

Antibacterial and antifungal activities of the fexofenadine and carbocysteine ligands and their complexes are carried out against the *Escherichia Coli* (Gram -ve), *Bacillus subtilis* (Gram +ve) and antifungal (tricoderma and penicillium activities). The antimicrobial activity estimated based on the size of inhibition zone around dishes. Both of Fexo and Car complexes are found to have high activity against *Bacillus subtilis* and penicillium, whereas the Cu(II) complex is more active than the Fe(III), Mn(II) and Co(III) complexes against tricoderma.

4. CONCLUSION

New complexes of Mn(II), Co(II), Fe(II) and Cu(II) with fexofenadine or carbocysteine have synthesized and characterized using infrared, electronic and thermal, mass and conductivity measurements. The two ligands have been found to act as bidentate chelating agents. Fexofenadine complexes coordinate through the carboxyl group with 1:2 molar ratio, while carbocysteine complexes coordinate through the oxygen of both hydroxyl groups with 1:1 molar ratio. Antibacterial screening of the complexes against *Escherichia Coli*, *Bacillus subtilis* and antifungal (tricoderma and penicillium activities) were also investigated. The metal complexes were found to have varied degree of inhibitory effect against the bacteria and fungi.

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The authors declare no conflict of interest

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