Spectrochimica Acta Part A 91 (2012) 11–17

Contents lists available at SciVerse ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Preparation, spectroscopic and thermal characterization of new metal complexes of verlipride drug. In vitro biological activity studies

M.H. Soliman [a,*], Gehad G. Mohamed [b]

[a] Chemistry Department, Faculty of Science, Helwan University, Helwan, Egypt
[b] Chemistry Department, Faculty of Science, Cairo University, 12613 Giza, Egypt

ARTICLE INFO

Article history:
Received 25 August 2011
Received in revised form
31 December 2011
Accepted 16 January 2012

Keywords:
Verlipride
Metal complexes
IR
Molar conductance
Magnetic moment
^{1}H NMR
Thermal analyses
Biological activity

ABSTRACT

Metal complexes of the general formula $[M(VER)_2Cl_2(H_2O)_2]\cdot yH_2O$ and $[Cr(VER)_2Cl_2(H_2O)_2]Cl\cdot H_2O$ (where VER = verlipride, M = Mn(II) ($y = 2$), Co(II) ($y = 2$), Ni(II) ($y = 2$), Cu(II) ($y = 1$) and Zn(II) ($y = 0$)) are prepared and characterized based on elemental analyses, IR, ^{1}H NMR, magnetic moment, molar conductance, and thermal analyses (TG and DTA) techniques. From the elemental analyses data, the complexes are formed in 1:2 [Metal]:[VER] ratio. The molar conductance data reveal that all the metal chelates are non-electrolytes except Cr(III) complex, it is 1:1 electrolyte. IR spectra show that VER is coordinated to the metal ions in a neutral monodentate manner with O donor site of the carbonyl O atom. On the basis of spectral studies and magnetic moment measurements an octahedral geometry has been assigned for the complexes. The thermal behavior of these chelates is studied using thermogravimetric analysis technique. The results obtained show that the complexes lose hydrated water, HCl and coordinated water molecules followed immediately by decomposition of the ligand molecules in the successive unseparate steps. The VER drug, in comparison to its metal complexes is also screened for its biological activity against Gram positive bacterial (*Staphylococcus aureus*) and Gram negative bacteria (*Escherichia coli*) and fungi (*Candida albicans* and *Aspergillus flavus*) in vitro. The activity data show that most of the metal complexes have antibacterial activity like or higher than that of the parent VER drug against one or more species.

Published by Elsevier B.V.

1. Introduction

Verlipride (VER) (Fig. 1) is an anti-psychotic drug, used in treatment of cardiovascular and psychological symptoms associated with the menopause [1–3]. It is N-[(1-allyl-2-pyrrolidinyl)methyl]-5-sulfamoyl-2-veretramide [4]. In literature, gas chromatography with mass spectrometry or flame ionization detector was used [5]. The international conference on harmonization (ICH) guidelines recommended that stress testing should be carried out to elucidate the inherent stability characteristics of the active substance. Acidic, alkaline and oxidative stability are required [6,7]. However, in this work, metal chelates of Mn(II), Cr(III), Co(II), Ni(II), Cu(II) and Zn(II) transition metals with VER drug molecule are prepared. The solid chelates are characterized using different physico-chemical methods like elemental analyses (C, H, N, and metal content), IR, ^{1}H NMR, magnetic moment, and thermogravimetric analysis (TG). Biological activities of the complexes are studied in vitro.

2. Experimental

2.1. Materials and reagents

All chemicals used were of the analytical reagent grade (AR) and of the highest purity available. They included VER (UniPharma), $CuCl_2\cdot 2H_2O$ (Prolabo), $CoCl_2\cdot 6H_2O$ and $NiCl_2\cdot 6H_2O$ (BDH), $ZnCl_2\cdot 2H_2O$ (Ubichem), $CrCl_3\cdot 6H_2O$ (Sigma), and $MnCl_2$ (Prolabo). Zinc oxide, disodium salt of ethylenediaminetetraacetic acid, EDTA were from Analar, ammonia solution (33%, v/v), and ammonium chloride from El-Nasr Pharm. Chem. Co., Egypt. Organic solvents used included absolute ethyl alcohol, diethylether, and dimethylformamide (DMF). These solvents were spectroscopic pure from BDH. Hydrogen peroxide, hydrochloric, and nitric acids (MERCK) were used. The test organisms were kindly supplied from the microbiological resource center, Ain Shams University, Faculty of Agricultural, Egypt (CAIM, Cairo Mircen), and from Bacteriological Department of National Organization for Drug Control and Research (NODACR), ATCC, American type culture collection. Bacterial test organisms were inoculated on nutrient agar slants for 24 h at 37 °C. Yeast and Fungi organisms were inoculated on Sabouraud's dextrose-agar slants and incubated at 28 °C for 48 h.

* Corresponding author.
E-mail address: drmadihahasan@yahoo.com (M.H. Soliman).

1386-1425/$ – see front matter. Published by Elsevier B.V.
doi:10.1016/j.saa.2012.01.021

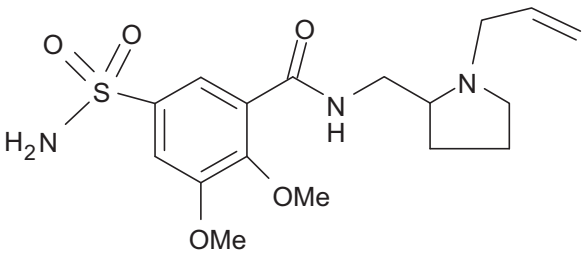


Fig. 1. Structural formula of VER drug.

2.2. Instruments

The molar conductance of the solid complexes in DMF was measured using Sybron–Barnstead conductometer (Meter-PM.6, $E = 3406$). Elemental microanalyses of the separated solid chelates for C, H, N, and S were performed at the Microanalytical Center, Cairo University. Infrared spectra were recorded on a Perkin-Elmer FT-IR type 1650 spectrophotometer in wave number region 4000–400 cm^{-1}. The spectra were recorded as KBr pellets. The ^1H NMR spectra were recorded using 300 MHz Varian-Oxford Mercury. The molar magnetic susceptibility was measured on powdered samples using the Faraday method. The diamagnetic corrections were made by Pascal's constant and $Hg[Co(SCN)_4]$ was used as a calibrant. The thermogravimetric (TG and DTG) analysis was carried out in dynamic nitrogen atmosphere (20 mL min^{-1}) with a heating rate of 10 °C min^{-1} using Shimadzu TG-60H thermal analyzers.

2.3. Synthesis of metal complexes

The metal complexes were prepared by the addition of hot solution (60 °C) of the appropriate metal chloride salts (0.278, 0.168, 0.277, 0.248, 0.225, and 0.217 g of Cr(III), Mn(II), Co(II), Ni(II), Cu(II) and Zn(II), respectively, 1 mmol) in an ethanol–water mixture (1:1, 25 mL) to the hot solution (60 °C) of VER (0.4 g, 2 mmol) in the same solvent (25 mL). The resulting mixture was stirred under reflux for 1 h whereupon the complexes precipitated. They were collected by filtration, washed with a 1:1 ethanol:water mixture and diethylether.

2.4. Biological activity

The antimicrobial activities were carried out by disc diffusion technique as described in British pharmacopoeia (2003). Nutrient agar was melted at 45 °C and inoculated by the cell suspension (1 mL/100 mL) bacteria or yeast. The flask was shaken well and poured into a petri-dish (15 cm in diameter). Filter paper discs (6 mm) Whatman No. 2 were thoroughly moistened by antibiotics (50 μg), the treated discs were aseptically transferred and placed upon the surface of the inoculated plates with tested organisms and kept in a refrigerator for 1 h to permit diffusion of antimicrobial substances. The plates were incubated at 37 °C for 24 h in case of bacteria and at 28 °C for 48 h in case of yeast. The zones of inhibition were measured in mm the mean values of inhibitions were calculated from triple reading in each test [7].

The following media were used in studying the antimicrobial properties of VER drug and its complexes. The weights are given in gram per 1-L medium.

2.4.1. Nutrient agar medium (pH 7.4)

It consists of beef extract (1.0 g), yeast extract (2.0 g), peptone (5.0 g), sodium chloride (5.0 g), agar (15.0 g), and distilled water (100 mL).

2.4.2. Sabouraud's dextrose agar medium (pH 5.6)

It consists of peptone (10 g), dextrose (20 g), agar (15 g), and distilled water (100 mL).

3. Results and discussion

The formation of metal complexes with drug compounds has long been recognized. However, the binary complexes of the cited drug with metal ions have not been studied yet, although they may be an area of interest. This is because these complexes may affect the bioavailability of this drug as certain metal ions were present in relatively appreciable concentration in biological fluids [8].

3.1. Mass spectrum of VER

The electron impact mass spectrum of VER is recorded and investigated at 70 eV of electron energy. The mass spectrum of the studied drug (Supplementary Fig. 1) is characterized by moderate to high relative intensity molecular ion peaks at 70 eV. The abundance of the molecular ion depends mainly on the structure (and therefore the potential energy surface) of the molecular ion. The mass spectrum of VER shows a well-defined parent peak at $m/z = 383.5$ (M^+) with a relative intensity = 5%. The parent ion and the fragments obtained by cleavage in different positions in VER molecule are shown in Scheme 1.

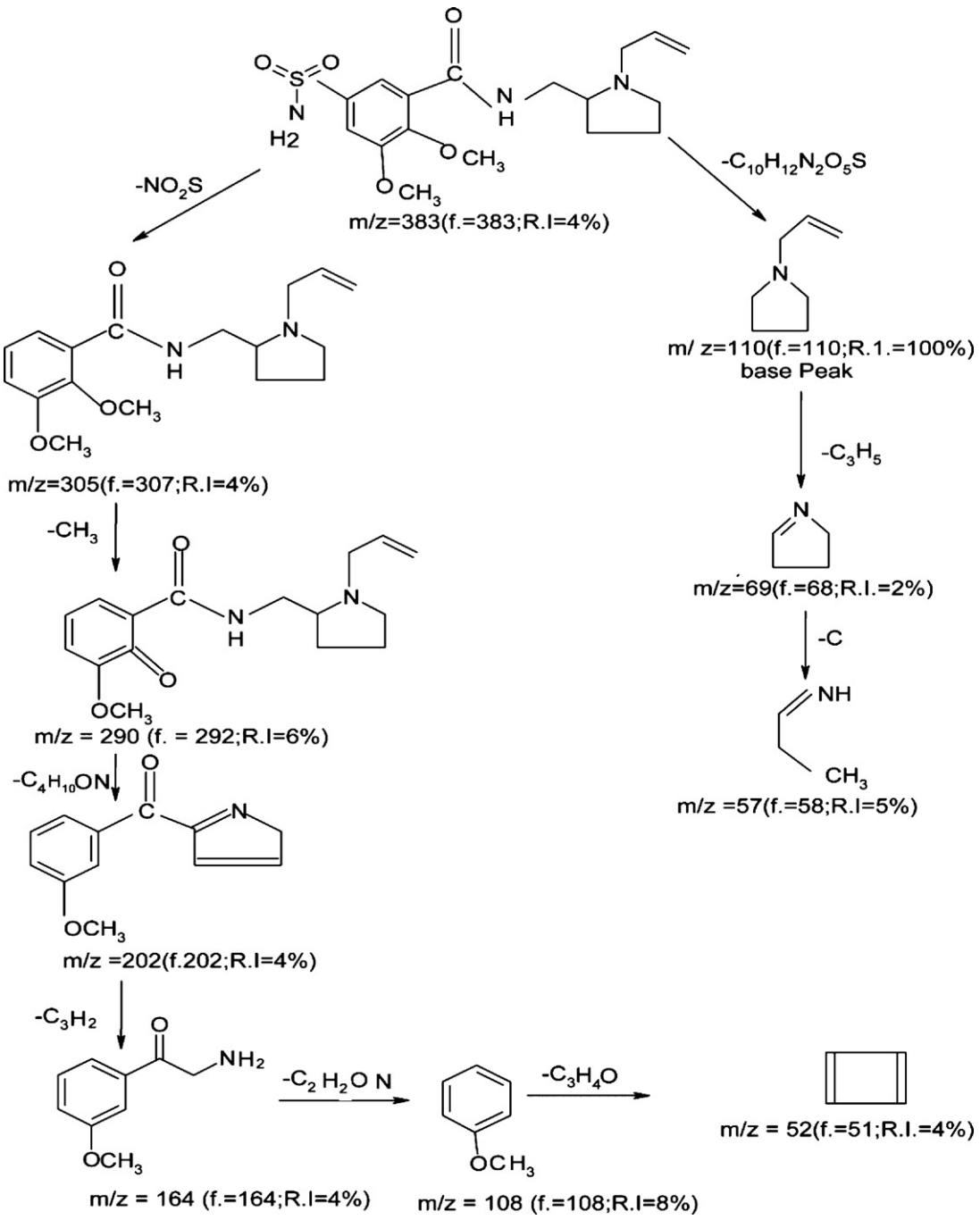
3.2. Composition and structures of metal complexes

The aim of this work is to prepare the solid complexes of the drug under investigation and carrying out complete characterization using different physicochemical techniques. Many attempts were done to prepare crystal(s) suitable for X-ray analysis in order to confirm the structures but all are failed. Therefore, IR spectra have proven to be the most suitable technique to give enough information's to elucidate the nature of bonding of the ligand to the metal ion. The present works deals specifically the coordination properties of VER drug (Fig. 1) concerning its interactions with Cr(III), Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) ions. The bioefficacy of these complexes has also been examined against the growth of bacteria and pathogenic fungi in vitro to evaluate their anti-microbial potential and in order to throw more light on the effect of chelation on the drug activity.

The isolated solid complexes of Cr(III), Mn(II), Co(II), Ni(II), Cu(II) and Zn(II) ions with the VER ligand are subjected to elemental analyses (C, H, N, S, Cl and metal content), IR, ^1H NMR, magnetic moment studies, molar conductance, and thermal analysis (TG), to identify their tentative formulae in a trial to elucidate their molecular structures. The results of elemental analyses listed in Table 1 suggest that the complexes are formed in 1:2 [Metal]:[VER] ratio and they proposed to have the general formulae $[MCl_2(VER)_2(H_2O)_2]\cdot yH_2O$ and $[CrCl_2(VER)_2(H_2O)_2]Cl\cdot H_2O$ (where M = Mn(II) ($y = 2$), Co(II) ($y = 2$), Ni(II) ($y = 2$), Cu(II) ($y = 1$) and Zn(II) ($y = 0$)).

3.3. Molar conductivity measurements

Table 1 summarizes the molar conductance values of the complexes (10^{-3} M) in DMF solvent at 25 °C. It is concluded from the results that, the divalent metal chelates are found to have molar conductance values of 15.40–24.50 Ω^{-1} mol^{-1} cm^2 indicating that all the divalent metal chelates are non-electrolytes. The Cr(III) complex is found to have a molar conductance value of 68 Ω^{-1} mol^{-1} cm^2 indicating its electrolytic nature and of the type 1:1 electrolyte.



Scheme 1. Mass fragmentation pattern of VER drug.

3.4. IR spectral studies

The IR data of the spectra of VER drug and its complexes are listed in Table 2. In order to determine the coordination sites that may be involved in chelation, the IR spectra of the complexes are compared with the free VER drug. It is found that:

(1) The $\upsilon_{asym}(SO_2)$ and $\upsilon_{sym}(SO_2)$ stretching vibrations are observed at 1336 and 1078 cm^{-1} for VER drug and at 1411–1291 and 1242–1106 cm^{-1} for VER–metal complexes, respectively. The shift of these bands to higher or lower wave numbers may be attributed to the involvement of the SO_2 in hydrogen bonding with the adjacent NH_2 atom.

(2) The NH_2 and NH stretching vibrations are found in VER drug at 3325–3249 and 3050 cm^{-1}, respectively. For VER–metal complexes, the bands at 3350–3075 and 3050–2918 cm^{-1}, are assigned to NH_2 and NH stretching vibrations, respectively. However, the shift in the NH_2 and NH stretching vibrations can be attributed to the keto–enol form or hydrogen bonding formation with the adjacent SO_2 group (in case of NH_2 group) or C=O group (in case of NH group).

(3) The υ(C=O) stretching vibrations are observed at 1638 cm^{-1} for VER drug. The participation of the carbonyl O atom in the complex formation is evidenced from the shift in position of this band to1651–1641 cm^{-1} for VER–metal complexes.

(4) In the 3550–3450, 950–880 and 850–820 cm^{-1} regions, one observes absorption bands due to the OH stretching of the water

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

Compound (chemical formula)	Color (%Yield)	M.p. (°C)	% Found (Calcd)						μ_{eff} (B.M.)	Λ_m (Ω^{-1} mol^{-1} cm^2)
			C	H	N	S	Cl	M		
$[Cr(VER)_2Cl_2(H_2O)_2]Cl.yH_2O$ $C_34H_56CrCl_3N_6O13S_2$	Green (68)	>300	42.03 (41.70)	5.41 (5.72)	8.29 (8.58)	6.92 (6.54)	11.06 (10.88)	5.03 (5.31)	4.95	68.0
$[Mn(VER)_2Cl_2(H_2O)_2].2H_2O$ $C_{34}H_{58}Cl_2MnN_6O14S_2$	Black (70)	>300	42.74 (42.37)	5.92 (6.02)	9.02 (8.72)	6.17 (6.65)	7.63 (7.37)	5.87 (5.61)	4.82	18.50
$[Co(VER)_2Cl_2(H_2O)_2].2H_2O$ $C_{34}H_{58}Cl_2CoN_6O14S_2$	Brown (62)	>300	42.54 (42.19)	5.88 (5.99)	8.68 (8.68)	6.34 (6.61)	7.43 (7.33)	5.89 (6.10)	5.28	24.50
$[Ni(VER)_2Cl_2(H_2O)_2].2H_2O$ $C_{34}H_{58}Cl_2NiN_6O14S_2$	Pale green (73)	>300	41.92 (42.19)	5.94 (5.99)	8.42 (8.68)	6.45 (6.61)	7.43 (7.33)	6.04 (6.10)	3.66	16.80
$[Cu(VER)_2Cl_2(H_2O)_2]$ $C_{34}H_54Cl_2CuN_6O12S_2$	Green (78)	>300	43.35 (43.57)	5.51 (5.77)	8.52 (8.97)	6.90 (6.83)	7.61 (7.58)	6.51 (6.78)	1.85	18.75
$[Zn(VER)_2Cl_2(H_2O)_2]$ $C_{34}H_54Cl_2N_6O12S_2Zn$	White (65)	>300	43.23 (43.50)	5.54 (5.76)	9.20 (8.96)	7.10 (6.82)	7.22 (7.57)	7.20 (6.93)	Diam.	15.40

molecules. Since, according to the elemental analysis and thermogravimetric studies, most of the complexes obtained contain water of coordination and crystallization.

(5) New bands are found in the spectra of the complexes in the region 523–459 cm^{-1}, which is assigned to υ(M–O) stretching vibration [9–13].

Therefore, from the IR spectra, it is concluded that VER behaves as a neutral monodentate ligand coordinated to the metal ions via the carbonyl O atom.

3.5. Magnetic susceptibility studies

The magnetic moment values of Cr(III) and Mn(II) complexes are found to be 4.95 and 4.82 B.M., respectively, which indicate their presence in octahedral structure [14].

The Ni(II) and Co(II) complexes reported herein are found to have a room temperature magnetic moment values of 3.66 and 5.28 B.M.; which are in the normal range observed for octahedral Ni(II) (μ_{eff} = 2.9–3.3 B.M.) [9,14] and Co(II) (μ_{eff} = 4.3–5.2 B.M.) [14–16] complexes, respectively.

The magnetic moment value of 2.15 B.M. falls within the range normally observed for octahedral Cu(II) complexes [8,14]. The Zn(II) complex is diamagnetic and according to the empirical formula, an octahedral geometry is proposed.

3.6. ^{1}H NMR spectra

The ^{1}HNMR spectra of VER drug and its Zn(II) complex are recorded in d_6-dimethylsulfoxide (*DMSO-d_6*) solvent using tetramethylsilane (TMS) as internal standard. The chemical shifts of the different types of protons of the VER drug and its diamagnetic Zn(II) complex are listed in Supplementary Table 1. It is found that:

(1) The NH_2 signal, appeared in the spectrum of VER drug at 2.19 ppm (Supplementary Table 1), the spectrum of its Zn(II) complex gives band at 2.115 ppm.
(2) The signal observed at 8.440 ppm for VER drug, is assigned to NH proton. This signal is found at 8.451 ppm for Zn(II) complex. This small shift can be attributed to change in the skeleton of VER drug as the results of metal chelation.
(3) The spectrum of Zn(II) complex shows a broad band at 4.045 ppm which can be attributed to the presence of coordinated water molecules.

Therefore, it is clear from these results that the data obtained from the elemental analyses, IR, and ^{1}H NMR spectral measurements are in agreement with each other.

3.7. Thermal analyses (TG and DTG) of VER drug

The TG curve of VER drug (Supplementary Fig. 2a) refers to two stages of mass losses at temperature ranges from 200 to 920 °C (Table 3). The first estimated mass loss of 51.10% (calcd. = 53.26%) within the temperature range from 200 to 400 °C, may be attributed to the liberation of $C_7H_{10}NSO_4$ molecule as gases. In the 2nd stage within the temperature range from 500 to 920 °C, VER losses the remaining part with an estimated loss of 49.45% (calcd. = 46.74%) which may be attributed to the liberation of $C_{10}H_{15}N_2O$ molecule with a complete decomposition as CO, CO_2, NO, NO_2, etc. gases.

Supplementary Fig. 2b–g and Table 3 show the TG and DTG results of thermal decomposition of VER chelates.

The thermogram of $[CrCl_2(VER)_2(H_2O)_2]Cl{\cdot}H_2O$ chelate (Supplementary Fig. 2b) shows five decomposition steps within the temperature range from 25 to 900 °C. The first step of

Table 2
IR spectra (4000-400 cm^{-1}) of VER and its binary metal complexes.

Compound	υ(C=O)	υ(SO_2) (asym)	υ(SO_2) (sym)	υ(NH_2)	υ(NH)	υ(M–O)
VER	1638 sh	1336 sh	1078 sh	3325 s, 3249 sh	3076 sh	–
$[Cr(VER)_2Cl_2(H_2O)_2]Cl{\cdot}H_2O$	1645 sh	1292 sh	1145 sh	3425 s, 3327 sh	3045 sh	523 m
$[Mn(VER)_2Cl_2(H_2O)_2]{\cdot}2H_2O$	1644 sh	1292 sh	1154 sh	3410 s, 3322 sh	2918 sh	523 m
$[Co(VER)_2Cl_2(H_2O)_2]{\cdot}2H_2O$	1641 sh	1291 sh	1154 sh	3345 s, 3290 sh	2923 sh	523 m
$[Ni(VER)_2Cl_2(H_2O)_2]{\cdot}2H_2O$	1645 sh	1328 sh	1106 sh	3450 s, 3344 sh	3050 sh	478 m
$[Cu(VER)_2Cl_2(H_2O)_2]$	1651 sh	1328 sh	1106 sh	3450 s, 3344 sh	3050 sh	478 m
$[Zn(VER)_2Cl_2(H_2O)_2]$	1631 sh	1399 sh	1295 sh	3333 s, 3075 sh	2997 sh	523 m

Sh = sharp, m = medium, br = broad, s = small, and w = weak.

decompositions within the temperature range 25–120 °C corresponds to the loss of H_2O and 3HCl with a mass loss of 12.30% (calcd. = 13.00%). The subsequent steps (120–900 °C) correspond to the removal of the organic part of the drug leaving metal oxide and carbon as a residue. The overall weight loss amounts to 57.90% (calcd. = 58.48%).

The TG curve of the $[MnCl_2(VER)(H_2O)_2]{\cdot}2H_2O$ chelate is shown in Supplementary Fig. 2c and listed in Table 3. It decomposes in six steps in the temperature range from 35 to 800 °C. The first two steps can be attributed to the loss of $2H_2O$ and HCl with mass loss of 7.98% (calcd. = 7.53%). The subsequent steps (150–800 °C) correspond to the removal of coordinated water, HCl and the residue of the drug molecules with mass loss of 58.81% (calcd. = 59.03%), leaving MnO and 21C as residues.

The TG curve of the $[CoCl_2(VER)_2(H_2O)_2]{\cdot}2H_2O$ chelate exhibits four decomposition steps (Supplementary Fig. 2d). The first step within the temperature range 30–100 °C in which the complex losses two hydrated water molecules with an estimated mass loss = 3.45% (calcd. = 3.72%) (Table 3). The three subsequent steps correspond to the removal of two coordinated water molecules, 2HCl and remaining part of the drug (estimated mass loss = 60.28%, calcd. = 60.49%). The total mass losses of the decomposition steps are found to be 63.73% (calcd. = 62.45%), leaving CoO and carbon as residues.

TG curve of the $[NiCl_2(VER)_2(H_2O)_2]{\cdot}2H_2O$ (Supplementary Fig. 2e) chelate shows six stages of decomposition within the temperature range from 30 to 650 °C. The first stage corresponds to the loss of two hydrated water molecules and HCl. While, the subsequent steps involve the loss of coordinated water molecules, HCl and the remaining organic part of VER drug molecules leaving NiO and carbon residues. The overall weight losses amount to 66.20% (calcd. = 66.18%).

The TG curve of the $[CuCl_2(VER)_2(H_2O)_2]$ chelate exhibits three decomposition steps (Supplementary Fig. 2f). The first step within the temperature range (100–220 °C) in which the complex losses two coordinated water and HCl molecules with an estimated mass loss of 7.38% (calcd. = 7.74%) (Table 3). The subsequent steps (220–800 °C) correspond to the removal of HCl and the organic part of the drug leaving CuO residue. The overall weight loss amounts to 90.14% (calcd. = 91.51%).

The TG curve of the $[ZnCl_2(VER)_2(H_2O)_2]$ (Supplementary Fig. 2g) chelate shows seven stages of decomposition within the temperature range from 35 to 650 °C. The first stage corresponds to the loss of 2HCl. While, the subsequent steps involve the loss of two coordinated water and the organic part of VER drug molecules. The overall weight losses amount to 71.15% (calcd. = 72.28%). ZnO and carbon are the residues of decomposition.

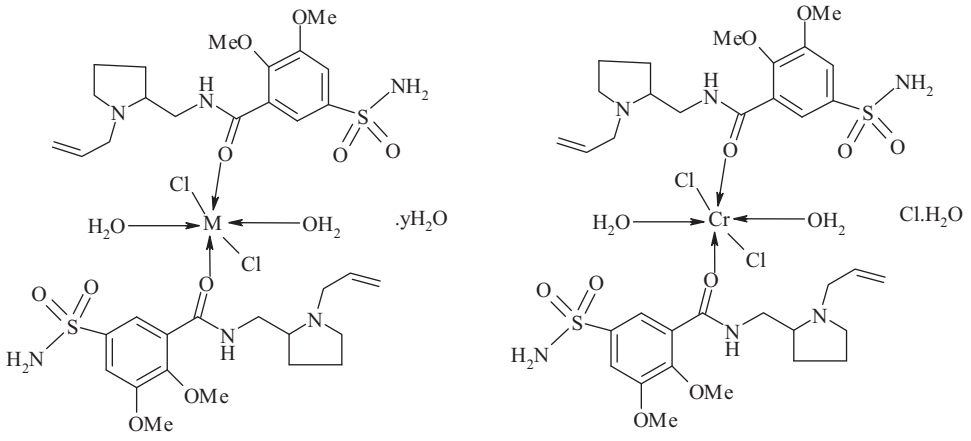
3.8. Calculation of activation thermodynamic parameters

The thermodynamic activation parameters of decomposition processes of complexes namely activation energy (E^*), enthalpy (ΔH^*), entropy (DS*), and Gibbs free energy change of the decomposition (DG*) are evaluated graphically by employing the Coats–Redfern relation [17].

$$\ln\left(-\frac{\ln(1-\alpha)}{T^2}\right) = \ln\left(\frac{AR}{bE}\right) - \left(\frac{E}{RT}\right) \quad (1)$$

Table 3
Thermoanalytical results (TG, DTG and DTA) of VER and its metal complexes.

Complex	TG range (°C)	DTG_{max} (°C)	n^*	Mass loss	Total mass loss	Assignment	Metallic residue
				Estim (Calcd) (%)			
VER	200–400	268	1	52.10 (53.26)	100.5 (100.0)	Loss of $C_7H_{10}NO_4S$	–
	400–950	780	1	48.45 (46.74)		Loss of $C_{10}H_{15}N_2O$	
$[Cr(VER)_2Cl_2(H_2O)_2]Cl{\cdot}H_2O$	25–120	56	1	12.30 (13.00)	57.90 (58.48)	Loss of H_2O and 3HCl	$1/2Cr_2O_3$ + 21C
	120–900	176, 236, 411, 550	4	45.60 (45.48)		Loss of $2H_2O$ and $C_{13}H_{47}N_6O_{8.5}S_2$ Phase transition	
$[Mn(VER)_2Cl_2(H_2O)_2]{\cdot}2H_2O$	35–150	74, 144	2	7.98 (7.53)	66.79 (66.56)	Loss of $2H_2O$ and HCl	MnO + 21C
	150–800	236, 364, 629, 717	4	58.81 (59.03)		Loss of $2H_2O$, HCl and $C_{13}H_{48}N_6O_9S_2$	
$[Co(VER)_2Cl_2(H_2O)_2]{\cdot}2H_2O$	30–100	51	1	3.45 (3.72)	63.73 (62.45)	Loss of $2H_2O$	CoO + 21C
	50–600	190, 340, 522	3	60.28 (58.73)		Loss of $2H_2O$, 2HCl and $C_{13}H_{48}N_6O_9S_2$	
$[Ni(VER)_2Cl_2(H_2O)_2]{\cdot}2H_2O$	30–130	51, 95	2	7.90 (7.45)	66.20 (66.18)	Loss of $2H_2O$ and HCl	NiO + 21C
	130–650	192, 294, 404, 553	4	58.30 (58.73)		Loss of $2H_2O$, HCl and $C_{13}H_{48}N_6O_9S_2$	
$[Cu(VER)_2Cl_2(H_2O)_2]$	100–220	150	1	7.38 (7.74)	90.14 (91.51)	Loss of $2H_2O$ and HCl	CuO
	220–430	303	1	40.51 (40.84)		Loss of HCl and $C_{14}H_{24}N_3O_5S$	
	430–800	620	1	42.25 (42.93)		Loss of $C_{20}H_{24}N_3O_4S$	
$[Zn(VER)_2Cl_2(H_2O)_2]$	35–100	57	1	7.94 (7.78)	71.15 (72.28)	Loss of 2HCl	ZnO + 15C
	100–650	169, 231, 300, 354, 441, 623	6	63.21 (64.50)		Loss of $2H_2O$ and $C_{19}H_{48}N_6O_9S_2$	



M = Mn(II) (y = 2), Co(II) (y = 4), Ni(II) (y = 4), Cu(II) (y = 1) and Zn(II) (y = 0).

Fig. 2. Structural formulae of metal complexes.

where α represents the fraction of sample decomposed at time t, defined by: $\alpha = (w_o - w_t)/(w_o - w_\infty)$, where w_o, w_t and w_∞ are the weight of the sample before the degradation, at temperature t and after total conversion, respectively. T is the derivative peak temperature, β is the heating rate = dT/dt, E and A are the activation energy and the Arrhenius pre-exponential factor, respectively.

A plot of the left-hand side of Eq. (1) against $1/T$ gives a slope from which E^* was calculated and A (Arrhenius factor) was determined from the intercept. The entropy of activation (ΔS^*), enthalpy of activation (ΔH^*), and the free energy change of activation (ΔG^*) are calculated using the following equations:

$$\Delta S* = 2.303 \left[\log\left(\frac{Ah}{kT}\right)\right] R \quad (2)$$

$$\Delta H* = E* - RT \quad (3)$$

$$\Delta G* = \Delta H* - T\Delta S* \quad (4)$$

The data are summarized in Supplementary Table 2. The activation energies of decomposition were found to be in the range 10.3–169.6 kJ mol^{-1}. The entropy of activation is found to be of negative values in all the complexes which indicate that the decomposition reactions proceed spontaneously.

3.9. Structural interpretation

The structures of the complexes of VER drug with metals are confirmed by the elemental analyses, ^{1}H NMR, IR, molar conductance, magnetic and thermal analyses data. The structures of the complexes are given as shown below in Fig. 2.

3.10. Biological activity

In testing the antibacterial activity of VER drug and its metal complexes, more than one test organism are used to increase the chance of detecting antibiotic principles in tested materials. The sensitivity of a microorganism to antibiotics and other antimicrobial agents is determined by the assay plates which are incubated at 37 °C for 2 days for bacteria. All the tested compounds show a remarkable biological activity against different types of Gram-positive (G^+) bacteria, Gram-negative (G^-) bacteria and fungi. The data are listed in Table 4. The data show that VER drug under investigation and its metal complexes have the capacity of inhibiting the metabolic growth of the investigated bacteria and fungi to different extent. The size of the inhibition zone depends upon the culture medium, incubation conditions, rate of diffusion, and the concentration of the antibacterial agent. The activities of all the tested complexes may be explained on the basis of chelation theory; chelation reduces the polarity of the metal atom mainly because of partial sharing of its positive charge with the donor groups and possible p electron delocalization within the whole chelate ring. Also, chelation increases the lipophilic nature of the central atom which subsequently favors its permeation through the lipid layer of the cell membrane [18].

On comparing the biological activity of the VER drug and its metal complexes, the following results are obtained:

(1) Biological activity against Gram-positive bacteria follow the order: $[ZnCl_2(VER)_2(H_2O)_2] > [NiCl_2(VER)_2(H_2O)_2]\cdot 2H_2O > [CoCl_2(VER)_2(H_2O)_2]\cdot 2H_2O > [CuCl_2(VER)_2(H_2O)_2] > [MnCl_2$

Table 4
Biological activity of VER and its binary metal complexes.

Sample	Inhibition zone diameter (mm/mg sample)			
	Esherichia coli (G^-)	*Staphylococcus aureus* (G^+)	*Aspergillus flavus* (Fungus)	*Candida albicans* (Fungus)
Control: DMSO	0.0	0.0	0.0	0.0
VER	12	11	0.0	0.0
$[Cr(VER)_2Cl_2(H_2O)_2]Cl\cdot H_2O$	11	12	0.0	0.0
$[Mn(VER)_2Cl_2(H_2O)_2]\cdot 2H_2O$	12	12	0.0	0.0
$[Co(VER)_2Cl_2(H_2O)_2]\cdot 2H_2O$	20	18	0.0	14
$[Ni(VER)_2Cl_2(H_2O)_2]\cdot 2H_2O$	15	22	0.0	22
$[Cu(VER)_2Cl_2(H_2O)_2]$	14	15	0.0	14
$[Zn(VER)_2Cl_2(H_2O)_2]$	15	23	0.0	12
Tetracycline antibacterial agent	33	31	–	–
Amphotericin B antifungal agent	–	–	16	19

$(VER)_2(H_2O)_2]\cdot 2H_2O = [CrCl_2(VER)_2(H_2O)_2]Cl\cdot H_2O >$ VER drug. It is obvious that the biological activity of the metal complexes are more than the parent VER drug which means that the complexes can have the same action like the parent drug. The biological activity of the VER drug and its complexes are lower than tetracycline standard.

(2) Biological activity against Gram-negative bacteria follow the order: $[CoCl_2(VER)_2(H_2O)_2]\cdot 2H_2O > [ZnCl_2(VER)_2(H_2O)_2] = [NiCl_2(VER)_2(H_2O)_2]\cdot 2H_2O > [CuCl_2(VER)_2(H_2O)_2] >$ VER $= [MnCl_2(VER)_2(H_2O)_2]\cdot 2H_2O > [CrCl_2(VER)_2(H_2O)_2]Cl\cdot H_2O$. The biological activity of the VER drug and its complexes are lower than tetracycline standard.

(3) The Co(II), Ni(II), Cu(II) and Zn(II) complexes also show antifungal activities against *Candida albicans* fungus while the parent VER drug has no such activity which makes these complexes of interest.

The importance of this lies in the fact that these complexes could be applied fairly in the treatment of some common diseases caused by *Escherichia coli*, e.g., septicemia, gastroenteritis, urinary tract infections, and hospital-acquired infections [19,20].

4. Conclusion

In conclusion, we have described the synthesis and spectroscopic and thermal properties of VER drug and its transition metal complexes. The structures of the complexes were proposed based on elemental analysis, ^{1}H NMR, FT-IR spectra, molar conductance, magnetic moment, solid reflectance and thermal analysis. It can be concluded from all the results given above that the VER ligand acts as monodentate chelating agent, coordinates with transition metal ions to give octahedral environments, around the metal ion. Molar conductance studies reveal the non electrolytic nature of the complexes except Cr(III) complex (1:1 electrolyte). The thermal properties of the metal complexes were investigated by thermogravimetry (TG) and different thermodynamic parameters are calculated using Coats–Redfern equation. The metal chelates of VER possess reasonable antimicrobial potential.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.saa.2012.01.021.

References

[1] Martindale: The Complete Drug Reference, 35th ed., The Pharmaceutical Press, London, 2007, p. 1736.
[2] R. Michele, A. Antonella, J. Neuropsychiatry Clin. Neurosci. 17 (2005) 252–253.
[3] D.L. Vincenzo, M. Giuseppe, C.M. Maria, F. Elisa, D. Ada, P. Felice, Expert Opin. Drug Saf. 5 (2006) 695–701, doi:10.1517/14740338.5.5.695.
[4] The Merck Index, 14th edn., Merck and Co. Inc., Whitehouse Station, 2006, p. 1710.
[5] S. Staveris, L. Jung, G. Gamet, J.C. Koel, J. Chromatogr. 338 (1985) 79–88.
[6] ICH Q2A, in: IFPMA (Ed.), Validation of Analytical Methods: Definitions and Terminology, International Conference on Harmonization, Geneva, 1994.
[7] R.J. Grayer, J.B. Harbone, Phytochemistry 37 (1994) 19–42.
[8] F. Salama, N. El-Abasawy, S.A. Abdel Razeq, M.M.F. Ismail, M.M. Fouad, J. Pharm. Biomed. Anal. 33 (2003) 411–421.
[9] G.G. Mohamed, F.A. Nour El-Dien, S.M. Khalil, A.S. Mohammad, J. Coord. Chem. 62 (2009) 645–654.
[10] H. Icbudak, Z. Heren, D.A. Kose, H. Necefoglu, J. Therm. Anal. Calorim. 76 (2004) 837–851.
[11] D.A. Kose, H. Necefogɛlu., J. Therm. Anal. Calorim. 93 (2008) 509–514.
[12] D.A. Kose, G. Gokce, S. Gokce, I. Uzun, J. Therm. Anal. Calorim. 95 (2009) 247–251.
[13] A.F.O. Santos, I.D. Basýlio, F.S. de Souza, A.F.D. Medeiros, M.F. Pinto, d.p. de Santana, J. Therm. Anal. Calorim. 93 (2008) 361–364.
[14] F.A. Cotton, G. Wilkinson, C.A. Murillo, M. Bochmann, Advanced Inorganic Chemistry, 6th ed., Wiley, New York, 1999.
[15] M.A. Zayed, F.A. Nour El-Dien, G.G. Mohamed, N.E.A. El-Gamel, J. Mol. Struct. 841 (2007) 41–50.
[16] G.G. Mohamed, Phosphorus Sulfur Silicon Relat. Elem. 180 (2005) 1569–1584.
[17] A.W. Coats, J.P. Redfern, Nature 20 (1964) 68–79.
[18] A. Caudhary, R.V. Singh, Phosphorus Sulfur Silicon Relat. Elem. 178 (2003) 603–613.
[19] E. Jawetz, J.L. Melnick, E.A. Adelberg, Review of Medical Microbiology, 16th ed., Lang Medical Publications, Los Anglos, CA, 1979.
[20] W.H. Hughes, H.C. Stewart, Concise Antibiotic Treatment, Butter Worth, London, 1970.