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ORIGINAL ARTICLE

Spectroscopic and thermal degradation behavior of Mg(II), Ca(II), Ba(II) and Sr(II) complexes with paracetamol drug

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Abstract Complexes of Mg(II), Ca(II), Ba(II) and Sr(II) with paracetamol drug were synthesized and characterized by elemental analysis, conductivity, UV–Vis, IR, and ^{1}H NMR spectroscopy and thermal analysis, as well as screened for antimicrobial activity. The IR spectral data suggested that the ligand behaves as paracetamol behaves as a neutral bidentate ligand coordinated to the metal ions via the lone pair of electrons of nitrogen and carbonyl-O atoms of the amide group. From the microanalytical data, the stoichiometry of the complexes reacts with Mg(II), Ca(II), Ba(II) and Sr(II) by molar ratios (2:1) (paracetamol:metal ion). The thermal behavior (TG/DTG) of the complexes was studied. The ligand and their metal complexes were screened against both of antibacterial and fungicidal activities.

1. Introduction

An analgesic (also known as a painkiller) is any member of the group of drugs used to relieve pain (achieve analgesia). The word analgesic derives from Greek an- (“without”) and algos (“pain”). Analgesic drugs act in various ways on the peripheral and central nervous systems. They include paracetamol (*para*-acetylaminophenol, also known in the US as acetaminophen), the non-steroidal anti-inflammatory drugs (NSAIDs) such as the salicylates, narcotic drugs such as morphine, synthetic drugs with narcotic properties such as tramadol. In choosing analgesics, the severity and response to other

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medication determines the choice of the agent; the WHO pain ladder, originally developed in cancer-related pain, is widely applied to find suitable drugs in a stepwise manner (World Health Organization, 1990). The analgesic choice is also determined by the type of pain. For neuropathic pain, traditional analgesics are less effective, and there is often benefit from classes of drugs that are not normally considered analgesics, such as tricyclic antidepressants and anticonvulsants (Dworkin et al., 2003).

Paracetamol or acetaminophen is a widely used over-the-counter analgesic (pain reliever) and antipyretic (fever reducer) (see Fig. 1). It is commonly used for the relief of fever, headaches, and other minor aches and pains, and is a major ingredient in numerous cold and flu remedies. In combination with non-steroidal anti-inflammatory drugs (NSAIDs) and opioid analgesics, paracetamol is used also in the management of more severe pain (such as postoperative pain).

While generally safe for human use at recommended doses (1000 mg per single dose and up to 4000 mg/day for adults, up to 2000 mg/day if drinking alcohol (www.drug.com/acetaminophen.html), acute overdoses of paracetamol can cause potentially fatal liver damage and, in rare individuals, a normal dose can do the same; the risk is heightened by alcohol consumption. Paracetamol toxicity is the foremost cause of acute liver failure in the Western world, and accounts for most drug overdoses in the United States, the United Kingdom, Australia and New Zealand (Daly et al., 2008; Khashab et al., 2007; Hawkins and Edwards, 2007).

Paracetamol is derived from coal tar, and is part of the class of drugs known as ''aniline analgesics''; it is the only such drug still in use today (Bertolini et al., 2006). It is the active metabolite of phenacetin, once popular as an analgesic and antipyretic in its own right, but unlike phenacetin and its combinations, paracetamol is not considered to be carcinogenic at therapeutic doses (Bergman et al., 1996). The words acetaminophen (used in the United States, Canada and Hong Kong) and paracetamol (used elsewhere) both come from chemical names for the compound: *para*-acetylaminophenol. In some contexts, it is simply abbreviated as APAP, for *N*-acetyl-*para*-aminophenol.

Acetanilide was the first aniline derivative serendipitously found to possess analgesic as well as antipyretic properties, and was quickly introduced into medical practice under the name of Antifebrin by Cahn and Hepp (1886). But its unacceptable toxic effects, the most alarming being cyanosis due to methemoglobinemia, prompted the search for less toxic aniline derivatives. Harmon Northrop Morse had already synthesized paracetamol at Johns Hopkins University via the reduction of *p*-nitrophenol with tin in glacial acetic acid in 1877 (Morse, 1878; Silverman et al., 1992), but it was not until 1887 that clinical pharmacologist Joseph von Mering tried paracetamol on patients. In 1893, von Mering published a paper reporting on the clinical results of paracetamol with phenacetin, another aniline derivative (Von Mering, 1893). Von Mering claimed that, unlike phenacetin, paracetamol had a slight tendency to produce methemoglobinemia. Paracetamol was then quickly discarded in favor of phenacetin. The sales of phenacetin established Bayer as a leading pharmaceutical company. Overshadowed in part by aspirin, introduced into medicine by Heinrich Dreser in 1899, phenacetin was popular for many decades, particularly in widely advertised over-the-counter ''headache mixtures,'' usually containing phenacetin, an aminopyrine derivative or aspirin, caffeine, and sometimes a barbiturate.

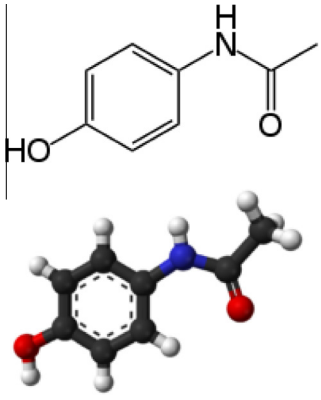

Figure 1 Structure of paracetamol or acetaminophen.

Paracetamol consists of a benzene ring core, substituted by one hydroxyl group and the nitrogen atom of an amide group in the *para* (Bales et al., 1985). The amide group is acetamide (ethanamide). It is an extensively conjugated system, as the lone pair on the hydroxyl oxygen, the benzene pi cloud, the nitrogen lone pair, the p-orbital on the carbonyl carbon, and the lone pair on the carbonyl oxygen are all conjugated. The presence of two activating groups also makes the benzene ring highly reactive toward electrophilic aromatic substitution. As the substituents are *ortho*, *para*-directing and *para* with respect to each other, all positions on the ring are more or less equally activated. The conjugation also greatly reduces the basicity of the oxygens and the nitrogen, while making the hydroxyl acidic through delocalisation of charge developed on the phenoxide anion.

Paracetamol is usually classified along with nonsteroidal antiinflammatory drugs (NSAID), but is not considered one. Like all drugs of this class, its main mechanism of action is the inhibition of cyclooxygenase (COX), an enzyme responsible for the production of prostaglandins, which are important mediators of inflammation, pain and fever. Therefore, all NSAIDs are said to possess anti-inflammatory, analgesic (anti-pain), and antipyretic (anti-fever) properties. The specific actions of each NSAID drug depend upon their pharmacological properties, distribution and metabolism (Ottani et al., 2006).

Complexes of paracetamol with various metal ions such as, Cu(II), Zn(II) or Fe(II) ions of ratio 2:1, respectively, have been prepared and their structure has been confirmed by elemental analysis, atomic absorption spectra, IR spectra and ^{1}H NMR spectra and finally it can be concluded that the structure of the complexes has C_2h point group symmetry in which two PA molecules are chelated to any one of the metal ions, Cu(II), Zn(II) and Fe(II) ions (El-Shahawy et al., 2007).

The kinetics of the oxidation of ruthenium(III)- and osmium(VIII)-catalyzed oxidation of paracetamol by diperiodatoargentate(III) (DPA) in aqueous alkaline medium at a constant ionic strength of 0.10 mol dm^{-3} was studied spectrophotometrically (Sirsalmath et al., 2006). The reaction between DPA and paracetamol in alkaline medium exhibits 2:1 stoichiometry in both catalyzed reactions (DPA:PAM). The main products were identified by spot test, IR, NMR and GC–MS. Probable mechanisms are proposed and discussed. The activation parameters with respect to the slow step of

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the mechanism are computed and discussed and thermodynamic quantities are also calculated. It has been observed that the catalytic efficiency for the present reaction is in the order of Os(VIII) > Ru(III). The active species of catalyst and oxidant has been identified.

The comparative study of Ru(III)- and Os(VIII)-catalyzed oxidation of paracetamol by diperiodatoargentate(III) was studied. Oxidation products were identified. Among various species of Ag(III) in alkaline medium, monoperiodatoargentate(III) is considered to be the active species for the title reaction. The active species of Ru(III) is found to be $[Ru(H_2O)_5OH]^{2+}$ and that for Os(VIII) is $[OsO_4(OH)_2]^{2-}$. Activation parameters were evaluated for both catalyzed and uncatalyzed reactions. Catalytic constants and the activation parameters with reference to the catalyst were also computed. The catalytic efficiency is Ru(III) < Os(VIII).

Elena V. Boldyreva summarized experimental X-ray diffraction and IR-spectroscopic data on the effect of pressure on a number of molecular and ionic-molecular crystals: monoclinic (I) and orthorhombic (II) polymorphs of paracetamol, fenacetin, monoclinic (a) and trigonal (g) polymorphs of glycine, *p*-benzoquinone, Co(III)-nitro- and nitrito-pentaammine complexes, and sodium oxalate (Boldyreva, 2003). Special attention is paid to the role of intermolecular interactions, in particular hydrogen bonds, in the anisotropy of structural distortion. For several compounds, the distortions induced by high-pressure and low-temperature are compared.

Pressure-induced polymorphic transitions attract much more attention than continuous structural changes in the same polymorph. However, the latter can also be valuable not only to predict the direction of a polymorphic transformation and to understand its mechanism but also to find parameters characterizing intermolecular interactions in crystals, in particular hydrogen bonds of various types (Boldyreva, 2003). This information can find various applications, ranging from crystal engineering, polymorph prediction and solid-state reactivity to the prediction of secondary and ternary structures of biopolymers and their response to various external actions.

It was found that polyvinylpyrrolidone (PVP) is an effective additive during crystallization of paracetamol and significantly influenced the crystallization and crystal habit of paracetamol (Garekani et al., 2000). These effects were attributed to adsorption of PVP onto the surfaces of growing crystals. It was found that the higher molecular weights of PVP (PVP 10,000 and PVP 50,000) were more effective additives than lower molecular weight PVP (PVP 2000). Paracetamol particles obtained in the presence of 0.5% w/v of PVP 10,000 or PVP 50,000 had near spherical structure and consisted of numerous rod-shaped microcrystals which had agglomerated together. Particles obtained in the presence of PVP 2000 consisted of fewer microcrystals. Differential scanning calorimetry (DSC) and X-ray powder diffraction (XPD) experiments showed that paracetamol particles, crystallized in the presence of PVP, did not undergo structural modifications. By increasing the molecular weight and/or the concentration of PVP in the crystallization medium the amount of PVP incorporated into the paracetamol particles increased. The maximum amount of PVP in the particles was 4.32% w/w.

After a large drug scanning (Alapont et al., 1999), the system Luminol–H_2O_2–$F(CN)_6^{3-}$ is proposed for first time for the indirect determination of paracetamol. The method is based on the oxidation of paracetamol by hexacyanoferrate (III) and the subsequent inhibitory effect on the reaction between luminol and hydrogen peroxide. The procedure resulted in a linear calibration graph over the range 2.5–12.5 mg ml^{-1} of paracetamol with a sample throughput of 87 samples/h. The influence of foreign compounds was studied and, the method was applied to the determination of the drug in three different pharmaceutical formulations.

The goal of this paper is to get a wide understanding of the structural and spectral properties as well as microbial activities of paracetamol and their Mg(II), Ca(II), Ba(II) and Sr(II) metal ion complexes. Metallo-ibuprofen complexes were investigated by spectral and thermal techniques.

2. Experimental

2.1. Chemicals

All chemicals used were of the purest laboratory grade (Merck). Selected metal-salts like $MgCl_2$, $CaCl_2$, $BaCl_2{\cdot}2H_2O$, and $SrCl_2{\cdot}7H_2O$ were used. Paracetamol was received from Egyptian international pharmaceutical industrial company (EIPICO).

2.2. Synthesis of Para complexes

The above complexes were prepared, employing a 1:2 (metal ions:para) ratio. A solution of 0.5 mmol of a salt of each Mg(II), Ca(II), Ba(II) and Sr(II) dissolved in 10 ml of distilled water was added to a solution of 1.0 mmol of paracetamol in 20 ml of methyl alcohol under magnetic stirring. The pH of each solution adjusted at pH 7 using 5% alcoholic ammonia solution. The resulting solutions stirred and refluxed on a hot plate at 50 °C for 1 h and left to evaporate slowly at room temperature. One day later, the obtained precipitates were filtered off, washed with hot water then dried at 60 °C.

2.3. Preparation of stock solutions

2.3.1. Sodium chloride solution

A standard solution of 0.01 M sodium chloride is prepared by dissolving 0.0584 g of NaCl in a small amount of distilled water then completed to 100 ml in a measuring flask.

2.3.2. Barium chloride solution

A 10 g of barium chloride dihydrate, $BaCl_2{\cdot}2H_2O$, was weighed and dissolved in the least amount of distilled water. The volume was completed to 100 ml in a measuring flask to give 10% solution.

2.3.3. Silver nitrate solution

A weight of 0.1701 g of $AgNO_3$ was dissolved in a small amount of distilled water then completed to 100 ml in a dark measuring flask to obtain an approximate 0.01 M solution. The concentration of $AgNO_3$ solution was checked by the titration against 0.01 M NaCl solution and the exact concentration was found to be 0.01004 M.

2.3.4. Ammonium hydroxide solution

The stock solution of NH_4OH was prepared by taking 15.15 ml of the concentrated NH_3 (33%) in 35 ml distilled

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water. The volume was then completed to 100 ml by methanol to give approximately 5% solution.

2.3.5. Complex solution

An accurate weight of 0.2 g from the solid complex in each case was dissolved in the least amount of 2 M nitric acid. The solution evaporated near to dryness. This process repeated twice and the residue dissolved in about 50 ml of hot distilled water to obtain a clear solution. The volume then completed to 100 ml in a measuring flask.

2.4. Apparatus and experimental conditions

2.4.1. Micro analytical techniques

Carbon, hydrogen and nitrogen contents were determined using a perkin–Elmer CHN 2400. The metal content was found gravimetrically by converting the compounds into their corresponding carbides or oxides. The Mg(II), Ca(II), Ba(II) and Sr(II) contents were determined gravimetrically by the direct ignition of the complexes at 1000 °C for 3 h till constant weight. The residue was then weighed in the forms of metal oxides.

2.4.2. Molar conductance

Molar conductivities of freshly prepared 1.0×10^{-3} mol/L DMSO solutions of the complexes were measured using Jenway 4010 conductivity meter.

2.4.3. Infrared spectra

IR spectra were recorded on Brüker FTIR Spectrophotometer (4000–400 cm^{-1}) in KBr pellets.

2.4.4. Electronic spectra

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 1 cm quartz cell, in the range 200–800 nm.

The solid reflectance spectra were performed on a Shimadzu 3101 pc spectrophotometer.

2.4.5. ^1H NMR spectra

^1H NMR spectra of the free ligands and their complexes were recorded on varian Gemini 200 MHZ spectrophotometer using DMSO-d_6 as solvent and TMS as an internal reference.

2.4.6. Thermal analysis (TG and DTG) techniques

Thermogravimetric analysis (TG and DTG) was carried out in the temperature range from 25 to 800 °C in a steam of nitrogen atmosphere by Shimadzu TG 50 H thermal analyzer. The experimental conditions were: platinum crucible, nitrogen atmosphere with a 30 ml/min flow rate and a heating rate 10 °C/min.

2.5. Microbiological investigation

2.5.1. Hole well method

The investigated isolates of bacteria and fungi were seeded in tubes with nutrient broth (NB) and Dox's broth (DB), respectively. The seeded (NB) for bacteria and (DB) for fungi (1 ml) were homogenized in the tubes with 9 ml of melted (45 °C) nutrient agar (NA) for bacteria and (DA) for fungi. The homogenous suspensions were poured into Petri dishes. The holes (diameter 0.5 cm) were done in the cool medium. After cooling in these holes, 100 l of the investigated compounds was applied using a micropipette. After incubation for 24 h in an incubator at 37 and 28 °C for bacteria and fungi, respectively, the inhibition zone diameters were measured and expressed in cm. The antimicrobial activities of the investigated compounds were tested against *Escherichia coli* and *Pseudomonas aeruginosa* as (Gram −ve) and *Bacillus subtilis* and *Bacillus cereus* as (Gram +ve) bacteria as well as some kinds of fungi; *Aspergillus flavus* and *Aspergillus niger*. In the same time with the antimicrobial investigations of the complexes, the pure solvent was also tested. The concentration of each solution was 1.0×10^{-3} mol/L. Commercial DMSO was employed to dissolve the tested samples.

3. Results and discussion

3.1. Paracetamol complexes

3.1.1. Molar conductivities of metal chelates of paracetamol

The molar conductance values for the Mg(II), Ca(II), Ba(II) and Sr(II) complexes of para in DMSO solvent (1.00×10^{-3} M) were found to be in the range 57.40–72.80 $^{-1}$ cm^2 mol^{-1} at 25 °C, suggesting them to be non-electrolytes Table 1. These data matched with the calculated elemental analysis that Cl^- ions were not detected by the addition of $AgNO_3$ solution to the solutions of the mentioned complexes in nitric acid. The above complexes are air-stable, with higher melting points, insoluble in H_2O, partially soluble in ethanol and methanol and most of organic solvents except for DMSO, DMF and concentrated acids are soluble.

3.1.2. Infrared spectra of Mg(II), Ca(II), Ba(II) and Sr(II) complexes of paracetamol

The IR data of paracetamol and its complexes are listed in Table 2 and shown in Figs. 2–5. From the comparative IR spectra

Table 1 Elemental analyses and physical data of para and its Mg(II), Ca(II), Ba(II) and Sr(II) compelxes.

Complexes (F.W)	M.wt (g/mol)	%C		%H		%N		%M		Λ (Ω^{-1} cm^2 mol^{-1})
		Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	
$[Mg(para)_2(OH)_2]\cdot 2H_2O$ $C_{16}H_{24}MgN_2O_8$	396.3	47.97	48.48	6.43	6.06	7.45	7.07	6.12	6.06	72.6
$[Ca(para)_2(OH)_2]\cdot 6H_2O$ $C_{16}H_{32}CaN_2O_{12}$	484.1	39.19	39.67	6.49	6.61	5.29	5.79	8.41	8.26	63.8
$[Ba(para)_2(OH)_2]\cdot 2H_2O$ $C_{16}H_{24}BaN_2O_8$	509.3	37.09	37.7	4.16	4.71	5.25	5.5	26.78	26.96	72.8
$[Sr(para)_2(OH)_2]\cdot 2H_2O$ $C_{16}H_{24}SrN_2O_8$	459.6	41.13	41.78	5.45	5.22	6.61	6.09	19.15	19.06	57.4

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Table 2 IR frequencies (4000–400 cm^{-1}) of para and its Mg(II), Ca(II), Ba(II) and Sr(II) complexes.

Compound	ν(NH) and ν(OH)	ν(C═O)	δ(CNH); amide group	ν(C–O); phenyl group	ν(M–N)	ν(M–O)
Paracetamol	3300s	1640vs	1540sh	1256vs	–	–
$[Mg(para)_2(OH)_2]\cdot 2H_2O$	3410br	1646sh	1566s	1252w	469w	509w
$[Ca(para)_2(OH)_2]\cdot 6H_2O$	3427br	1647sh	1564s	1252w	465w	511s
$[Ba(para)_2(OH)_2]\cdot 2H_2O$	3206w, 3325s, 3459s	1651m	1563sh	1251w	413s	567s, 512 m
$[Sr(para)_2(OH)_2]\cdot 2H_2O$	3325s	1653m	1562sh	1253s	417s	507sh

s, small, sh, sharp, m, medium, w, weak, br, broad.

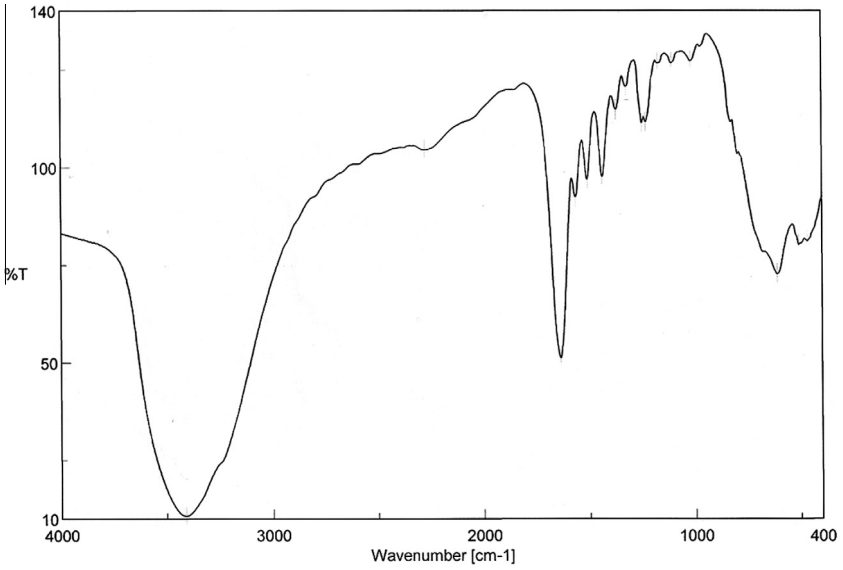

Figure 2 FTIR spectrum of Mg(II) complex of paracetamol.

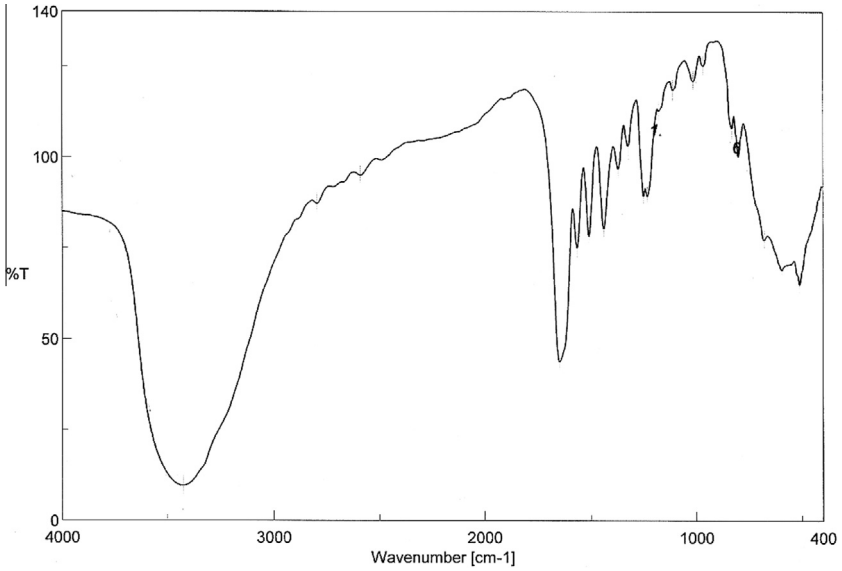

Figure 3 FTIR spectrum of Ca(II) complex of paracetamol.

of paracetamol and its complexes, a slight blue shift of the stretching band of the carebonyl group, (C═O) of paracetamol which is found at 1640 cm^{-1} from 1646 to 1653 cm^{-1} in the complexes spectra has been noticed. Also, a slight shift of the in-plane bending band of the carbonyl group of the paracetamol spectrum at 840–830 cm^{-1} in the complex spectra and the disappearance of the in-plane bending bands of CNH at positions 1540 and 1260 cm^{-1} in the IR spectra of

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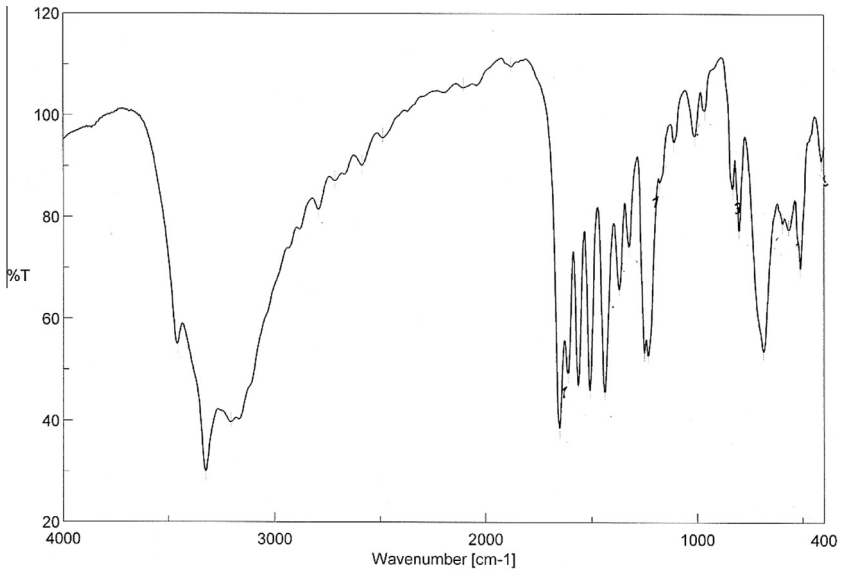


Figure 4 FTIR spectrum of Ba(II) complex of paracetamol.

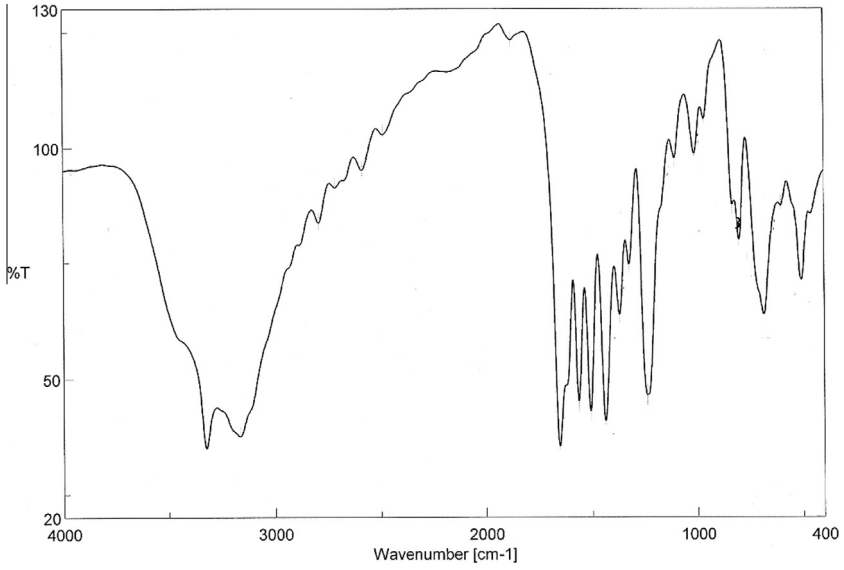


Figure 5 FTIR spectrum of Sr(II) complex of paracetamol.

Table 3 ^{1}H NMR spectral data of para and its Ba(II) complex.

Compound	δ_{ppm} of hydrogen			
	H; CH_3	H; H_2O	H; ArH	H; NH
Paracetamol	1.96	–	6.57–7.28	9.27
Ba(II) complex	1.97	3.39	6.66–7.36	9.83

the complexes in addition to the appearance and disappearance of the stretching band and the out-of-plane wagging band of NH in the amide group in the complex spectra have been noticed (Nakamato and Mc Carthy, 1968). On the basis of the above observations, we concluded that the coordination mode proceeds via the participation of the carbonyl-O and NH atoms of the amide group. The appearance of the stretching band and the in-plane bending band of the hydroxyl group, with respect to the phenyl moiety at positions around 1256 and 620 cm^{-1}, respectively, excludes the contribution of the hydroxyl oxygen atom to be chelated with the metal ion as well as the appearance of the stretching band in the hydroxyl group

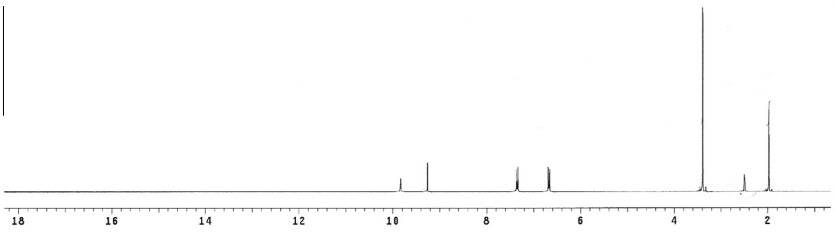


Figure 6 ^{1}H NMR spectrum of Ba(II) complex of paracetamol.

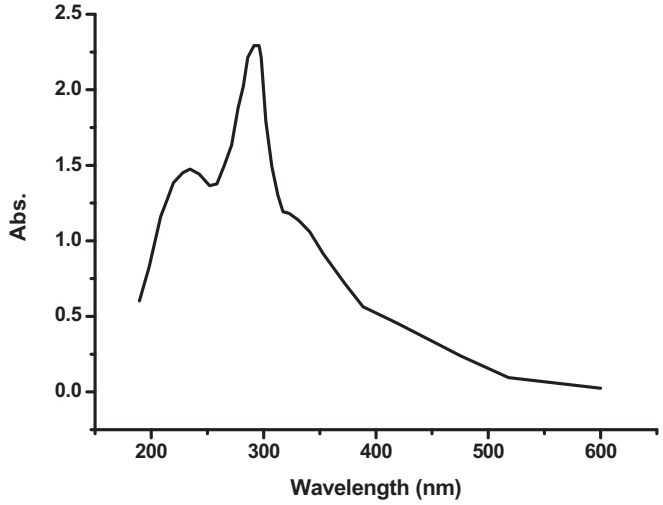


Figure 7 Electronic absorption spectrum of Mg(II) complex of paracetamol.

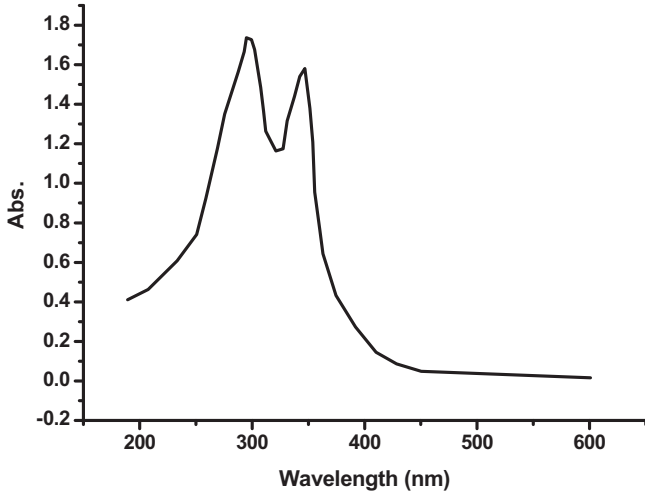


Figure 8 Electronic absorption spectrum of Ca(II) complex of paracetamol.

between oxygen and hydrogen atom at position 3300 cm^{-1} verifies the assumption of the exclusion of the hydroxyl oxygen atom to be chelated with the metal ion in the complex (Nakamoto, 1997).

3.1.3. ^{1}H NMR of paracetamol and its Ba(II) complex

The ^{1}H NMR data of para and its Ba(II) complex, as an example are listed in Table 3 and shown in Fig. 6. The ^{1}H NMR spectrum of paracetamol shows the signals at δ = 9.27 ppm, which are assigned to the protons of the amide group and the appearance of a large systematic shift of this signal of the amide hydrogen atom at δ = 9.83 ppm in the ^{1}H NMR spectrum of Ba(II) complex of paracetamol confirms the participation of the amide nitrogen atom in the complexation between para and M(II) ion. The persistence of the signal of the proton of the hydroxyl group in the ^{1}H NMR spectrum of the complex confirms that the hydroxyl group does not contribute in the complexation between para and M(II) ion therefore, the hydroxyl group is still free in the complex of paracetamol. So, the complexation between two molecules of paracetamol with M(II) ion has been formed by the chelation of the metal ion with the carbonyl-O and the amide-N atoms containing the amide hydrogen atoms to form the complex (para)2-M including the nitrogen metal (Trinchero et al., 2004).

3.1.4. Electronic absorption spectra of paracetamol complexes

The formation of the Mg(II), Ca(II), Ba(II) and Sr(II) complexes of paracetamol was also confirmed by UV–Vis spectra. Figs. 7–10 show the electronic absorption spectra of the M(II) complexes in DMSO in the 200–600 nm range. It can be seen that free paracetamol has two distinct absorption bands. The first one at 300 nm may be attributed to $\pi \rightarrow \pi^{*}$ intra-ligand transition of the aromatic ring. The second band observed at 390 nm is attributed to $n \rightarrow \pi^{*}$ electronic transition. In the spectra of the M(II) complexes, the two bands are hypsochromically affected clearly, suggesting the ligand is not deprotonated, but the lone pair of electrons on nitrogen and carbonyl-oxygen atoms of the amide group is participated in

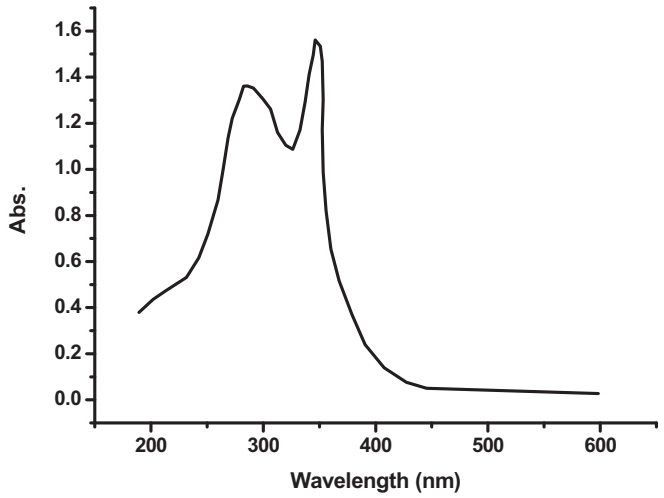
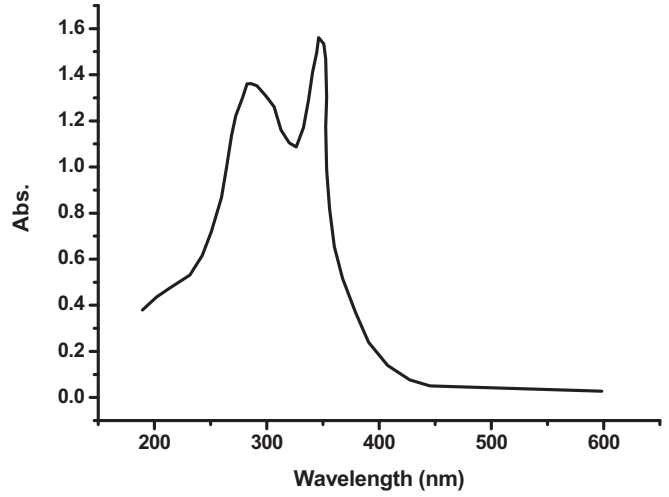


Figure 9 Electronic absorption spectrum of Ba(II) complex of paracetamol.



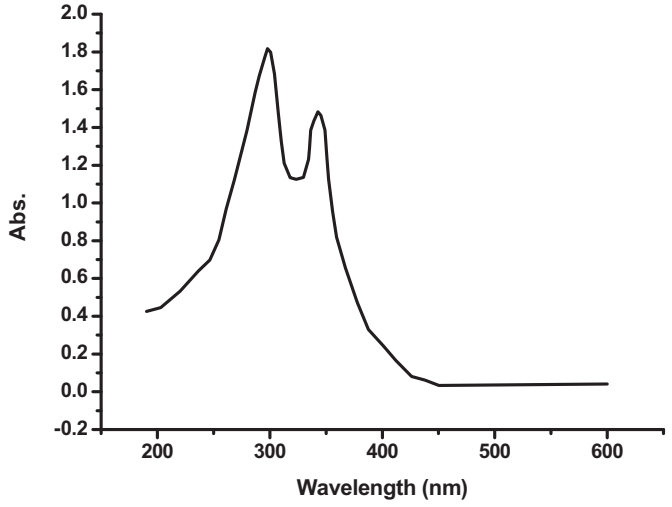


Figure 10 Electronic absorption spectrum of Sr(II) complex of paracetamol.

Table 4 Thermal data of Mg(II), Ca(II), Ba(II) 'and Sr(II) complexes of para.

Complex	TG range (°C)	DTG_{max} (°C)	n[a]	Mass loss % found (calcd.)	Total mass left	Assignment	Residue
$[Mg(para)_2(OH)_2]\cdot 2H_2O$	35–135	51, 123	2	23.01 (23.23)	16.32 (16.16)	Loss of $2(H_2O)$ and 2(CO)	MgO + 2C
	135–425	258, 356	2	28.36 (28.28)		Loss of 2(NO) and $2(C_2H_2)$	
	425–695	537, 668	2	32.31 (32.33)		Loss of $4(C_2H_2)$, $1/2O_2$ and $4H_2$	
$[Ca(para)_2(OH)_2]\cdot 6H_2O$	20–130	53, 110	2	22.03 (22.31)	26.90 (26.45)	Loss of $6(H_2O)$	CaO + 6C
	135–315	266	1	33.02 (33.06)		Loss of 2(OH), 2(CO), C_2H_2, NO and $1/2N_2$	
	315–625	358, 512	2	18.05 (18.18)		Loss of $3(C_2H_2)$ and $5H_2$	
$[Ba(para)_2(OH)_2]\cdot 2H_2O$	50–135	72, 107	2	6.80 (7.07)	34.58 (34.81)	Loss of $2(H_2O)$.	BaO + 2C
	135–490	266, 377	2	58.62 (58.12)		Loss of 2(OH), C_6H_6, 2(CO), C_6H_6O and $2(NH_3)$	
$[Sr(para)_2(OH)_2]\cdot 2H_2O$	35–175	49, 93, 138	3	8.31 (7.83)	38.39 (38.21)	Loss of $2(H_2O)$	SrO + 6C
	175–300	264	1	45.68 (46.13)		Loss of $2(H_2O)$,C_6H_6O,C_2H_2 and 2(CO)	
	300–605	306, 362	2	7.62 (7.83)		Loss of $2(NH_3)$ and H_2	

[a] n, number of decomposition steps.

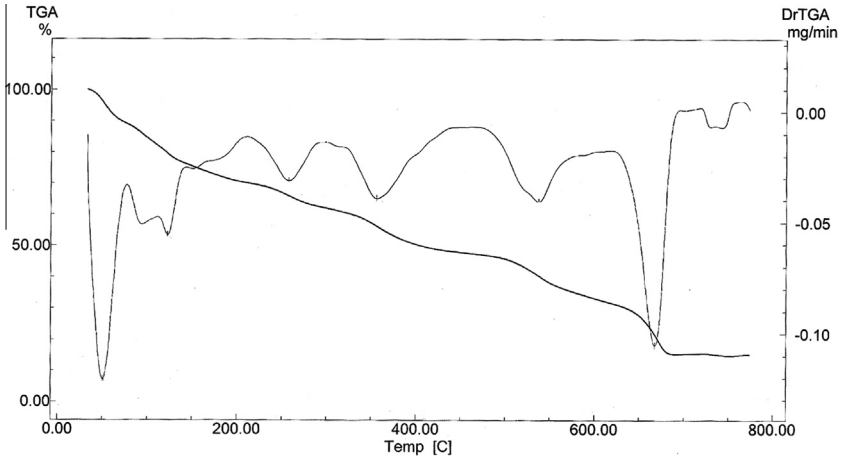


Figure 11 TG/DTG curve of Mg(II) complex of paracetamol.

the complexation. These results are clearly in accordance with the results of the FTIR and ^1H NMR spectra.

3.1.5. Thermal analysis of para and its Mg(II), Ca(II), Ba(II) and Sr(II) complexes

The heating rates were controlled at 10 °C/min under nitrogen atmosphere and the weight loss was measured from ambient temperature up to ≅1000 °C. The data are listed in Table 4 and shown in Figs. 11–14. The weight losses for each chelate were calculated within the corresponding temperature ranges.

3.1.5.1. $[Mg(para)_2(OH)_2]\cdot 2H_2O$. The thermal decomposition of $[Mg(para)_2(OH)_2]\cdot 2H_2O$ complex occurs at six steps. The first and second degradation steps take place in the range of 35–135 °C and they correspond to the elimination of $2(H_2O)$ and 2(CO) molecules with an observed weight loss of 23.01% (calcd. = 23.23%). The third and fourth steps fall in the range of 135–425 °C which are assigned to the loss of 2(NO) and 2 (C_2H_2) molecules with a weight loss (obs. = 28.36%, calcd. = 28.28%). The fifth and sixth decomposition steps within the temperature range 425–695 °C were accompanied by a mass loss of 32.31% (calcd. = 32.33%), which are assigned to the loss of $4(C_2H_2)$, $1/2O_2$ and $4(H_2)$ molecules. The MgO and 2C are the final products remaining stable till 800 °C.

3.1.5.2. $[Ca(para)_2(OH)_2]\cdot 6H_2O$. The calcium (II) paracetamol complex is decomposed in five steps. The first and second steps are exhibited at 20–130 °C and corresponding to the loss of $6(H_2O)$ molecules, representing a weight loss of (obs. = 22.03%, calcd. = 22.31%). The third step takes place within the temperature range 130–315 °C and can be assigned to the loss of 2(OH), 2(CO), C_2H_2, NO and $1/2N_2$ molecules and the mass loss due to this step was (obs. = 33.02%, calcd. = 33.06%). The last two steps are occurring at 315–625 °C and corresponding to the evolution of $3(C_2H_2)$ and $5H_2$ gases, representing a weight loss of 18.05% and its calculated value is 18.18%. The final products resulted at 800 °C contain CaO polluted with six carbon atoms.

3.1.5.3. $[Ba(para)_2(OH)_2]\cdot 2H_2O$. The mentioned complex is decomposed in four steps. The first and second steps are occurring at 50–135 °C and corresponding to the evolution of $2(H_2O)$ molecules, representing a weight loss of 6.80% and its calculated value is 7.07%. While, the last two decomposition steps are occurring at 135–490 °C and corresponding to

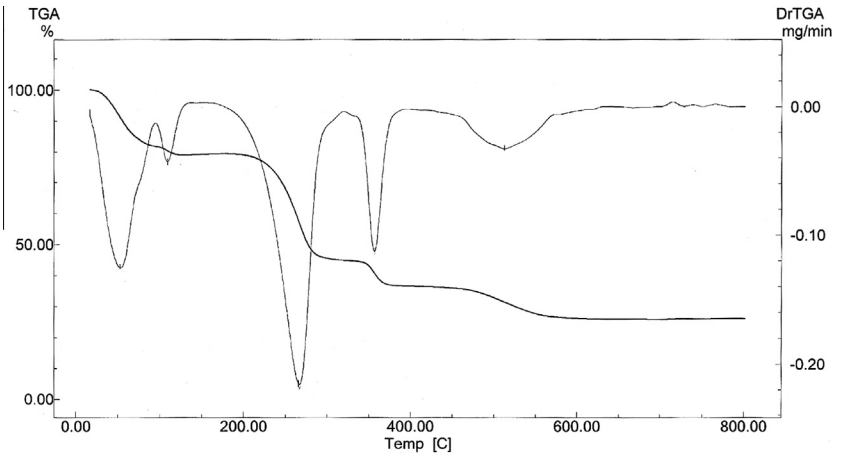


Figure 12 TG/DTG curve of Ca(II) complex of paracetamol.

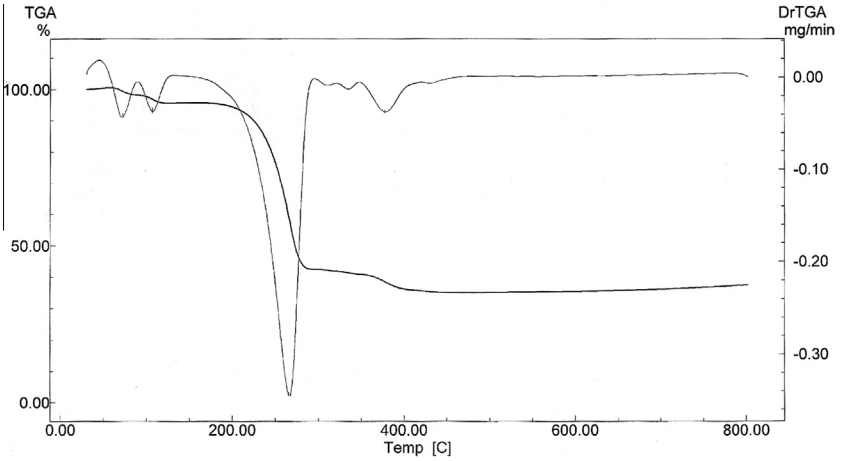


Figure 13 TG/DTG curve of Ba(II) complex of paracetamol.

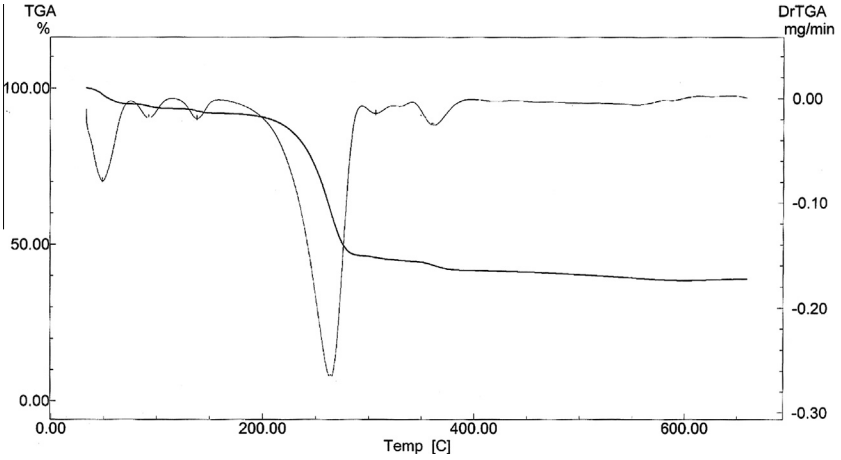


Figure 14 TG/DTG curve of Sr(II) complex of paracetamol.

the loss of 2(OH), C_6H_6, 2(CO), C_6H_6O and 2(NH_3) molecules, representing a weight loss of 58.62% and its calculated value is 58.12%. The final products resulting at 800 °C contain BaO polluted with two carbon atoms.

3.1.5.4. [Sr(para)$_2$(OH)$_2$]·2H$_2$O. The thermal decomposition of [Sr(para)$_2$(OH)$_2$]·2H_2O complex occurs at six steps. The first, second and third decomposition steps take place in the range of 35–175 °C and correspond to the elimination of

Table 5 Antimicrobial data of paracetamol complexes.

Complexes	Diameter of inhibition zone (cm)					
	Bacillus subtilis	*Bacillus cereus*	*E. coli*	*Pseudomonas aeruginosa*	*A. niger*	*A. flavus*
Control	0	0	0	0	0	0
$[Mg(para)_2(OH)_2]\cdot 2H_2O$	0	0	0.3	0	0.5	0.3
$[Ca(para)_2(OH)_2]\cdot 6H_2O$	0	0	0.4	0	1.5	0.2
$[Ba(para)_2(OH)_2]\cdot 2H_2O$	0	0	0.5	0	1.3	0.4
$[Sr(para)_2(OH)_2]\cdot 2H_2O$	0	0	0.3	0	1	0.5

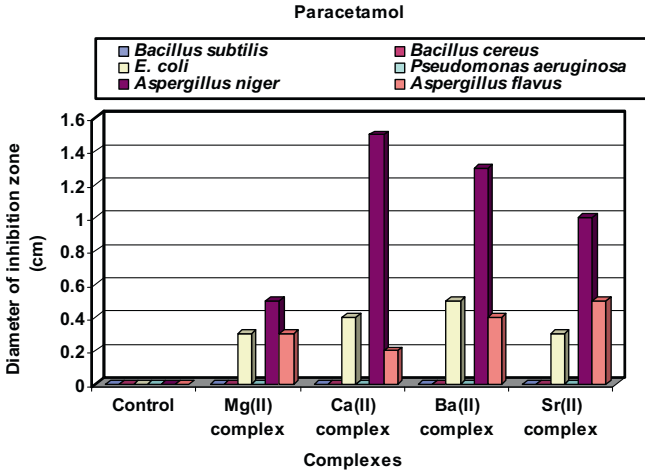


Figure 15 Statistical representation for biological activity of paracetamol complexes.

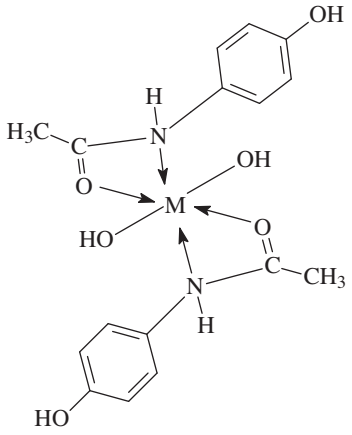


Figure 16 Structure of paracetamol complexes, where [M = Mg(II), Ca(II), Ba(II) and Sr(II)].

$2(H_2O)$ molecules with an observed weight loss of 8.31% (calcd. = 7.83%). The fourth step falls in the range of 175–300 °C which is assigned to the loss of $2(H_2O)$, C_6H_6O, C_2H_2 and 2(CO) molecules with a weight loss of (obs. = 45.68%, calcd. = 46.13%). The last two decomposition steps are occurring at 300–605 °C and corresponding to the evolution of $2(NH_3)$ and H_2 gases, representing a weight loss of 7.62% and its calculated value is 7.83%. The SrO and 6C are the final products remaining stable till 800 °C.

3.1.6. Microbiological investigation of the paracetamol complexes

Antibacterial and antifungal activities of paracetamol complexes are carried out against the (Gram −ve) as *E. coli* and *P. aeruginosa*, (Gram +ve) as *B. subtilis* and *B. cereus* and antifungal (*A. niger* and *A. flavus*). The antimicrobial activity was estimated based on the size of inhibition zone around dishes. The M(II) complexes are found to have high activity against bacteria especially *E. coli* and two kinds of fungi, where as the Ca(II) complex is more active than the Ba(II), Sr(II) and Mg(II) complexes, respectively against *A. niger*. The data are listed in Table 5 and shown in Fig. 15.

3.1.7. Structure of the paracetamol complexes

The structures of the complexes of paracetamol with alkaline earth metals such as Mg(II), Ca(II), Ba(II) and Sr(II) ions have been confirmed form the elemental analyses, IR, molar conductance, UV–Vis, ^{1}H NMR and thermal analysis data. Thus, from the IR spectra, it is concluded that paracetamol behaves as a neutral bidentate ligand coordinated to the metal ions via the lone pair of electrons of nitrogen and carbonyl O atoms of the amide group. From the molar conductance data, it is found that the complexes seem to be non-electrolytes. On the basis of the above observations, octahedral geometries are suggested for the investigated complexes. As a general conclusion, the investigated complex structures can be given as shown in Fig. 16.

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