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Synthesis of New Zirconium(IV) Paracetamol Drug.

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ABSTRACT

The structure of the Zr(IV) complex of paracetamol has been confirmed from elemental analysis, IR, molar conductance, UV-Vis, ^{1}H-NMR and thermal analysis data. The ^{1}H-NMR and IR spectra confirm that paracetamol behave as monodentate ligand coordinated to the zirconium(IV) ion via the oxygen atom of phenolic group. From the molar conductance data, it is found that the complex seem to be non-electrolyte. The antimicrobial test of investigated complex was checked against some kind of bacteria and fungi and recorded enhancement efficiency.

Keywords: Paracetamol, zirconium(IV) ion, Chelation, antimicrobial assessment, thermal analyses.

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INTRODUCTION

Paracetamol (N-acetyl-4-amino-phenol or 4-hydroxy acetanilide) is a well-known drug that have application in pharmaceutical industries, is a popular analgesic and antipyretic medication that is readily absorbed after administration and little toxicity when used in recommended dose [1-7]. Paracetamol in pharmaceutical preparation can be determined by different method such as fluormetry [8], chemiluminescence [9], electro chemical method [10], nuclear magnetic resonance, mass spectroscopy [11], and liquid chromatography [12]. Paracetamol has high therapeutic value, it is also used as an intermediate for pharmaceutical (as a precursor in penicillin) and azo dye, stabilizer for hydrogen peroxide, photographic chemical [13]. Paracetamol is also known to be hepatotoxic in man and various experimental animals upon over dose [14], paracetamol is also oxidized by cytochrome P450 into the reactive intermediate N-acetyl-p-benzoquinone imine [15]. Several different approaches have previously been utilized in an attempt to achieve rapidly absorbed paracetamol solid dose formulations. These including enhancing tablet disintegration rate [16], or alkalimetal salt or antiacid [17] to paracetamol tables. In the present work, we focused on raising the efficiency of the drug by adding zirconium(IV) ion and formation of new complex which to be proven using thermal and spectroscopic characterization.

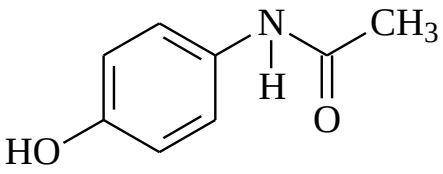
EXPERIMENTAL

Material And Instrumentations

All used reagent were of analytical grade and were employed without further purification. The Elemental analysis data of carbon and hydrogen were performed in a CHN 2400 Perkin Elmer analyzer. FT-IR spectra were recorded on Bruker FT-IR Spectrophotometer in the 4000-400 cm^{-1}. The electronic spectra were recorded in dimethylsulphoxide using Perkin-Elmer Lambda 4B Spectrophotometer. H^1-NMR spectrometer was recorded using DMSO as solvent, chemical shift are given in ppm relative to tetramethylsilane. The thermal analysis (TG & DTG) were carried out in nitrogen atmosphere using Schimadzu TGA-50H thermal analyzer.

Synthesis

The Zr(IV) sulphate (1 mmol, Aldrich company) were dissolved in 20 cm^3 distilled water and then added to 20 cm^3 of methanolic solution with 4 mmol of paracetamol (Fig. 1) under magnetic stirring. The pH of each solution was adjusted to 7-9 using ammonium hydroxide. The resulting mixture was heated to 60 °C and left to evaporate slowly at room temperature. The precipitate was filtered off, washy with hot methanol and dried at 60 °C.



Paracetamol

Fig 1: Structure formula of paracetamol drug

Microbiological investigation

The biological activity of Zr(IV) paracetamol complex was tested against bacteria and fungi. In testing bacterial activity of this compound, we used more than one test organism. The organisms used in the present investigation including two bacteria [(B.subtilis Gram +ve), (E. coli Gram –ve)] and two fungi (Aspergillus niger, Aspergillus flarus). The results of the bacterial and fungicidal scanning of synthesized complex are assigned.

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RESULTS AND DISCUSSION

Molar conductivities

The molar conductance value for the Zr(IV) complex of para in DMSO solvent 10^{-3} M was found to be 34 $\Omega^{-1}.cm^2.mol^{-1}$ at 25 °C, suggesting that to be non-electrolyte, as shown in Table 1. The conductance data matched with the calculated elemental analysis that SO_4^{-2} ion was not detected by using of $AgNO_3$ reagent to the solution of mentioned complex. The above complex was air stable with higher melting point.

Table 1: Elemental analysis and physical data of Zr(IV) para complex

Complexes (F.W)	M.wt (g/mole)	%C		%H		%N		%M		Λ ($\Omega^{-1}.cm^2.mol^{-1}$)
		Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	
$[Zr(para)_4(H_2O)_2].7H_2O$	853	44.34	45	5.13	5.80	6.43	6.5	9.76	10	34

Infrared spectrum

The IR data of paracetamol and its Zr(IV) complex are listed in Table (2) and shown in Fig (2). From the comparative IR spectra of paracetamol and its complex, it has been noticed that, the stretching vibration bands at 3300 cm^{-1} and 3200 cm^{-1} of free paracetamol have been assigned to OH and N-H stretching vibration motions. These bands have been unshifted in the spectra of the metal complex due to faraway of coordination. The strong absorption band at 509 cm^{-1} in the spectra of metal complex which doesn't appear in free paracentamol has been tentatively assigned to Zr-OH stretch band of metal complex. The blue shift of stretching band and the in-plane banding band of hydroxyl group, with respect to phenyl moiety from 1260 to 1240 cm^{-1}, this is evidence that contribution of the hydroxyl oxygen atom to be chelated with the metal ion upon deprotonated (Scheme 1).

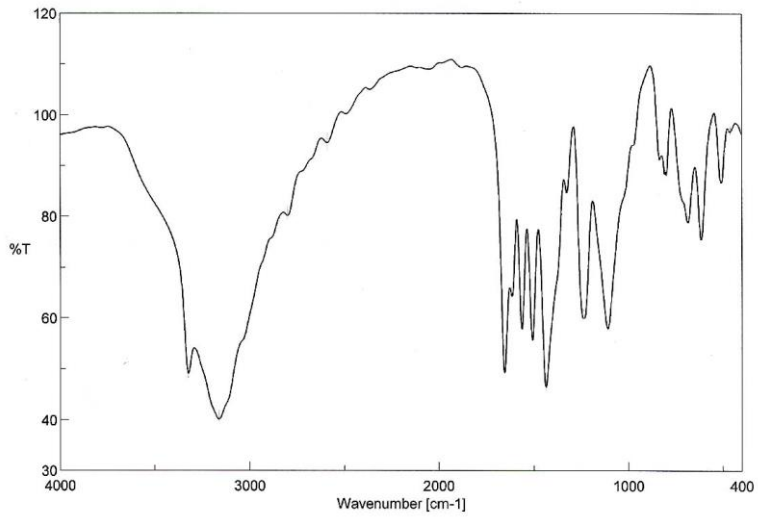

Fig 2: FT-IR spectrum of Zr(IV) complex of paracetamol

Table 2: IR frequencies (4000-400cm^{-1}) of Zr(IV) para complex

Compound	ν(OH) and νNH	νC=O	δ(CNH) amide group	ν(C-O) phenyl group	νM-O
Paracetamol	3300 3200	1650	1560	1260	-
$[Zr(para)_4(H_2O)_2].7H_2O$	3322 3160	1653	1563	1240	509

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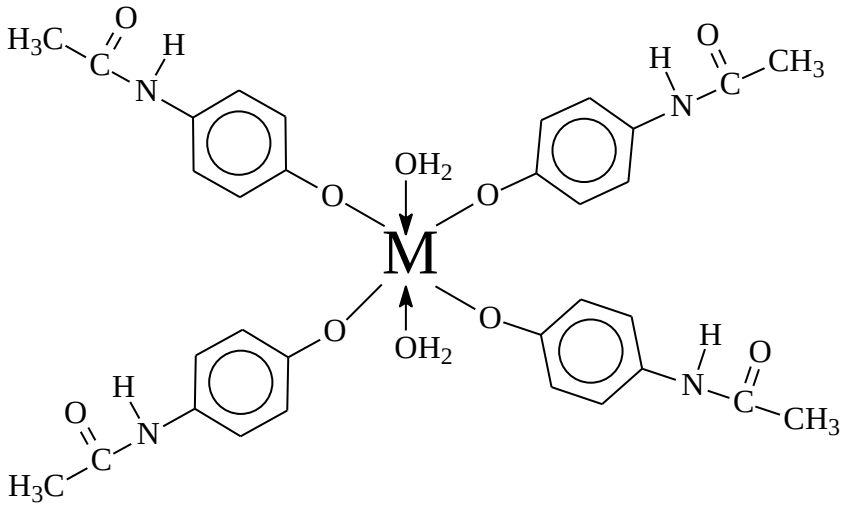

Scheme 1: Structure of Zr(IV) paracetamol complexes

^{1}HNMR spectra

^{1}H-NMR spectrum of paracetamol (Table 3) include to the signals (δ = 9.37 and 10.00 ppm) which are due to the proton of the amide and hydroxyl groups, respectively. The disappearance of signal (δ = 10.00 ppm) of the proton of hydroxyl group in the ^{1}H-NMR spectrum of the Zr(IV) complex (Fig. 6), confirm the consumption of hydroxyl group in the complexation between para and zirconium(IV) ion after deprotonated. The persistence of the signal of the proton of the amide group in the ^{1}H-NMR spectrum of the complex confirm that the amide proton does not contribute in the complexation process.

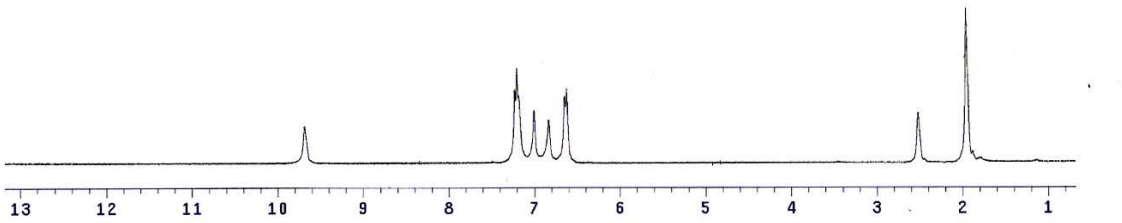

Fig 3: ^{1}H-NMR spectrum of Zr(IV) complex of paracetamol.

Table 3: ^{1}H-NMR spectral data and it Zr(IV) complex

Compound	δ(ppm) of protons				
	H; CH_3	H; H_2O	H; ArH	H; NH	H; OH
Paracetamol	1.9	-	6.57-7.28	9.37	10
Zr(IV) complex	1.96	2.5	6.6-7.22	9.60	-

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Electronic absorption spectra

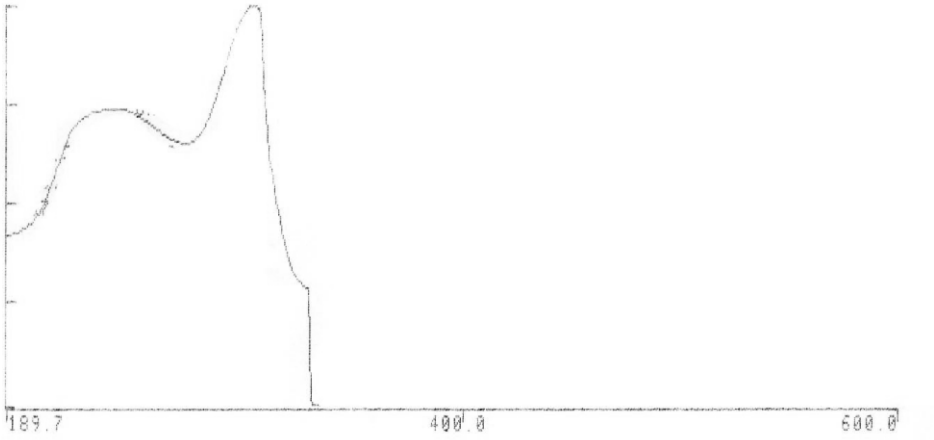

Fig 4: Electronic absorption spectrum of Zr(IV) complex of paracetamol

The formation of the Zr(IV) complex of paracetamol was also confirmed by UV-Vis. spectrum Fig. (4), this spectrum was scanned in DMSO solvent within the 200-600 nm range. It can be seen that free paracetamol has two distinct absorption bands, the first one at 300 nm due be π-π* intra-ligand transition of the aromatic ring and the second band observed at 390 nm is attributed to n-π* electronic transition.

Thermal analysis

The heating rate 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 Fig. (5). The weight losses were calculated within the corresponding temperature ranges. The thermal decomposition of $[Zr(para)_4)(H_2O)_2]$. $7H_2O$ complex occur at three steps. The first step take place in the range of 50-190 °C which correspond to the elimination of H_2O with an observed weight loss of 2.07% (calcd. = 2.11%). The second step place take in the range of 190-422 °C which is assigned to the loss of two molecule of para and $6H_2O$ with an observed weight loss of 47.59% (calcd. = 47.80%). The third step take place in the range 422-700 °C which is assigned to the loss of two molecules of para and $2H_2$ with weight loss obs. = 36.10% (calcd. = 35.60%). The ZrO_2 is final product remain stable till 800 °C.

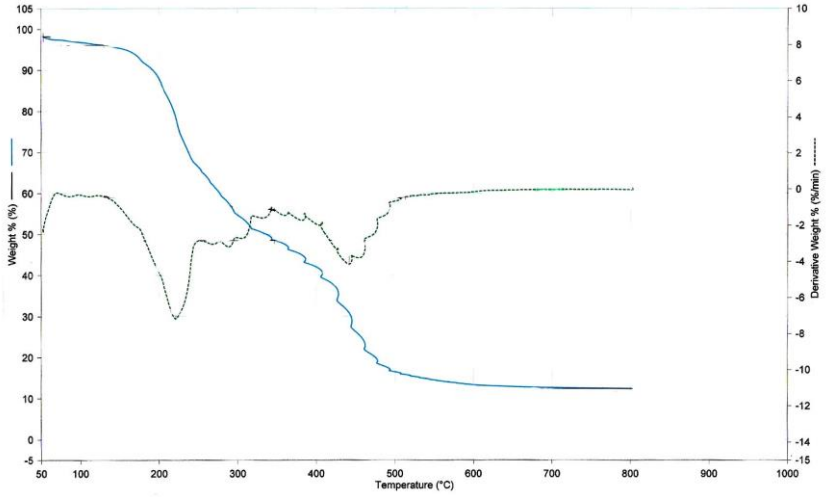

Fig 5: TG/DTG curve of Zr(IV) complex of paracetamol

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Table 4: Thermal data of Zr(IV) para complex

TG range (°C)	DTGmax (°C)	Mass loss %found (calcd.)	Total mass left	Assignment	Residue
50-190	130	2.07 (2.11)		loss of H_2O	
190-422	346	47.59 (47.80)		loss 2para + $6H_2O$	
422-700	513	36.10 (35.60)		loss 2para + $2H_2$	
			14.22 (14.50)		ZrO_2

Microbiological investigation

Antibacterial and antifungal activities of paracetamol zirconium(IV) complex is carried out against the (Gram –ve) as Escherichia coli, (Gram +ve) as Bacillus subtilis and antifungal (Aspergillus niger and Aspergillus flavus). The antimicrobial activity estimated based on the size of inhibition zone around dishes. Zr(IV) complex is found to have high activity against bacteria and two kind of fungi. The data listed in Table (5) and shown are shown in Fig. (6).

Table 5: Antimicrobial data of Zr(IV) paracetamol complex

	Bacillus subtilis	E. coli	Aspergillus niger	Aspergillus flavus
Control	0	0	0	0
Zr(IV) complex	1.5	1	2.3	2.1

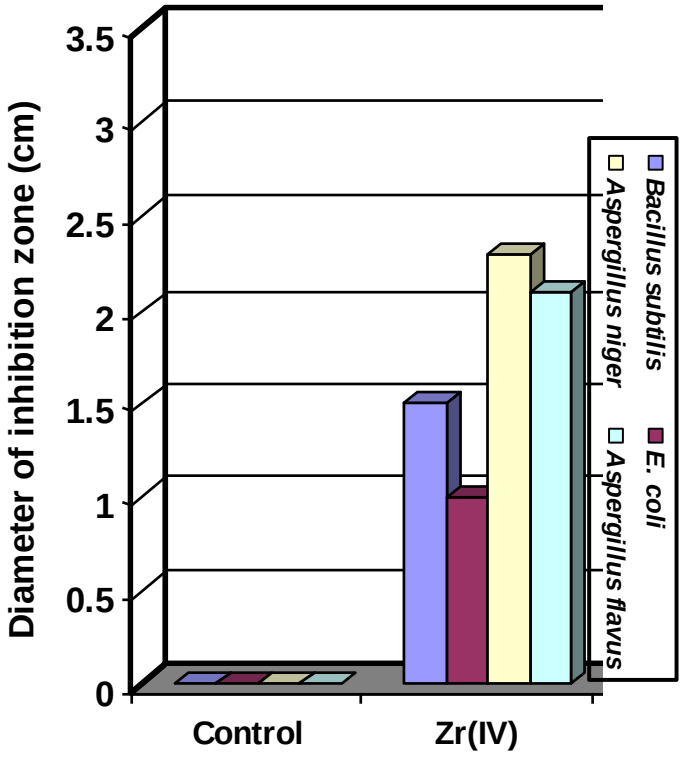

Fig 6: Statistical representation for biological activity Zr(IV) paracetanol complex

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