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NEW BARIUM(II) INDOMETHACIN MEDICAL COMPLEX: SYNTHESIS, SPECTROSCOPIC AND BIOLOGICAL DISCUSSIONS

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ABSTRACT

Herein this paper dealing with the synthesis, spectroscopic and thermal discussions of Ba(II) indomethacin complex. New $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex was studied using elemental analysis, spectroscopic measurements (infrared, $^1\text{H-NMR}$ and electronic). Elemental analysis of the chelates suggests the stoichiometry is 1:2 (metal-ligand). Infrared spectra of this complex agree with the coordination to the central metal atom through the carboxylate group as monodentate fashion. The TGA/DTG analyses of Ba(II) complex was performed. The Ba(II) complex has been screened in vitro against antimicrobial activities. The Ba(II) complex has great antimicrobial assessment than the free indomethacin drug.

Keywords: Indomethacin, Barium salt, Chelation, TGA, Antimicrobial assessments.

INTRODUCTION

Indomethacin (Fig. 1) is one of the most potent of the clinically used non-steroidal anti-inflammatory drugs, NSAIDS, and interferes with prostaglandin synthesis by direct inhibition of the two cyclooxygenase enzyme systems [1]. Indomethacin is used as analgesic and antipyretic but its efficacy is offset by significant incidence of gastrointestinal ulceration and hemorrhage. The absorption of indomethacin is associated within minutes [2]. It emerged that copper complexes with NSAID ligand are even that pharmacologically in active drugs become potent anti-inflammatory agent when associated with Cu^{2+} , suggesting the hypothesis that the active agent could be not the drug alone but that the drug alone but that the drug acts as a metal complex or through the inhibition of the activity of some metal-enzyme involved in inflammatory pathologies complexing the metal ion-determinant for the enzyme's [3-6]. Carboxylate containing ligand has attracted attention because of the diversity of the binding modes of the carboxylate group [7]. Indomethacin is mono carboxylic acid which is capable of forming coordination bond with many metals. This paper reports the synthesis and spectral characterization of barium(II) complex of indomethacin

drug. This complex has been structurally characterized in the solid state by IR, $^1\text{H-NMR}$ and conductivity measurement and biological evaluation.

EXPERIMENTAL

Material and instrumentation

Indomethacin (Fig. 1) was gift from (EIPICO) and all other chemical involved in sample preparation was purchased from (Aldrich) as analytical pure reagent. Carbon and hydrogen content were determined using Perkin-Elmer CHN 2400, FT-IR spectra were recorded on Bruker FT-IR spectrophotometer ($400\text{--}4000\text{ cm}^{-1}$) in KBr pellets, $^1\text{H-NMR}$ spectrometer was recorded using DMSO as solvent chemical shift are given in ppm relative to tetramethylsilane, the absorption spectra were recorded using Perkin-Elmer lambda Spectrophotometer within the range 200-600 nm. Molar conductivity of the freshly prepared for the dissolved complex with $1.0 \times 10^{-3}\text{ M}$ was measured using Jenway 4010 conductivity meter. Thermogravimetric analysis (TG and DTG) were carried out in nitrogen atmosphere (30 ml/min) with heating rate of $10\text{ }^\circ\text{C/min}$ using Shimadzu TGA-50H thermal analyzer.

Microbiological investigation

The biological activity of Cd^{2+} diclofenac complex was tested against bacteria and fungi. The organisms used in the present investigation included two bacteria [*B. subtilis* Gram +ve), (*E. coli* Gram -ve)] and two fungi (*Aspergillusniger*, *Aspergillusflavus*).

Synthesis

Thebarium(II) complex was synthesized by reaction of barium(II) chloride (1 mmol) in 20 mL distilled water to solution of indomethacin (2 mmol) in 20 mL 99% CH_3OH), with stiochiometric 1:2. The pH was adjusted in between 7-9 using 5% NH_4OH which dissolve in CH_3OH . The resulting solution was stirred and heated on hot plate at 60 °C for 1 h. At the moment of mixing of the solution, precipitate was obtained the precipitate was filtered; wash the precipitate several time with distilled H_2O , to remove chloride ion from filtrate. The complex resulted has low solubility in water and in common organic solvents and will soluble in DMSO. The analytical data are in a good agreement with the proposed stoichiometry of the complex.

RESULTS AND DISCUSSIONS

The results of elemental analysis and physical properties of the indomethacin barium(II) complex are discussed. This complex is stable, insoluble in H_2O and is soluble in most organic solvent. The isolated solid complex is $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$, resulted from interaction between the barium(II) chloride salt and the IndoH ligand. Table 1 gives the percentage of the experimental and calculated data of the carbon, hydrogen, nitrogen and barium ion contents, which are in good agreement with each other and with the predicted structural.

Molar conductivity of barium(II) indomethacin complex in DMF solvent ($1.0 \times 10^{-3}\text{M}$) was $35 \text{ Scm}^2\text{mol}^{-1}$, suggesting that to be non-electrolyte nature. The conductivity measurements play an important role to detect the place of counter ion inside or outside the coordination sphere. This method testing the degree of ionization of the complex, the higher molar conductivity value due to the presence of counter ion outside the coordination sphere and vice versa. Under this prediction, it is clear from the obtained data that the indomethacin complex is non electrolyte. Also the molar conductivity values indicate that the anion absence or exhibit inside the sphere. These data matched with the calculated elemental analysis that Cl^- ion was not detected by added AgNO_3 solution after soluble the complexes using nitric acid.

Infrared spectra

The main infrared bands are summarized in Table 2 and Fig. 2. Indomethacin exhibits a very strong absorption band at 1716 cm^{-1} due to stretching vibration of $\nu(\text{C}=\text{O})$ of free ketonic of carboxylic group [8]. This group is shifted or disappeared in the spectra of its

complex. The major characteristic of the IR spectra is the frequency of the $\nu_{\text{asym}}(\text{COO})$ and $\nu_{\text{sym}}(\text{COO})$ stretching vibrations. The frequency of these bands depends upon the coordination mode of the carboxyl to ligand. The $\nu_{\text{asym}}(\text{COO})$ and $\nu_{\text{sym}}(\text{COO})$ bands appear at 1552 cm^{-1} and 1370 cm^{-1} for the Ba(II) complex, respectively [9]. The difference, $\Delta [\nu_{\text{asym}}(\text{COO}) - \nu_{\text{sym}}(\text{COO})]$ between these frequencies for Br-Indo complex is 182 cm^{-1} . Nakamoto and McCarthy [10] have established that if the coordination is monodentate, the $\nu_{\text{asym}}(\text{COO})$ and $\nu_{\text{sym}}(\text{COO})$ will be shifted to higher and lower frequencies, respectively. Whereas, if the coordination is chelating bidentate or bridging bidentate, both, both the $\nu_{\text{asym}}(\text{COO})$ and $\nu_{\text{sym}}(\text{COO})$ change in the same direction because the bond order of both ($\text{C}=\text{O}$) bonds would change by the same amounts. On the basis of these facts and comparison of the $\nu_{\text{asym}}(\text{COO})$ and $\nu_{\text{sym}}(\text{COO})$ frequencies of the indomethacin complex by the $\nu_{\text{asym}}(\text{COO})$ and $\nu_{\text{sym}}(\text{COO})$ frequencies of sodium carboxylate [9], it can be said that barium(II) complex has monodentate structure (Fig. 3). The stretching broad band vibration of (OH^-) group $\nu(\text{O}-\text{H})$ occurred as expected [9, 11] at range $3400\text{-}2500 \text{ cm}^{-1}$. The angular deformation motion of the coordinated water in the hydrated indomethacin complex as can be classified into four type of vibration $\delta_b(\text{bend})$, $\delta_r(\text{rock})$, $\delta_t(\text{twist})$ and $\delta_w(\text{wag})$. It should be mentioned here that these assignment for both the bond stretches and angular deformation of the coordinated water molecule fall in the frequency regions reported for related complexes [11]. The work or medium intensity were observed in the wave number range (596 and 476 cm^{-1}) can be assigned to $\nu(\text{M}-\text{O})$ vibration of indomethacin chleates.

Electronic spectra

The UV-vis spectra for $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex show strong absorption bands at 240-370 nm range. These bands (375, 307, 250) nm are due to mainly to ligand charge transfer bands as shown in Fig. 4.

$^1\text{H-NMR}$ spectra

To make sure about the proposed structure, the $^1\text{H-NMR}$ spectra were carried out in DMSO for indoH and Ba(II) complex under investigation. The $^1\text{H-NMR}$ data for free indoH: $\delta = 11.1$ [H, COOH], 2.1 [2H, CH_2], 3.5 [3H, CH_3], 4.1 [3H, CH_3O], 6.15-7.15 [H, aromatic rings]. The $^1\text{H-NMR}$ data for the Ba(II)/indo solid complex (Fig. 5 and Table 3) are in agreement with coordination through the carboxylic group by the absence of the H (1) signal in Ba(II) complex and aromatic signals decreased in the intensities, thus showing that the magnetic environment of aromatic ring has changed significantly with coordination. The signal observed at 2.48-2.51 and 3.37 ppm in case of Ba(II) complex in Fig. 3, are assigned to the coordination water molecules which present in the coordinated sphere of the illustrated Ba(II) complex.

Thermogravimetric analysis

Thermal analysis curve (TG/DTG) of $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex is shown in Fig. 6 and interpreted in Table 4. The thermal decomposition of Ba(II)/Indo complex proceed within three degradation steps. The first decomposition stage occurs at the maximum temperature 291°C. The weight loss at this step is (obs= 20.50%, Calc. =20.40%) associated with the loss of $4\text{H}_2\text{O}+\text{C}_8\text{H}_{20}$. The second decomposition stage occurs at the maximum temperature 444 °C. The observed weight loss of this step is (obs= 28.90%, calc= 29.10%) associated with the loss of $\text{C}_8\text{H}_{10}\text{O}_4\text{N}_2\text{Cl}_2$. The third step of the degradation occurs of maximum temperature of 520 °C is accompanied by weight loss of (obs= 9.10%, calc= 9.10%) correspond to the loss of 3CO. The final product formed at 700 °C, consists of BaO with contaminated carbon atoms.

Antimicrobial activity

Antimicrobial activity of the tested samples against (Gram (+) bacteria and Gram (-) bacteria) and fungi were determined using a modified Kirby-Bauer disc diffusion method [12]. Antibacterial and antifungal activities of the IndoH ligand and its barium(II) complex are carried out against two kind of bacteria, *B. subtilis* (Gram +ve), *Escherichia coli* (Gram -ve) and fungal (*Aspergillusniger*, *Aspergillusflavus*) in Fig. 7 and Table 5. The antimicrobial activity estimated based on the size of inhibition zone around dishes. This complex is found to have high activity against *Aspergillusniger* and *B. subtilis*. The high sensitivity of the indomethacin complex has been attributed to hyper conjugation of the coordinated aromatic Lewis bases, which increase the net electron density on the coordination metal(II) ion and consequently higher antimicrobial activity.

Table 1. Elemental analysis and physical data of Ba(II) indomethacin complex

Complex	Mwt.	Content (calculate) found)				Δ $\text{Scm}^2\text{mol}^{-1}$
		C %	H %	N %	Ba %	
$[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$	953.02	(50.41)49.60	(4.65)4.26	(2.94)2.69	(14.41)14.31	35

Table 2. IR spectra of indomethacin and its Ba(II) complex

Assignments	indoH	Ba(II)
$\nu(\text{OH}); \text{H}_2\text{O}$	3412	3406
$\nu_{\text{as}}(\text{CH})$	3058, 2974	2931
$\nu_{\text{s}}(\text{CH})$	2870	-
$\nu(\text{COOH})$	1716	-
$\nu(\text{CO})$ amide	1685	1623
$\nu_{\text{as}}(\text{COO}^-)$	1585	1552
$\nu_{\text{s}}(\text{COO}^-)$	1440	1475
$\delta(\text{CH}), 7(\text{C-O})$	1370	1370, 1318
$\nu_{\text{as}}(\text{CC})$	1274, 1246, 1178, 1129	1226, 1147, 1080, 1036
$\nu(\text{C-N})$	1074	
$\nu_{\text{s}}(\text{CC})$	974	918
$\delta(\text{CC})$	819, 78	835, 787, 748, 680
$\nu(\text{M-O})$	-	596, 476

Table 3. $^1\text{H-NMR}$ spectral data of Indo and its Ba(II) complex

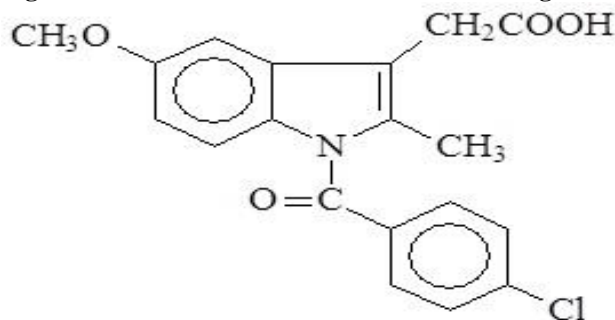
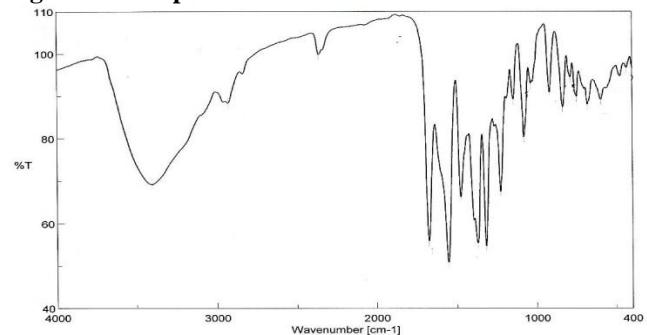
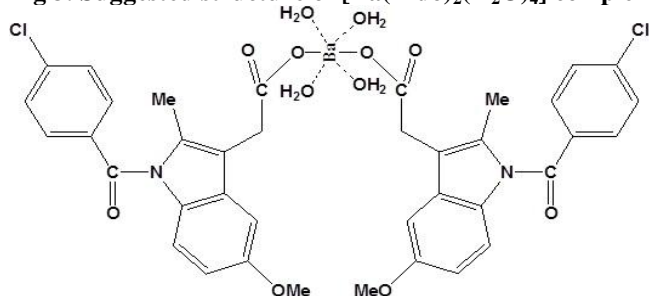
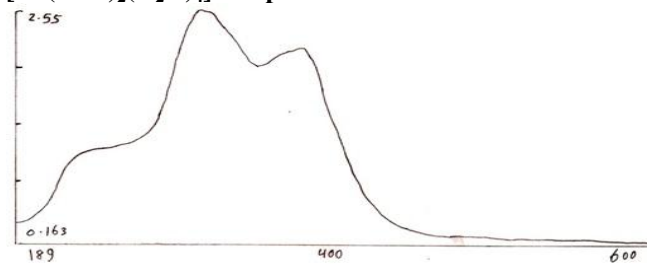
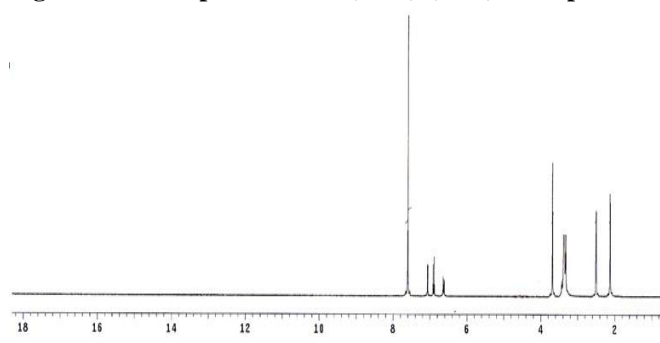
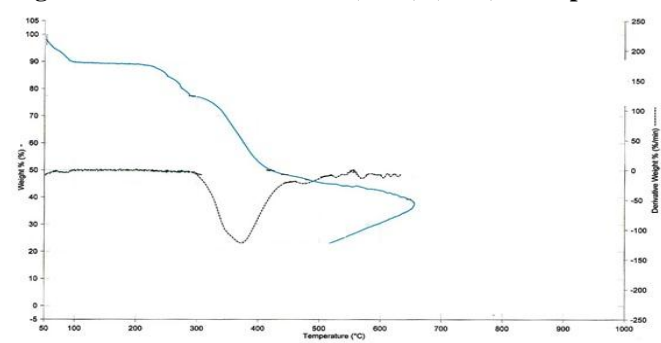
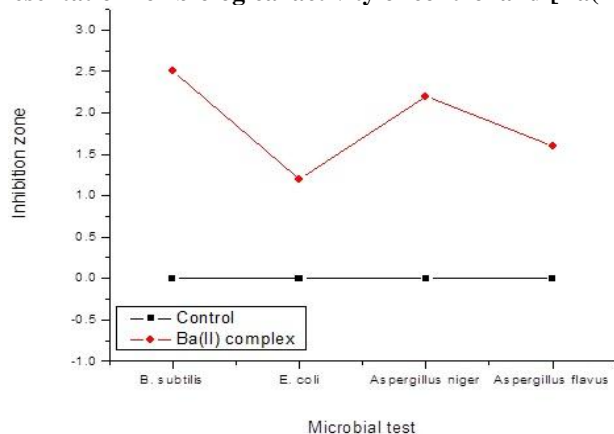
Compound	δ ppm of hydrogen				
	2H; CH_2	3H; CH_3	3H; CH_3O	5H; ArH	H; COOH
IndoH	2.10	3.50	4.10	6.15-7.15	11.10
Ba(II)	2.12	3.43	3.68	6.61-7.6	-

Table 4. Thermal analysis data for $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex

Steps	Temp Rang(c)	DTG Peak(c °)	TGAWeight loss %		Assignment
			Calc.	Found	
1	100-375	291	20.40	20.50	$\text{C}_8\text{H}_{20}+4\text{H}_2\text{O}$
2	375-477	444	29.10	28.90	$\text{C}_8\text{H}_{10}\text{O}_4\text{N}_2\text{Cl}_2$
3	477-650	520	9.10	9.10	3CO
					BaO + Carbon residual

Table 5. Antimicrobial of $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex

Samples	Diameter of inhibition zone (cm)			
	<i>B. subtilis</i>	<i>E. coli</i>	<i>Aspergillus niger</i>	<i>Aspergillus flavus</i>
Control	0	0	0	0
Indo/Ba	2.5	1.2	2.2	1.6

Fig 1. Schematic structure of indomethacin drug**Fig 2. FT-IR spectrum of Indo/Ba²⁺****Fig 3. Suggested structure of $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex****Fig 4. UV-visible absorption spectrum of $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex****Fig 5. ¹H-NMR spectra of $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex****Fig 6. TGA/DTG curve of $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex****Fig 7. Statistical representation for biological activity of control and $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex**

CONCLUSION

This paper was described the synthesis and structural characterizations of new $[\text{Ba}(\text{Indo})_2(\text{H}_2\text{O})_4]$ complex. Some of analytical techniques were used like elemental analysis, spectroscopic measurements. The analyses of this complex are agreement with the

complexation of barium(II) ions via the carboxylate group as monodentate fashion. The antimicrobial of barium(II) indomethacin complex was screened against bacteria and the free indomethacin drug.

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