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Synthesis, characterization and antimicrobial studies of Zn(II) complex of chemotherapeutic importance

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Abstract

The Zn (II) complex of Schiff base derived from salicyladehyde and acetazolamide have been synthesized keeping in view that some metal complexes are found to be more potent than their parent drugs. The synthesized complex is characterized on the basis of elemental analysis, conductivity, magnetic measurements, particle size analysis, IR and NMR spectral studies. Comparative antibacterial behavior of Schiff base with their complex has also been studied.

Key words: Schiff base, Acetazolamide, Spectral studies, Conductivity.

INTRODUCTION

Acetazolamide (5-acetamido- 1, 3, 4 - thiadiazole - 2 – sulphonamide) sold under the trade name ‘Diamox’ is a weak diuretic drug that acts to increase the amount of bicarbonates lost from the body. Bicarbonates draw water with them from the kidney, thus increase the amount of water being lost from the body. Schiff base metal chelates have played a central role in the development of coordination chemistry. Metal chelation is a very important process in order to enhance the pharmacological properties of a drug [1-3]. Schiff bases are widely applicable because of their wide range of applications like anti-tumor [4], antibacterial [5], antifungal [6] and antiviral [7] activities**.** In the present communication, we report the synthesis, spectroscopic and biocidal studies of Zn (II) complex with Schiff base (AZM-SA) derived from acetazolamide (AZM).

MATERIALS AND METHODS

All the chemicals used were of AR/GR grade. Pure sample of Acetazolamide (AZM), molecular formula $C_4H_6N_4O_3S_2$, molecular weight 222.24, was obtained from Shalak's pharmaceuticals.

Metal salts used were of Merck. Solvents used were methanol, acetone and deionized double distilled water.

Preparation of Schiff base

Equimolar solutions of pure drug and salicylaldehyde were separately prepared in methanol-water mixture (1:1) and refluxed for four hours and kept for a day. Pale yellow crystals of acetazolamide Schiff base were formed in the reaction mixture, which were filtered and washed thoroughly with 50% methanol, dried over vacuum and weighed. Melting point of Schiff base was recorded.

Synthesis of Complex

For the synthesis of complex, ligand-metal ratio was confirmed by conductometric titrations using monovariation method on systronics conductivitymeter using dip type electrode. Conductometric titrations supported 2:1 (L:M) ratio in the complex which was further supported by Job's method [18] of continuous variation as modified by Turner & Anderson [19].The stability constant and free energy change values were also calculated

The metal complexes were prepared by refluxing 60% acetone solution of ligand (0.006M) and metal salt (0.003M) for four hours. The refluxed solutions were kept for some days. Solid crystalline compounds appeared in the solution, which were filtered, washed with 60% acetone and dried over fused $CaCl_2$.

Analytical procedure

Elemental analyses were carried out on a model 240 Perkin elemental analyzer. Metal contents were determined gravimetrically. The infrared spectra were measured on a Nicolet 400 D FT- IR spectrophotometer using KBr pellets. Molar conductance measurements were made in anhydrous DMF on a Systronics (model 305) conductivity bridge. The particle size analysis has been studied by laser diffraction particle size analyzer. The melting points of the ligand and complexes were recorded in open capillaries on a capillary melting point apparatus.

Antibacterial Activity

Above synthesized compound and the ligand (schiff base) have been screened against bacteria Escherichia coli and Pseudomonas aeruginosa by the filter paper disc method at various concentrations using nutrient agar as medium. Sterilized filter papers of 5 mm diameter were soaked in solutions of different concentrations of test samples and introduced on nutrient agar plates. These plates were incubated for 48 hours at 35 ± 0.5^0C.

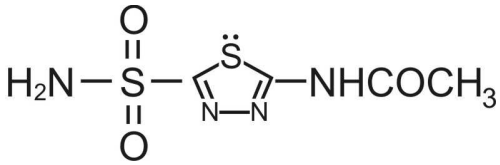

Fig. 1: Structure of Pure Drug (Acetazolamide)

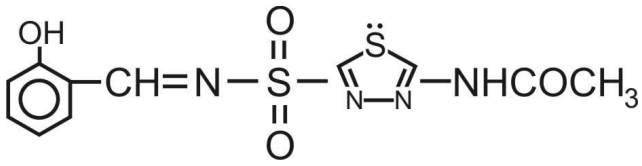

Fig.2: Structure of Schiff base

RESULTS AND DISCUSSION

The structure of complex was confirmed by its analytical and spectral data. On the basis of physicochemical characteristics and analytical data (Table1) it has been found that the complex is non- hygroscopic, stable at room temperature, insoluble in water but fairly soluble in DMSO. The magnetic moment data indicates that the complex is diamagnetic in nature. The molar conductance value for the complex in 10^{-3} M DMSO is14 Ω^{-1} cm^2 mol^{-1} suggesting its non-electrolytic nature[8]. Elemental analysis data, formula weights and melting points are given in Table 2.

The IR spectra [9-10] of Schiff base shows a sharp band near 1610 cm^{-1} which may be due to azomethine linkage and shows lowering in frequency in metal complex indicating the coordination of metal ion through azomethine linkage. Strong band observed at 1585 cm^{-1} indicates the presence of (CH=N) bond in complex. Bands observed at 1176 cm^{-1} and1177 cm^{-1} are the characteristics of SO_2-N linkages in Schiff base and Zn complex respectively. Absorption band at 1449 cm^{-1} show the presence of chelate ring in complex. The appearance of the M-O band at 410 cm^{-1} and M-N band at 515 cm^{-1} in complex indicates that AZM-SA is coordinated through O & N atom. The disappearance of phenolic-OH group in complex supports its involvement in complexation.

The PMR [11] spectra of Schiff base and its Zn(II) complex have been recorded. The ligand displays a triplet in the range 8.59-8.63 ppm which can be assigned to azomethine proton [12]. The peak shows downfield shifting in the complex suggesting the coordination of metal through nitrogen of azomethine group. The ligand shows a peak at 4.57-4.59 ppm that can be assigned to phenolic-OH proton [13] and the absence of this signal in the complex suggests the coordination of phenolic oxygen to the metal. The above results have also been supported by IR spectral data.
Acetazolamide pure drug, its Schiff base and Zn complex derived from the schiff base were evaluated for particle size distribution and average particle diameter using laser diffraction method. The average particle size of AZM-SA-Zn was found to be 2.93 μm which is smaller than schiff base (AZM-SA) with average diameter 4.01μm and pure drug (AZM) with average diameter 4.16 μm. Smaller particle size of the complex is also responsible for the enhanced solubility of the drug [14, 15].

The zone of inhibition based upon size around the disc was measured. Inhibition zone percentages are recorded in Table 3. The percentage inhibition of growth by an inhibitor at different dilutions is determined as 100 x (C-T)/C (where C=diameter of microbial colony in control plate, T=diameter of bacterial colony in the test plate). From the results it is observed that the complex shows greater activity against microorganisms as compared to the Schiff base. This

indicates that chelation increases the antibacterial activity [16, 17]. Results are presented in Table 3.

Table 1: Synthesis and Physicochemical Characteristics of Complex

	Ligand-metal ratio	Colour	Yield	Stability constant log K (Lit/mole)	Δ F K cal/mole
AZM-SA	---------	Pale yellow	54.5%	--------	--------
$(AZM)_2$ Zn	2:1	Off White	41.5%	8.151	-11.180

Table 2: Analytical data of Complex

Complex	Elemental analysis % Found (calculated)					Melting point
	C	H	N	S	Metal	
$(C_{11}H_9N_4O_4S_2)_2Zn$	35.80 (36.50)	2.53 (2.34)	15.53 (16.60)	17.18 (17.50)	9.01 (9.70)	$150^{O}C$

Table 3: Antibacterial activity of Schiff base and its Zn (II) Complex

Ligand/Complexes	% of inhibition zone			
	Escherichia coli		Pseudomonas aeruginosa	
	Conc. in ppm		Conc. in ppm	
	500	1000	500	1000
AZM-SA	51.23	81.89	59.47	73.33
$(AZM\text{-}SA)_2$ Zn	66.38	100	71.23	100

CONCLUSION

Hence on the basis of elemental analysis, IR spectra, NMR spectra, magnetic moment data and conductivity measurement, following tentative structure is produced for complex (Figure 3).

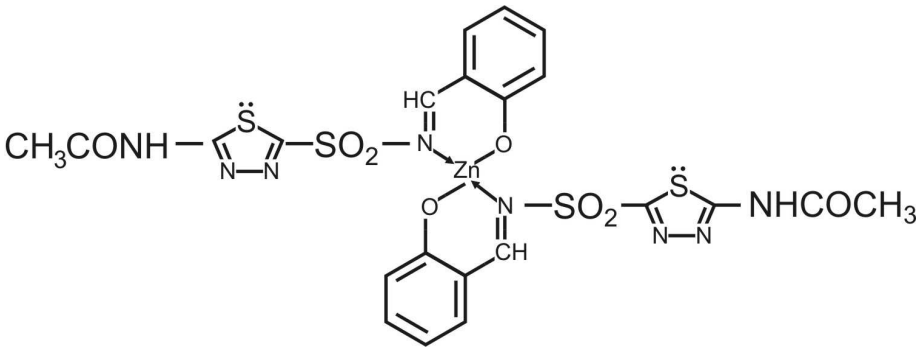

Fig.: 3

The particle size analysis concluded that complexation of acetazolamide (pure drug) with Zn(II) via the formation of Schiff base can enhance the dissolution rate of the pure drug and thereby improve its bioavailability and has the potential to produce faster onset of action[20].

The results of antibacterial activity conclude that synthesized Zn (II) complex of AZM-SA has better antibacterial activity at different concentrations.

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