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Physiochemical Microbial and Pharmacological studies of Zn (II) – Cytarabine Complex

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ABSTRACT:
A new complex has been synthesized of Zn (II) complex with Cytarabine with the help of physicochemical methods. M:L ratio considered by amperometry and polarography. The prepared complex characterized by elemental analysis and IR spectroscopy. After Synthesis of metal complex, it was evaluated it for antibacterial activities against various pathogenic microorganisms such as; Streptococcus aureus, Klebsiella pneumonia, Bacillus subtilis *and* Escheria coli. Sarcoma-180 tumor cell has been used for anticancer screening of metal complex for *in vitro* study. The result of pharmacological studies with M: L revealed that the complex is more potent as compared to the pure drug as regards to its anticancer activity.

KEYWORDS: Zn (II) Complex, Polarography, Amperometry, Biological investigation, anticancer activity.

1. INTRODUCTION

Cytarabine, chemically known as **cytosine arabinoside (Ara-C)**, is a pyrimidine nucleoside analog that serves as a cornerstone in modern chemotherapy. It is primarily utilized in the treatment of hematological malignancies, particularly leukemia's. Cytarabine is known as cytosine arabinoside (Ara-C), is a chemotherapeutic drug used in treatment of acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), non-Hodgkin's lymphoma, and chronic myelogenous leukemia (CML). It can be administered by injection, either subcutaneously or directly into the cerebrospinal fluid. A liposomal formulation of this drug is available, which shows preliminary evidence of improved outcomes in lymphoma cases involving the meninges **(1)**.

Organo-metallic compounds have been used in medicine for centuries. Metal play essential role in pharmaceutical industry. The metalloelements present in trace quantities play vital role at the molecular level in the system. Zinc is most abundant and essential metal in our body system (2).

Zn (II) is recognized as an essential metal for normal functioning of our biological system. It is a major constituent of many enzymes involved in the metabolism of DNA and RNA (3). Zn deficiency is associated with impaired growth and large number of diseases (4). Beside several other important role of Zn in our body system are well known (5- 6). It has been observed in favorable cases that metal drug complexes show increase potency then the parent drug (7). Keeping this view in mind the present investigation deal with the bioinorganic studies of the interacting such biologically essential metal Zn (II) and an anticancer drug with

Cytarabine.

The metal ligand complexation equilibrium have been studied and elemental and IR spectral analysis has been worked out which given probable formula for complex is to 1:1. Various pathogenic bacteria

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like **Streptococcus aureus, Klebsiella pneumonia, Bacillus subtilis and Escheria coli** have been applied for microbial study using disc diffusion method. **Sarcoma-180 tumor cell**s are used for the in vitro anticancer study of complex compound, respectively.

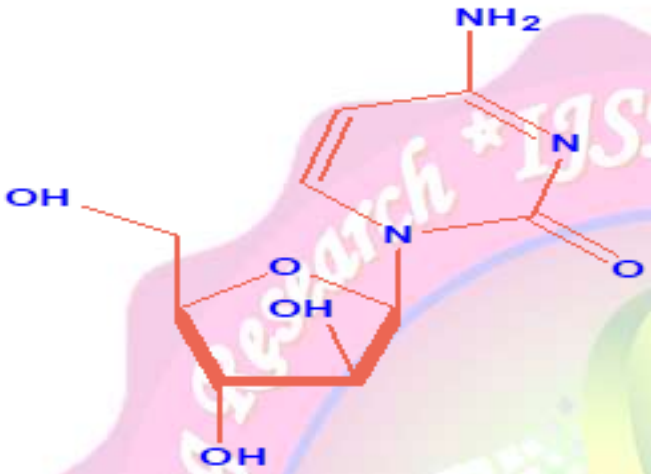

Fig 1: **Chemical structure of Cytarabine**

2. MATERIALS AND METHODS

All the chemical used were of analytical grade, the drug **Cytarabine** was procured form Sigma Chemical Company, USA. Standard solution of Zn (II) 2 Mm, Cytarabine 2mM and Ammonium Buffer 0.1 M solutions 5% of 95% ethyl alcohol prepared, Polarographic /voltammetric measurement was carried out using a ion analyzer, Model 797A Computrace Metrohm, Herisau, Switzerland with stand three electrodes containing a DME (working electrode), a coiled platinum wire (auxiliary electrode) and saturated calomel electrode as reference electrode.

2.1 Electrochemical Studies of Zn (II)-Cytarabine Complex

For the study of metal: ligand (M: L) complexation equilibrium experiment sets were prepared by keeping overall Zn (II) and Ammonium Buffer (supporting electrolyte) concentration fixed at 2 mM and 0.1M, respectively. The ligand concentration varied from 0.0 to 15mM. The pH of the test solution was adjusted to10.4 ±0.02 using HCl/NaOH solution. The test solutions were de-aerated by bubbling nitrogen gas for 15min before recording the polarogram.

The amperometric titrations were performed on a manually operated set up equipped with a poly flex galvanometer and an ajco vernier potentiometer. The capillary characteristics of DME had m2/3 t 1/6 value of 2.5 mg2/3 S-1/2 at 50 cm effective height of mercury column. A systronics digital pH meter- 335 was used for the pH measurements. Experimental sets each having different but known amount of Zn(II) were prepared in appropriate quantity of supporting electrolyte Ammonium Buffer and pH was adjusted to10.4 ±0.2 and titrated separately against the standard solution of the titled 6-thioguanine whose pH was also adjusted to that of the titrate (10.4± 0.2 using NaOH /HCl) at -0.04 V Versus SCE The plateau potential of Zn (II) The current offer each addition of the titrant was read and a curve was plotted between current against volume of titrant added.

2.2 Synthesis of Solid Complex

Zn (II) and **Cytarabine** were prepared separately in water and were mixed in 1:1 molar ratio the mixture was then refluxed in a round bottom flask for 2h. The complex was marked by precipitation after reducing (complex) was filtered and washed thoroughly to remove any un reacted material, the complex was dried at low temperature and store over P4O10.The results of elemental (C, H, N) and O analysis on the drug and Zn (II)- **Cytarabine** complex was furnished by CDRI Lucknow, India., whereas gravimetric method was used for the estimation of Zinc in synthesized complex (8).

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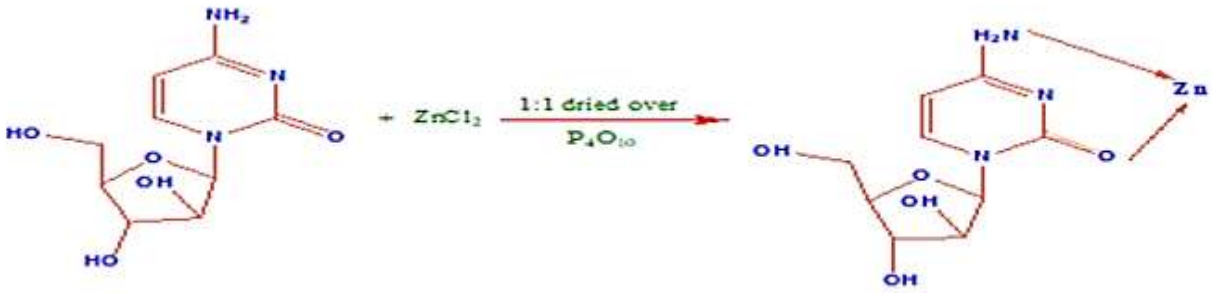

Fig 2: **synthesis of Cytarabine -Zn (II) complex**

2.3. Antimicrobial Screening

The microorganisms used in this study were **Klebsiella pneumonia, Streptococcus aureus**, **Bacillus subtilis and Escheria coli**. All strains were obtained from the department of microbiology, Dr. H.S.G.V.V. Sagar (M.P.). Each Microorganism maintained on Meuller-Hinton (MH) agar medium at 4ºC. Kirby-Baller *et al*. disc diffusion was followed for the antimicrobial activity screening of the complex against various microorganisms: ***Klebsiella pneumonia, Streptococcus aureus,*** **Bacillus subtilis and Escheria coli** [9]. The number of replicates in each case was three and the percentage of inhibition was calculated using the following Formula [10].

$$\text{Percentage inhibition} = \frac{a-b}{b} \text{ x } 100$$

Where 'a', represents the diameter of inhibition zone for control 6-thiguanine and 'b' represent the diameter of inhibition zones of complex (Zn (II) - **Cytarabine**).

2.4. Pharmacological Studies *In-vitro study* of anticancer activity of prepared metal drug complex have been done using the following procedure [11-13].

Sarcoma-180 tumor cell (14) obtained were culture in 5ml 24 well culture plate (corning plastics). The cells were seeded in 2x105 cell per well were grown in 1.0 ml dulbecco's modified Eagles medium (DMEM) supplemented with10% fetal bovine serum (FBS), 1% non-essential amino acid. 1mM sodium pyruvate, 100 µg/ml penicillin, 100 µg/ml streptomycin and 5% v/v heat inactivated foetal calf serum. The **Sarcoma-180 tumor** cell line was growth at the cells, was kept in incubator at 37°C for 8h in 5% CO2 atmosphere and 95% humidity. The cell counter was made on Neubaurs Chamber.

Two dilutions viz, 1µm, 10µm of pure drug and its complex was made and then the cells were treated as follows

Column	Free Drug	Metal Complex
A	1µm (1ML)	1µm (1ML)
B	10µm (1ML)	10µm (1ML)

After addition of the respective solutions, the culture plate was incubated at 37°C for 8 hours. Finally, the cell counts and viability were conducted under microscope after trypan blue staining and compared to the cell cultured in DMEM medium without treatment as control.

Cells Vialibility Counts

Cell Vialibility counts were made by trypan blue dye exclusion test. Two drops of trypan blue were added to each cell culture well and kept for 15 minutes. Now a drop of culture was added to hemocytometer and the number of stained, non-

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stained and total numbers of cells were counted, then the % inhibition was calculated using the following equation:

$$\%\text{inhibition} = \frac{\text{No.of viable cells before treatment} - \text{No.of viable cells after treatment}}{\text{No.of viable cells beforewithout treatment}} \times 100$$

The experiment of each concentration of the drug and the complex was repeated three times and statistical conclusions were drawn.

3. RESULTS AND DISCUSSION

3.1. Polarographic Behavior of Cytarabine with Zn (II)

In 0.1 M KCl at pH 10.4±0.2 the Zn (II) and its complex with ligand under study were found to be reversible and diffusion controlled Polarographic wave which revealed by the log plot slop id versus √h respectively on gradual addition of ligand the E1/2 of metal shifted towards more electronegative value indicating the formation of complex (Figure **1**). Lingane's treatment [15] of observed Polarographic data revealed 1:1 [M: L] Complex formation in solution.

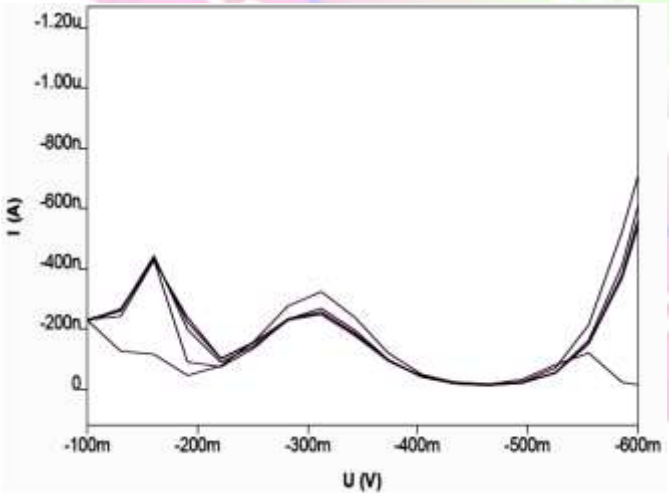

Figure 3: Polarogram of Zn (II) (2.0 mM) in 0.1M Ammonium buffer Solution at pH 7.0±0.1 and 2.0 mM **Cytarabine**.

3.2. Amperometric Determination of Cytarabine with Zn (II)

Zn (II) with **Cytarabine** gives a well-defined polarographic waves / peak in 0.1 M KCl at 10.4±0.2pH the diffusion current was found proportional to the concentration of Zn (II). The platue potential for the polarographic wave of Zn (II) (-0.40V) Vs Hg Pool was applied for carrying out amperometric titration. The Current goes on decreasing to minimum and then attends a constant value. The plot of id versus volume (V+vV) of titrant added, revealed L shaped curve (Figure **4**). The end point was indicated by the intersection of the two lines, which confirmed 1:1 [M: L] complex formation.

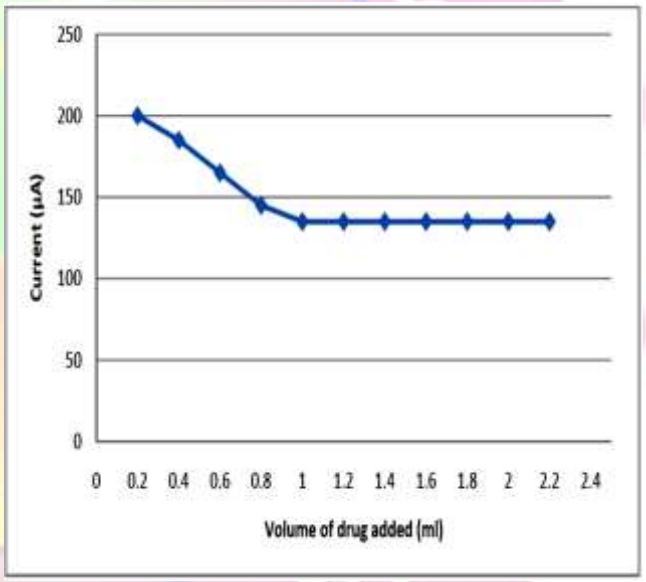

Figure 4: Amperometry titration of (2mM/10ml) **Cytarabine** (2mM/ml) Zn (II) solution in 0.1 M Ammonium buffer Solution.

3.3. Elemental Analysis

Elemental analyses were carried out on a model 240 Perkin elemental analyzer, Massachusetts USA. Metal contents were determined gravimetrically. Percentage of **Cytarabine** drug found and Calculated in %

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Compound	M.W.	%Metal	% of C	% of H	% of N	% of O
Cytarabine	243.22	-	44.40	5.34	17.26	32.89
Cytarabine Zn (II) – Complex (Calculated)	308.4	21.2	35.0	4.2	13.61	26
Cytarabine Zn (II) – Complex (Found)	308.4	21.3	35,1	4.19	13.51	25.9

Reaction of **Cytarabine** with metal ion in near quantitative yield are good agreement with each other elemental analysis.

3.4. Spectrometric Measurement

Cytarabine contains more than a few functional groups, such as amino (–NH_2) and hydroxyl (–OH) groups, it is determined by IR spectrophotometer. Amino (–NH_2) and hydroxyl (–OH) groups can act as donor sites for coordination with metal ions. In the Zn (II) complex, the zinc ion typically coordinates with these donor atoms, forming a stable chelate structure. The structurally important IR bands in the spectra of cytarabine and its complex with Zn (II) are given in table 3.4. Critical comparison of the IR spectra of cytarabine and Zn(II) cytarabine complex shows that band due to –NH_2 group at 3477 cm^{-1} in the spectrum of cytarabine is shifted to 3445 cm^{-1} in the spectrum of the complex. Similarly, the bands at 1658 cm^{-1} in the IR spectrum of pure drug which are due to >C=O group stretching vibrations shifted to 1668 cm^{-1} in the IR spectrum of the complex.

S.No.	Assignment	Cytarabine	Zn(II) Complex
1.	-NH_2 stretching due to primary amine	3477 cm^{-1} (w)	3445 cm^{-1} (s)
2.	-NH stretching due to secondary amine	3358 cm^{-1} (m)	3358 cm^{-1} (m)
3.	Due to –OH group Abroad band appear at	3265 cm^{-1} (b)	3265 cm^{-1} (b)
4.	- CH stretching vibration	2939 cm^{-1} (s)	2939 cm^{-1}
5.	>C=O strong stretching	1658 cm^{-1}	1668 cm^{-1}
6.	-C=C band due to stretching cyclic alkene	1582 cm^{-1}	1582 cm^{-1}
7.	-C=N- medium stretching	1483 cm^{-1}	1483 cm^{-1}
8.	-NH_2 band due to out of plane	713 cm^{-1}	713 cm^{-1}
9.	N-stretching due to tertiary amine	653 cm^{-1}	653 cm^{-1}

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3.5. Antimicrobial Activity

The antimicrobial activity of Zn (II) cytarabine against different type of pathogenic bacteria and show variable result against Klebsiella pneumonia, Staphylococcus aureus, Bacillus subtilis and E. coli, it is very clear that the prepared complex is less effective against all the four pathogens understudied compared to the parent cytarabine drug show in table.

S.No.	Test organism	Inhibition Zone* (mm)		% Inhibition
		Complex	Control Drug	
1.	Klebsiella pneumonia	14	17	27.6
2	Staphylococcus aureus	12	15	20
3.	Bacillus subtilis	16	20	20
4.	Escheria coli	9	11	18.1

3.6. Pharmacological Studies

In Vitro

The result of *in-vitro* experiments of pure drugs and its complex are shown Table **2**. Perusals of the data it is compared shown that Zinc 6-thioguanine complex was found to be more effective than pure drug.

The complex under study showed an increased inhibition against the **Sarcoma-180 tumor** cell line at all the test concentrations.

Compound	Concentration	% Inhibition after		
		2 hrs	4 hrs	6 hrs
Cytarabine	10	5.6	11.5	23.1
	50	15.4	28.7	35.2
	100	35.7	65.4	70.7
Zn(II)-Cytarabine complex	10	6.7	11.6	24.3
	50	19.6	30.4	36.5
	100	36.5	69.1	72.3

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4. CONCLUSION

To investigate the structure and behavior of complex of Cytarabine with life essential metal ion Zn (II) some physicochemical method i.e. IR spectral analysis, elemental analysis, amperometry and polarography has been successfully used. The results obtained of these methods suggested that complexes having more stable as compared to pure drug. On the basis of observed results of pharmaceutical study Zn (II) with Cytarabine complex it could be concluded that drug complex with life essential metal more effective and nontoxic in nature as compared to the parent drug. Thus, polarographic and amperometric method may be recommended as more potent drug in lieu of the drug taken for present study has excellent potential for clinical application.

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